LITHUANIAN UNIVERSITY OF HEALTH SCIENCES
MEDICAL ACADEMY

Gabrielė Pranckevičienė

PHARMACOEPIDEMIOLOGIC ASSESSMENT OF LOW-MOLECULAR-WEIGHT HEPARINS UTILIZATION IN LITHUANIA AND DEVELOPMENT OF PHARMACOECONOMIC MODEL

Doctoral Dissertation
Biomedical Sciences,
Pharmacy (08B)

Kaunas, 2014

Dissertation was prepared at the Medical Academy of Lithuanian University of Health Sciences during the period of 2008–2012.

Scientific Consultant

Prof. Dr. Vitalis Briedis (Lithuanian University of Health Sciences, Medical Academy, Biomedical Sciences, Pharmacy – 08B)

Dissertation is defended extramurally.

Dissertation is defended at the Pharmacy Research Council of Lithuanian University of Health Sciences.

Chairperson

Prof. Dr. Kristina Ramanauskienė (Lithuanian University of Health Sciences, Medical Academy, Biomedical Sciences, Pharmacy – 08B)

Members:

Prof. Dr. Romaldas Mačiulaitis (Lithuanian University of Health Sciences, Medical Academy, Biomedical Sciences, Medicine – 06B)
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Prof. Dr. Ruta Muceniene (University of Latvia, Biomedical Sciences, Pharmacy – 08B)
Assoc. Prof. Dr. Reinis Vilskersts (Latvian Institute of Organic Synthesis, Biomedical Sciences, Pharmacy – 08B)

Dissertation will be defended at the open session of the Pharmacy Research Council of Lithuanian University of Health Sciences at 11 a.m. on the 7th of March, 2014 at the Conference Hall of the Institute of Cardiology of Lithuanian University of Health Sciences.

Address: Sukilėlių 17, LT-50009 Kaunas, Lithuania.

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS
MEDICINOS AKADEMIJA

Gabrielė Pranckevičienė

MAŽOS MOLEKULINĖS MASĖS HEPARINŲ SUVARTOJIMO LIETUVOJE FARMAKOEPIDEMIOLOGINIS ĮVERTINIMAS IR FARMAKOEKONOMINIO MODELIO PARENGIMAS

Daktaro disertacija
Biomedicinos mokslai,
Farmacija (08B)

Kaunas, 2014

Disertacija rengta 2008–2012 metais Lietuvos sveikatos mokslų universiteto Medicinos akademijoje.

Disertacija ginama eksternu.

Mokslinis konsultantas

Prof. dr. Vitalis Briedis (Lietuvos sveikatos mokslų universitetas, Medicinos akademija, biomedicinos mokslai, farmacija – 08B)

Disertacija ginama Lietuvos sveikatos mokslų universiteto Farmacijos mokslo krypties taryboje:

Pirmininkas

Prof. dr. Kristina Ramanauskienė (Lietuvos sveikatos mokslų universitetas, Medicinos akademija, biomedicinos mokslai, farmacija – 08B)

Nariai:

Prof. dr. Romaldas Mačiulaitis (Lietuvos sveikatos mokslų universitetas, Medicinos akademija, biomedicinos mokslai, medicina – 06B)
Prof. dr. Giedrius Vanagas (Lietuvos sveikatos mokslų universitetas, Medicinos akademija, biomedicinos mokslai, visuomenės sveikata – 09B)
Prof. dr. Ruta Muceniene (Latvijos universitetas, biomedicinos mokslai, farmacija – 08B)
Doc. dr. Reinis Vilskersts (Latvijos organinės sintezės institutas, biomedicinos mokslai, farmacija – 08B)

Disertacija bus ginama viešame Farmacijos mokslo krypties tarybos posėdyje 2014 m. kovo 7 d. 11 val. Kardiologijos instituto posėdžių salėje.

Disertacijos gynimo vietos adresas:
Sukilėlių pr. 17, LT-50009 Kaunas, Lietuva.

CONTENT

ABBREVIATIONS

ACCP	American Colleague of Chest Physicians
ACS	Acute coronary syndrome
ACT	Active clotting time
ADR	Adverse drug reaction
APTT	Activated partially thromboplastin time
ATC	Anatomic therapeutic classification
AT	Antithrombin
BMI	Body mass index
CI	Confidence Interval
CMA	Cost-minimization analysis
DDD	Defined daily dose
DU	Drug utilization rate
DVT	Deep venous thrombosis
ECG	Electrocardiogram
HD	Hospitalization days
HTA	Health technology assessment
INR	International normalized ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IUA	International Union of Angiology
IV	Intra venous
K^+	Potassium
KMU	Kaunas Medical University
KMUH	Kaunas Medical University Hospital
LUHS	Lithuanian University of Health Sciences
LMWH	Low-molecular-weight heparin
LMWHs	Low-molecular-weight heparins
MI	Myocardial infarction
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
PD	Pharmacodynamics
PDD	Prescribed daily dose
PE	Pulmonary embolism
PK	Pharmacokinetics
PTS	Post-traumatic syndrome
QALY	Quality adjusted life year
RR	Relative risk
r_s	Spearman correlation coefficient

SC	Subcutaneous
SPA	Stago Prothrombin Assay (Prothrombin time)
TFPI	Tissue factor pathway inhibitor
UFH	Un-fractionated heparin
UCAD	Unstable coronary artery disease
VKA	Vitamin K antagonist
VT	Venous thrombosis
VTE	Venous thromboembolism
WHO	World Health Organization

INTRODUCTION

In recent years, many countries have struggled with the fact that expenditures on health care are growing much faster than the overall level of wealth [1]. The healthcare systems in most industrialized countries face similar difficulties, including limited resources, a growing chronically ill population, and demand for high quality care [24]. In general, the ageing population, the introduction of expensive technologies and increasing expectations of the population with regards to better health care are given as the main reason for significant growth of expenditures. These increasing expenditures include in-patient care costs and out-patient care costs as well as medical goods / medicines costs. Other problems are the great variation in the quality of care, non-optimal coordination between health care providers, waiting times and unequal access to care. Rising prescription drug expenditure is also a growing concern and it is extremely important that cause(s) for such increases are identified. In dealing with these challenges, some policy makers and decision makers are tempting to focus in the first place on reducing health care expenses and keeping the budget under control [1, 25].

The health care sector should be seen as a productive sector aiming is to produce health, by avoiding or curing diseases, and by ensuring longer and healthier life. Health can be seen as an extremely important intermediate product in our economies: without health we are less productive or not productive. On average the money invested in health care more that pays for itself. Savings should be made wherever possible, as long as this does not stand in the way of good quality health care and therefore the production of health [1, 24].

The economic evaluation of the health and health care programs is a discipline which has received increasing interest in recent years. Health economic evaluation is one part of the broad discipline of health economics. A health economic evaluation is defined as a comparative analysis of both the costs and the health effects of two or more alternative interventions / treatments. The important elements of the definition are, on the one hand, the comparison of alternatives and on the other hand, the two dimensions of costs and health effects [1].

As the single most expensive aspect of medical care, drugs have become the fastest growing component of healthcare costs: expenditures on medications set to outstrip hospital costs in many healthcare systems. Drug expenditure growth should continue outpacing the growth in overall healthcare expenditures and the growth in economy [28, 30, 31].

The benefits of unfractionated (UFH) heparin were described more than 20 years ago. Ever since, a wide variety of anticoagulant drugs have become available for clinical use, including low-molecular-weight heparins (LMWH), direct thrombin inhibitors and selective factor Xa inhibitors [26].

The utilization of heparins has been continually 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 [36, 37]. Worldwide heparin utilization trends have shown 10% to 15% yearly growth in past decade. These medicines were primarily used in the inpatient setting and heparins consumed up to 10% of the total medication costs in hospitals. As per statistics, the annual global LMWHs market amounts to approximately 3.5 billion USD. The antithrombotic market peak over 20 billion USD in 2012 across the seven major markets, including United States, France, Germany, Italy, Spain, United Kingdom, and Japan. In the meantime, the increase in expenditures for low-molecular-weight heparins is expected to continue [29, 30].

Un-fractionated heparin (UFH) and low molecular weight heparins (LMWHs) were selected for our investigation, as in the recent decade, utilization rates of heparins have been constantly increasing. Very frequent use of these medicines in daily medical practice is determined by the comprehensive list of indications this pharmaceutical group has [33, 34]. In Lithuania, the utilization of heparins increased from 322,000 Defined Daily Doses (DDDs) in 2003 to 2,306,529 DDDs in 2011, which is more than seven-fold (Table 3.3.1.1). Although total heparins expenditures increased almost ten-fold during this period, from 1,088,000 LTL in 2003 up to 10,284,000 LTL in 2011. Expenditures demonstrated the tendency of markedly faster increase, which could not be equally covered by the increased heparins utilization rates in the country [32, 35]. It became very important to identify reasons behind that disproportional growth and to foresee relevant actions that could be taken in the future in order to control effectively this rapid grow of expenditures. Such a dramatic increase justifies the need to search for suitable pharmacoeconomic models that could be applied and used by payers and decision makers for costs management.

Taken as a whole, the usefulness of economic studies of anticoagulants in patients is undermined by the quality of the evidence about their effectiveness and safety; the narrow spectrum of the analyzed scenarios; the lack of economic evaluations based on systematic reviews; the limitations of sensitivity analyses reported by the available economic evaluations; and their substantial risk of commercial bias [26]. Thus there is still a great need for comprehensive pharmacoeconomic assessments of different types

evaluating the value of heparins and establishing their role in different treatment protocols.

Several descriptive analyses were performed and published by other authors [38–41] that characterize heparins' use, patient safety, and compliance with national prescription guidelines at particular hospitals in many countries to improve safe use of heparins in hospital practice. Despite availability of evidence-based guidelines for the use of low-molecular-weight heparins, substantial variability is found in practice [27]. This research also aimed to investigate if heparins were rationally used in the daily medical practice and if reasonable correlation could be identified between heparins daily medical use and constant increase of utilization and expenditures of heparins in the country. Based on research figures, it was expected to identify possible limitations in this area.

Heparins safety and efficacy monitoring practices and their adhered to international recommendations were investigated in this research. It was substantial to find out if national treatment guidelines and medical auditing could be suggested as solutions promoting the rational use of heparins in the country.

1. STUDY AIM AND OBJECTIVES, NOVELTY OF THIS WORK

1.1. Aim of the study

To conduct pharmacoepidemiological assessment of low-molecular-weight heparins general utilization trends in Lithuania, and to develop pharmacoeconomic model for payers and decision makers allowing rationalizing the expenditures on this class of medicines in the country.

1.2. Objectives of the study

- to conduct a meta-analysis of heparins by the means of their efficacy, safety parameters and treatment outcomes;
- to conduct pharmacoepidemiological assessment of long-term heparins utilization in Lithuania;
- to develop a pharmacoeconomic cost-minimization model for low-molecular-weight heparins based on reference pricing methodology;
- to investigate heparins prescribing trends and to evaluate heparins prescription adherence to international clinical guidelines at a secondary level clinical hospital.

1.3. The novelty, importance and value of this work

Pharmacoeconomic decision modelling is a novel and powerful tool extensively used by the decision makers and payers in different countries to support their decisions regarding new and existing therapies [2].

Pharmacoeconomic decision models can be useful tools for evaluating the cost-minimization, cost-effectiveness and cost-utility of a selected medicine during research, development and marketing phases. Decision analysis provides a structured process for comparing the costs and consequences of standard drug therapies. Decision analyses mainly using data from clinical trials are a great potential source of information on the economic impact of medicines. However, the development and use of such models require tolerance of uncertainty, the ability to represent complex relationships accurately, and awareness of all factors that might influence the results. The advantage of clinical decision models is that they encourage the consideration and explicit representation of all possible inputs and outcomes. They clearly differentiate knowledge supported by data from assumptions, and compel assessment of the effect of those

assumptions on the findings. The model includes the possible clinical management pathways and the use of medical resources in treating a particular illness or a complex disease [2].

This type of research is novel in terms of content complexity, research area, and research outcomes. Similar investigations have not been conducted for the group of low-molecular-weight heparins in Lithuania in the past. This research was designed as a three-step investigation aiming to construct a broad picture displaying heparins utilization practices in the most common utilization areas, identifying heparins utilization related issued (from pharmacoeconomic and clinical perspective) and suggesting solutions enabling further improvement in this area.

- Step # 1 – comprehensive literature review and meta-analysis of heparins utilization. The performed meta-analysis differed from other meta-analyses accomplished and published by numerous other authors [43–60]. This meta-analysis was designed to evaluate all low-molecular-weight heparins available and used in Lithuania and un-fractionated heparin taking into consideration their safety, efficacy parameters and treatments outcomes. This meta-analysis was not focused on a particular indication or area, but summarized the results of trials in most frequent indications for LMWH use (i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE) treatment and prophylaxis, recurrent angina (RA), myocardial infarction (nonfatal MI, acute MI, and re-infarction), prophylaxis during surgical interventions, prophylaxis for bed-ridden patients). Meta-analysis was also designed to allow direct comparison of two low-molecular-weight heparins – this type of analysis have not been previously published by other authors.
- Step # 2 – *real-world* prospective pharmacoepidemiological study conducted at the in-patient setting, which assessed existing heparins prescription patterns at the average secondary level clinical hospital in Lithuania. Such analyses are regularly performed in many hospitals worldwide as part of their routine practice, although they are not part of the routine practice in Lithuania. Results from such analyses characterize heparin use, patient safety, and compliance with national prescription guidelines. Conducting this study we aimed to investigate if there were any gaps in heparins orders and documentation of information regarding the use of low molecular weight heparins at the in-patient setting. The study also explored adherence of LMWH effectiveness and safety monitoring in local hospital with international guidelines, as local heparins

prescription guidelines were not available. It was expected research results to identify, whether implementation of national guidelines on the use of LMWH in Lithuania could be beneficial.

- Step # 3 – implementation of pharmacoepidemiologic and pharmacoeconomic methodologies aiming to investigate general heparins utilization trends in Lithuania and to prepare a pharmacoeconomic decision model that could potentially be used by health-care decision makers to justify their decisions regarding future expenditures on heparins. Financial considerations are crucial in the current medical and pharmaceutical environment. Therefore, comprehensive scientific tools enabling the selection of the best medical practice should be widely implemented in order to balance health-care budgets in the country. In Lithuania this type of study was new and results were expected to have direct implications for drug related decision making in healthcare institutions. It would enable all healthcare providers to rationalize the use of financial resources for heparins in considering choices among alternative use of economic resources. That could yield cost savings without compromising clinical outcomes or patient safety [42].

The principal aim of drug utilization research is to facilitate rational use of drugs in populations [1, 2]. Initially it is essential to knowledge how drugs are being prescribed and used; having these data it is reasonable to initiate a discussion on rational drug use and later on to suggest measures to change prescribing habits. Information on the past performance of prescribers is considered to be crucial for any further investigation or auditing / review system. All these factors were taken into consideration while designing this research. It also proves that this type of research is important and relevant in today's health-care environment – where we are looking for solutions helping rationalize prescription of medicines and control constantly and rapidly increasing health-care budgets.

Heparins are extensively used in various indications at the in-patient and out-patient settings and they have important roles in many treatment protocols, when prescribed for prevention and/or treatment purposes. Due to these reasons rational utilization of heparins has become an essential part of many medical conditions management. The appropriate and rational prescribing of heparins is expected to have a positive impact on treatment outcomes, also should decrease the number of adverse drug reactions reported and could potentially decrease the expenditures on medicines. As mentioned, since this type of research has not been performed in Lithuania in the past, it was substantial to conduct appropriate analysis and identify where we stand in terms of heparins utilization and corresponding costs management on the country level.

2. LITERATURE REVIEW

2.1. Heparins general overview

Un-fractionated heparin and low-molecular-weight heparins belong to B01AB ATC / DDD drug class of antithrombotic agents used for anticoagulation in various clinical indications for thrombosis treatment and thrombosis prophylaxis.

The word *"heparin"* is originated from the Greek word that means *"liver";* also it refers to the tissue from which it was first prepared. A heparin is a type of carbohydrate termed glycosaminoglycan. It is a heterogeneous mixture of polymers with a variable number of sulfated saccharides. The different molecules comprising UFH differ in length, in the pattern of sugars, and in the extent and type of modifications of the sugars. The molecular weight of the constituent molecules in heparin might range from 3,000 to 30,000 Daltons. Un-fractionated heparin is extracted from biological sources, usually porcine intestine or bovine lung [104, 111].

Low molecular weight heparins first became available in the US market in the early middle 1990s. The low molecular weight heparins (LMWHs) are prepared by chemical cleaving of porcine heparin through depolymerization. Their molecular weight ranges from 4,000 Da to 6,500 Daltons. The anticoagulant action of heparin is primarily a result of it ability to bind to antithrombin (AT), thereby accelerating and enhancing the latter's rate of inhibition of the major coagulation enzymes (i.e. factor IIa and Xa and two lesser extents IXa, Xia and XIIa). The two main effects of heparin, the AT and the anti-Xa effects are differentially dependent on the size of the heparin molecule [104, 111].

Low-molecular-weight heparins (LMWHs) are anticoagulants (thrombolytic medicines). Their mechanism of action is based on following steps – (a) activating of antithrombin III factor; and (b) direct inhibition of thrombin (IIa factor) and Xa factor. The size of LMWH molecule also affects the antithrombotic activity. Each LMWH consists of various pentasacharides with different molecular weight. LMWHs are produced depolymeririzing heparin sodium salt, and obtaining lykozaminglycanes with the average molecular weight of 5000 Daltons (from < 2000 Daltons up to > 8000 Daltons) [104].

Low-molecular-weight heparins along with un-fractionated heparin are prescribed for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), MI and UCAD, also for the protection of extracorporeal system at the time of dialysis.

All heparins are effective and indicated for the following conditions: treatment of venous thrombosis and pulmonary embolism, prevention of venous thromboembolism, treatment of UCAD and acute myocardial infarction, for patients who undergo general, cardiac and orthopedic surgery [105–110, 112].

- Prophylaxis of venous thrombosis – that is partucularly important in general surgery and for high-risk medical patients. In these cases low doses of LMWHs habe to be administered once daily subcutaneously. LMWHs are the anticoagulants of choice for the prevention of venous thrombosis following major orthopedic surgery and in anticoagulant-eligible victims of major trauma. The risk of bleeding with LMWH is small.
- General surgery – LMWHs were proved to be safe and effective for prevention of thromboembolism in patients undergoing non-cardiovascular surgery.
- Orthopedic surgery and trauma – LMWHs were proved to be effective for prevention of venous thomboembolism and safe in high-risk patients undergoing major orthopedic surgical interventions.
- Stroke Patients – for ischemic stroke patients low-dose heparins reduce the risk of venous thrombosis, without an increase in clinically important bleeding.
- Treatments of venous thromboembolism – heparins are the first choice anticoagulants for venous thromboembolism. A number of low-molecular-weight heparins are now available for prescription and use. LMWHs are now being used widely or the prevention and treatment of venous thromboembolism in various indications.
- Unstable CAD and non-Q wave MI – the combination of heparin and aspirin is effective for short-term treatment use for patients with UCAD. The short-term effectiveness of LMWH in combination with aspirin for treatment of UCAD and non-Q wave MI provide beneficial effect compared to aspirin alone in this population.

Pharmacodynamic properties – low-molecular-weight heparins antithrombotic effect is rapid and long-lasting; also the anti-Xa and anti-IIa ratio is high. Compared to un-fractionated heparin, platelet function and aggregation are less affected.

Table 2.1.1. *Low-molecular-weight heparins pharmacokinetic properties*

Absobtion (when administered subcutaneously)	• The highest anti-Xa concentration in plasma (C_{max}) ir reached within approximately 3–5 hours • Bioavailability exceeds 90%
Elimination (when administered subcutaneously)	• Half-life period is approximately 3–6 hours • The length of biological activity exceeds 18 hours, due to this reasons these medicines are administered once daily • Metabolized in liver • Eliminated via kidney

Haparins pharmacokinetics is extremely complicated, mainly as s result of molecular size variation. Large molecules are cleared by a rapid saturable cellular mechanism and bind to numerous acute-phase protein. Smaller molecules are cleared by nonsaturable renal route and bind to plasma proteins. As a result, therapeutic doses of UFH result in a variable degree of anticoagulation and require close monitoring. The dose-response is much more predictable for the LMWHs, and most trials have not monitored therapy with these agents, which are simply given as a "unit per kg" basis. Thus the approach to monitoring heparin therapy varies according to the type of heparin used and the clinical circumstance (Table 2.1.1) [104].

Following medical conditions should be taken into consideration before prescribing heparins for patients (Table 2.1.2):

- Liver function impairments
- Kidney function impairments
- Age > 65 years
- Low body weight
- Severe arterial hypertension
- Eye blood flow disturbances
- Previously reported injuries associated with the increased risk of bleeding
- Post-surgery period after brain, spinal, eye surgery

In case of these precautions, the dosage o heparins should be adjusted per individual patient needs, and following manufacturers' recommendations [105–110, 113–116].

Table 2.1.2. *Contraindications of low-molecular-weight heparins*

Contraindications	**Bemiparin**	**Dalteparin**	**Enoxaparin**	**Nadroparin**	**Tinzaparin**
Previously reported heparin induced thrombocytopenia	+	+		+	+
Active clinically significant bleeding	+	+	+	+	+
Severe blood clotting impairments	+	+	+	+	
Septic endocarditis	+	+			+
Recently performed central nervous system, eyes, ears injuries or surgery	+	+			+
Allergic reactions to active compound, other LMWHs or UFH	+	+	+	+	+
Recently reported stroke (except stroke due to systemic embolism), as it increases the risk of brain hemorrhages		+	+		+
Severe liver or kidney impairments	+			+	+

Low-molecular-weight heparins mechanism of actions is affected when heparins are administered together with other thrombolytic medicines, systemic salycilates, NSAIDs, vitamin K antagonists, dextrane, ticlopidine, clopidogrelum, other platelet inhibitors, and systemic glucocorticosteroids. All these compounds directly affect thrombosis and platelets and consequently increase the risk of bleeding.

In case specific contraindications are not reported, low doses of acetylsalicylic acid have to be prescribed for patients with unstable angina pectoris or with non Q-wave myocardial infarction. Medicines that increase potassium level in blood can be administered together with heparins only if adequate safety monitoring is conducted. Adequate safety monitoring is also an essential condition that has to be followed in case heparins are prescribed together with any of the compounds increasing the risk of bleeding.

2.2. Meta-analyses of heparins

A number of various meta-analyses of heparins were conducted by many authors and published in scientific literature during the last decade. The primary objective of these meta-analyses was to compare safety and efficacy parameters along with treatment outcomes of un-fractionated heparin compared to one of low-molecular-weight heparins, and to summarize their superiorities and advantages / disadvantages in a particular indication.

When several low-molecular-weight heparins became available on the market, it was scientifically sound to conduct meta-analyses directly comparing safety and efficacy parameters of these compounds. The main limiting factor in this area was lack of reported outcomes or randomized clinical trials directly comparing safety and efficacy parameters of different low-molecular weight heparins. Due to this reason, the number of LMWHs meta-analyses is very limited.

The results of various meta-analyses directly comparing un-fractionated heparin with different low-molecular-weight heparins and published in scientific literature were discussed in the Table 2.2.1.

Table 2.2.1. *UFH compared to LMWHs – meta-analyses data*

Mata-analysis authors	**Research design**	**Conclusions**
Nicholson T, et al. [88]	Benefits and costs of short-term treatment (2–8 days) with enoxaparin and unfractionated heparin in UCAD were compared.	Enoxaparin appears cost saving compared with unfractionated heparin in patients with unstable coronary artery disease.
Antman EM, el al. [89]	A significant treatment benefit of enoxaparin on the rate of death / non-fatal myocardial infarction / urgent revascularization was observed at 1 year (hazard ratio 0.88; P=0.008). The event rate was 25.8% in the unfractionated heparin group and 23.3% in the enoxaparin group, an absolute difference of 2.5%. A progressively greater treatment benefit of enoxaparin was observed as the level of patient risk at baseline increased. Treatment effects for the individual endpoint elements ranged from 9–14%, favouring enoxaparin	The stable absolute difference in event rates of 2.5% seen at 8 days and again at 1 year favouring enoxaparin may be due to more effective control of the thrombotic process surrounding the index event. Once the pharmacological effect of enoxaparin had dissipated there was no rebound increase in events.
Le Nguyeb MT, et la. [90]	A meta-analysis was performed including all randomized clinical trials comparing LMWH and UFH for the treatment of non-ST segment elevation acute coronary syndromes. In total 13,320 patients were included. Death (RR 0.98, 95% CI 0.73–1.31), death and myocardial infarction (MI) (RR 0.86, 95% CI 0.74–1.01), death, MI, recurrent angina or revascularization (RR 0.89, 95% CI 0.74–1.07) and major hemorrhage (RR 1.01, 95% CI 0.81–1.25) occurred with similar frequencies for the anticoagulant-based strategies.	Fixed dose LMWH therapy given subcutaneously compares favorably with UFH titrated to a target level of anticoagulation and should be considered a safe, effective, and clinically acceptable alternative in the early management of patients with non-ST segment elevation ACS. The superiority of LMWH preparations characterized by high *in vitro* factor Xa to thrombin inhibitory capacity is supported by clinic trial data.

Table 2.2.1. *Continued*

Mata-analysis authors	Research design	Conclusions
Magee KD, et al. [91]	Primary objective was To assess the effects of LMWH compared to UFH for acute coronary syndromes.Cochrane Controlled Trials Register (the Cochrane Library issue 4, 2000), MEDLINE (January 1966 to December 2000), EMBASE (1980 to December 2000) and CINAHL (1982 to December 2000) and reference lists of articles were reviewed. Randomized controlled trials of subcutaneous LMWH versus intravenous UFH in people with acute coronary syndromes (unstable angina or non-ST segment elevation MI). 27 potentially relevant studies, 7 studies (11,092 participants) were included in this review. No evidence was found for difference in overall mortality between the groups treated with LMWH and UFH. LMWH reduced the occurrence of MI and the need for revascularization. No evidence was found for difference in occurrence of recurrent angina, major or minor bleeds. A decrease in the incidence of thrombocytopenia was observed for patients given LMWH.	LMWH and UFH had similar risk of mortality, recurrent angina, and major or minor bleeding but LMWH had decreased risk of MI, revascularization and thrombocytopenia. New Trials with longer follow up are required.
Quinlan DJ, et al. [74]	Efficacy and safety of fixed-dose subcutaneous low-molecular-weight heparin with that of dose-adjusted intravenous unfractionated heparin to treat acute pulmonary embolism were compared. The MEDLINE, EMBASE, and Cochrane Library databases were searched up to 1 August 2003. Randomized trials comparing fixed-dose subcutaneous low-molecular-weight heparin with dose-adjusted were involved in this analysis. Fourteen trials involving 2,110 patients with pulmonary embolism met the inclusion criteria. Compared with unfractionated heparin, low-molecular-weight heparin was associated with a non-statistically significant decrease in recurrent symptomatic venous thromboembolism at the end of treatment. For major bleeding complications, the odds ratio favoring low-molecular-weight heparin was also not statistically significant.	Fixed-dose low-molecular-weight heparin treatment appears to be as effective and safe as dose-adjusted intravenous unfractionated heparin for the initial treatment of nonmassive pulmonary embolism

Table 2.2.1. *Continued*

Mata-analysis authors	Research design	Conclusions
Borentain M, et al. [75].	This meta-analysis assessed the rates of the efficacy and safety endpoints with intravenous low-molecular-weight heparin (LMWH) compared with unfractionated heparin (UFH) in patients undergoing percutaneous coronary intervention (PCI). The meta-analysis included data from eight randomized trials in which patients received LMWH (n = 1,037) or UFH (n = 978) during PCI. Efficacy endpoints were ischemic events (usually a composite of death, myocardial infarction, and urgent revascularization) and the safety endpoint was bleeding (major, minor, or all bleeding). The analysis of pooled data, randomized or not, suggests potential improved efficacy and reduced major bleeding with compared to UFH.	During PCI, intravenous LMWH without coagulation monitoring has the potential to be at least as safe and efficacious as intravenous UFH.
Lim W, et al. [76]	The purpose of this study was to evaluate the safety and efficacy of LMWH compared with unfractionated heparin (UFH) for preventing thrombosis of the extracorporeal dialysis circuit. Studies were identified with the use of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and FirstSearch; Seventeen randomized, controlled trials were included in this systematic review. It was found that LMWH did not significantly affect the number of bleeding or extracorporeal circuit thrombosis as compared with UFH.	LMWH seem to be as safe as UFH in terms of bleeding complications and as effective as UFH in preventing extra-corporeal circuit thrombosis.
Van Dongen CJ, et al. [77]	Primary objective – to determine the effect of LMWH compared with unfractionated heparin (UFH) for the initial treatment of VTE. Trials were identified from the Cochrane Peripheral Vascular Diseases Group's Specialised Register, CENTRAL and LILACS. Twenty-two studies were included (n = 8,867). Thrombotic complications occurred in 151/4,181 (3.6%) participants treated with LMWH, compared with 211/3,941 (5.4%) participants treated with UFH. Major haemorrhages occurred in 41/3,500 (1.2%) participants treated with LMWH, compared with 73/3,624 (2.0%) participants treated with UFH.	LMWH is more effective than UFH for the initial treatment of VTE. LMWH significantly reduces the occu-rrence of major haemorrhage during initial treatment and overall mortality at follow up.

Table 2.2.1. *Continued*

Mata-analysis authors	**Research design**	**Conclusions**
Eikelboom JW, et al. [78]	A meta-analysis of the randomized trials was conducted to assess the effect of UFH and LMWH on reinfarction, death, stroke, and bleeding. Fourteen trials involving a total of 25,280 patients were included (1,239 comparing intravenous UFH versus placebo or no heparin; 16,943 comparing LMWH versus placebo; and 7,098 comparing LMWH versus intravenous UFH). Intravenous UFH during hospitalization did not reduce reinfarction or death and did not increase major bleeding, but increased minor bleeding. During hospitalization of 7 days, LMWH reduced the risk of reinfarction. The reduction in death with LMWH remained evident at 30 days. LMWH compared with UFH during hospitalization of 7 days reduced reinfarction.	LMWH given for 4–8 days when directly compared with UFH reduces reinfarction by almost one half.
Martel N., et al. [79]	The objective was to determine and compare the incidences of HIT in surgical and medical patients receiving thromboprophylaxis with either UFH or LMWH. All relevant studies identified in the MEDLINE database (1984–2004), not limited by language, and from reference lists of key articles were evaluated. Randomized and nonrandomized controlled trials comparing prophylaxis with UFH and LMWH and measuring HIT or thrombocytopenia as outcomes were included. Fifteen studies (7,287 patients) were eligible.	These analyses favored the use of LMWH in terms of HIT incidence and thrombocytopenia.
Spyropoulos AC. [80]	Infusion of unfractionated heparin (UFH) has been the standard pharmacologic therapy for treatment of venous thromboembolism (VTE), and for initial therapy of acute coronary syndrome (ACS). More recently, low-molecular-weight heparins (LMWHs) have been shown to provide at least as good efficacy and safety outcomes as UFH regimens for prevention of these conditions. In addition to good efficacy outcomes with LMWHs compared with UFH, LMWHs have other advantages, such as improved bioavailability, administration, predictable anticoagulant response, no need for monitoring, suitability for outpatient use.	LMWH offers a cost-effective, convenient, and safe alternative to UFH for thrombosis management. The aim of this article is to summarize efficacy, safety, and pharmacoeconomic considerations when selecting LMWH versus UFH for thrombosis management in VTE and NSTE ACS.

Table 2.2.1. *Continued*

Mata-analysis authors	Research design	Conclusions
Murphy SA, et al. [81]	Primary objective was to determine whether enoxaparin remained favourable when compared with unfractionated heparin (UFH) among patients with acute coronary syndromes (ACS) when incorporating efficacy and safety of these adjunctive therapies using a net clinical endpoint. A meta-analysis of randomized trials of enoxaparin vs. UFH was performed (n = 49,088 patients in 12 trials). Death or MI was significantly reduced with enoxaparin when compared with UFH. The net clinical endpoint occurred less frequently with enoxaparin than UFH. Major bleeding was higher with enoxaparin.	Compared to UFH, enoxaparin was associated with superior efficacy as adjunctive antithrombin therapy among > 49 000 patients across the ACS spectrum. Although bleeding was increased with enoxaparin, this increase was offset by a reduction in death or MI.
Dumaine R, et al. [82]	The objective was to perform a meta-analysis of randomized trials comparing the efficacy and safety of LMWH vs UFH as anticoagulants in the setting of PCI. MEDLINE database was used, randomized trials presented at major cardiology conferences, and journal article bibliographies from January 1998 and September 2006. Thirteen trials including 7,318 patients met the inclusion criteria. LMWH use was associated with a significant reduction in the risk of major bleeding compared with UFH. A trend toward a reduction in minor bleeding was also observed among LMWH-treated patients. Similar efficacy was observed between LMWH and UFH regarding the double end point of death or myocardial infarction.	The use of LMWH during PCI is associated with a significant reduction in major bleeding events compared with UFH, without compromising outcomes on hard ischemic end points.
De Luca G, et al. [83]	The aim of the study was to perform an updated meta-analysis of all randomized trials comparing low-molecular-weight heparins (LMWHs) versus unfractionated heparin (UFH) in patients with STEMI treated with thrombolysis. Results from all randomized trials comparing LMWHs versus UFH among patients with STEMI treated with thrombolysis were obtained. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to June 2007. A total of 8 randomized trials were identified, including 13,940 patients randomized. Low-molecular-weight heparins were associated with a trend in reduction in mortality.	Among patients with STEMI treated with thrombolysis, LMWHs, as compared to UFH, are associated with a trend in mortality benefits and a significant reduction in reinfarction. Other practical practical advantages – reduced interindividual variability in therapeutic response and no need for frequent (aPTT) monitoring and dose adjustment, LMWHs

Table 2.2.1. *Continued*

Mata-analysis authors	Research design	Conclusions
De Luca G, et al. [83] *continued*		should be considered, instead of UFH, among patients with STEMI treated with thrombolysis.
Shorr AF, et al. [84]	Randomized trials comparing UFH to low-molecular-weight heparin (LMWH) for VTE prevention in ischemic stroke patients were identified. In total, three trials including 2,028 patients were reviewed. The use of LMWH was associated with a significant risk reduction for any VTE. There were no differences in rates of overall bleeding, intracranial hemorrhage, or mortality based on the type of agent employed.	The prophylactic use of LMWH compared to UFH following ischemic stroke is associated with a reduction in both VTE and PE. Broader use of LMWH for VTE prevention after ischemic stroke is warranted.
Morris TA, et al. [85]	A meta-analysis was performed to compare the incidence of thrombocytopenia between LMWH and UFH during PE and / or DVT treatment. Randomized trials comparing LMWH with UFH for PE and / or DVT treatment were searched for in the MEDLINE database. Thirteen studies involving 5,275 patients met inclusion criteria. There were no statistically significant differences in HAT rates between the two treatments (LMWH, 1.2%; UFH, 1.5%; $p = 0.246$). The incidence of documented HIT and HITT was too low to make an adequate comparison between groups.	This review disclosed no statistically significant difference in HAT between LMWH and UFH and insufficient evidence to conclude that HIT and HITT rates were different between them.

Table 2.2.1. *Continued*

Mata-analysis authors	**Research design**	**Conclusions**
Akl EA, et al. [86]	The relative benefits and harms of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) required further judgments regarding the appropriate perioperative thromboprophylaxis in patients with cancer. We systematically reviewed the literature to quantify these effects. The comprehensive searches included MEDLINE, EMBASE, ISI the Web of Science, and CENTRAL databases. 14 randomized clinical trials were included in the meta-analysis. The meta-analysis showed no differences in mortality in patients receiving LMWH compared with UFH or in clinically suspected deep venous thrombosis. Though in the analysis including all studies assessing deep venous thrombosis, irrespective of the diagnostic strategy used, LMWH was superior to UFH.	No differences in mortality in patients with cancer receiving perioperative thromboprophylaxis with LMWH vs UFH were found. Further trials are needed to more carefully evaluate the benefits and harms of different heparin thromboprophylaxis strategies in this population.
Wade WE, et al. [87]	Primary objective was to perform an individual patient data meta-analysis to evaluate the relative efficacy and safety of the LMWH enoxaparin and UFH in preventing VTE in hospitalized medical patients. Randomized clinical trials comparing subcutaneous enoxaparin and for VTE prevention were identified by a systematic search. Four trials were eligible, including 3,600 patients randomized to receive enoxaparin or UFH. Compared with UFH, enoxaparin was associated with risk reductions for total VTE and for symptomatic VTE. Major bleeding rates were consistently low and similar between treatment groups. There was also a positive trend towards reduced risk for mortality in patients receiving enoxaparin compared with UFH.	Enoxaparin significantly reduced VTE in hospitalized medical in-patients, compared with UFH, without increasing the risk for major bleeding. Consequently, it was associated with a trend towards reduced mortality.

The results of very few meta-analyses directly comparing different low-molecular-weight heparins with each other were available in MEDLINE and *Cochrane* databases and scientific literature. The results of these meta-analyses were discussed in the Table 2.2.2.

Though, it has to be emphasized that there is a significant lack of reliable and evident low-molecular-weight heparins direct comparisons and respective meta-analyses of these compounds.

Table 2.2.2. *UFH compared to LMWHs – meta-analyses data*

Mata-analysis authors	Research design	Conclusions
McCart GM, et al. [88]	Primary objective was to review the recent literature on the approved uses of enoxaparin, dalteparin, ardeparin, and tinzaparin and the evidence for therapeutic equivalence. A MEDLINE search (from 1993 to 2001) was conducted to identify available literature. Compounds were reviewed with regard to safety and efficacy parameters. In general, as a class of drugs, LMWHs have chemical, physical, and clinical similarities. LMWHs have very similar bioavailability, half-lives, pharmacologic responses, safety parameters.	Just one trial evaluated 2 LMWHs in a direct comparison in the same study. There is insufficient evidence for determining the therapeutic equivalence of LMWHs.

2.3. Pharmacoeconomic and pharmacoepidemiologic research

Diversity in methodologies of epidemiological studies evaluating the utilization trends of heparins has to be mentioned. It has to be emphasized that heparins utilizations tendencies have not been consistently monitored in reported in literature. Though, some of epidemiological studies deserve to be mentioned due to their valuable and interesting outcomes.

For example, a survey of community hospitals was conducted to assess the formulary status of currently available anticoagulants, assess the current status of anticoagulant prescribing guidelines and the existing scope of such guidelines in community hospitals in the United States. Of 224 hospitals, 127 participated in the survey, a response rate of 59.6%. Warfarin, unfractionated heparin (UFH), and enoxaparin were the anticoagulants most commonly included (>80%) on the hospitals' drug formularies. Guidelines relating to the use of UFH and low-molecular-weight heparins (LMWHs) existed in approximately 87.4% and 55.1% of responding hospitals, respectively. Among hospitals without guidelines, the majority reported that

such guidelines would be useful if they included LMWHs, warfarin and UFH. Guidelines for prophylaxis of venous thromboembolism (VTE), appropriate drug selection, and dosing for VTE prophylaxis and treatment existed in almost half of these hospitals. The study found that a sizable percentage of the responding community hospitals did not have guidelines, protocols, or policies related to the use of anticoagulants. Further, those hospitals without such guidelines commonly reported a need for clinical practice guidelines [103].

The aim of pharmacoepidemiological study was to investigate the pattern of prescription of LMWHs in different departments of French teaching hospitals. This prospective study was performed in two teaching hospitals in France in different medical wards. All patients (n=334) receiving a prescription for a LMWH were included in the survey. 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. Ninety-nine patients received a LMWH for curative treatment. Indications included therapy for deep venous thrombosis, pulmonary embolism, acute coronary syndrome, unstable angina pectoris, non-Q-wave myocardial infarction. The incidence of LMWHs induced ADRs was 10.5 percent occurring in 22 cases during preventive treatment of deep venous thrombosis and in 13 cases during curative therapy. Reported ADRs were bleeding events (n = 15), thrombocytosis (n = 13), thrombopenia (n = 4) and hepatic cytolysis (n = 1). As stressed by authors, these data firstly showed 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 [102].

The majority of conducted and published pharmacoeconomic studies were designed to compare the cost-effectiveness of one particular LMWH with UFH. It has to be noted that a substantial number of studies involved enoxaparin, and pharmacoeconomic properties of other low-molecular-weight heparins have been reviewed just in several other investigations.

The pharmacoeconomics of enoxaparin for VTE treatment and prophylaxis have been investigated in cost-effectiveness studies that estimated direct costs associated with treatment, using clinical outcome data from clinical trials. These studies showed enoxaparin to be cost effective compared with UFH in short-term thromboprophylaxis for hospital in-patients

undergoing orthopaedic surgery. Outpatient treatment of DVT with enoxaparin has also been shown to be cost effective compared with in-patient treatment using UFH. The cost-effectiveness of enoxaparin compared with UFH in the treatment of unstable angina and non-Q-wave MI has also been investigated in several countries using clinical outcomes data. It was demonstrated that enoxaparin was superior to UFH in terms of tolerability and efficacy. A large number of studies named enoxaparin to be of economic benefit when used for prevention and treatment of VTE and treatment of ACS [95].

The results of ESSENCE mega-trial showed superior efficacy and lower total treatment and follow-up costs with enoxaparin compared with UFH. The total savings in direct health costs per patient with enoxaparin ranged between 448 EUR and 659 EUR (2001 rates). The pharmacoeconomic analysis in this trial aimed to evaluate the cost-effectiveness of treatment with enoxaparin compared with UFH in Spanish patients with ACS. It was concluded that enoxaparin was a more effective and less expensive treatment option than UFH in secondary prevention of patients with ACS in Spain, confirming the results obtained in other pharmacoeconomic analyses performed in the UK, USA, France and Canada [97].

Results of the cost-effectiveness study conducted in Germany suggested that in immobilized acutely ill medical inpatients, enoxaparin may offer a very cost-effective option for thromboprophylaxis compared with no prophylaxis and a cost-saving alternative compared with UFH. The study was designed to estimate, from the hospital perspective in Germany, the cost effectiveness of enoxaparin compared to unfractionated heparin [100]. Another pharmacoeconomic research estimated the incremental cost-effectiveness of enoxaparin versus unfractionated heparin for the prophylaxis of DVT following major trauma. It was also concluded that enoxaparin appeared to be a cost-effective alternative when considering the intermediate endpoint of DVTs [101].

Several other pharmacoeconomic studies directly compared the use of un-fractionated heparin with one of the following low-molecular weight heparins: tinzaparin, dalteparin and bemiparin.

Another research aimed to evaluate economic and health implications of tinzaparin sodium versus UFH in the treatment of acute deep vein thrombosis (DVT) from a US healthcare payer perspective. Clinical trial results were combined with data from long-term follow-up studies of DVT in a model that estimates the health and economic consequences of treatment. After the research, it was concluded that tinzaparin sodium led to better health outcomes and substantial economic savings compared with UFH treatment when all management costs were considered [96]. Another cost-

utility study was conducted to evaluate the cost effectiveness of dalteparin compared with UFH for preventing VTE in patients undergoing elective abdominal surgery. Patients undergoing abdominal surgeries face substantial risk of experiencing venous thromboembolic events in the perioperative period. The low-molecular-weight heparin dalteparin sodium is clinically effective in reducing the incidence of VTE in these patients. This base-case analysis showed that dalteparin 5000 IUwas cost effective compared with dalteparin 2500 IU and UFH for prophylaxis of VTE in patients undergoing abdominal surgery [99].

It has to be emphasized that the number of studies, directly comparing low-molecular-weight heparins in terms of pharmacoeconomic parameters, is limited. Though, some of them were conducted and their results were published in scientific literature. One of these studies was conducted at the healthcare setting in Spain. That research aimed to investigate the potential economic impact of bemiparin compared with enoxaparin as prophylaxis for VTE in patients undergoing total knee replacement surgery. Hospital and post-discharge outcomes and costs were involved in the study. Decision modeling approach was used for cost-effectiveness analysis. Study results showed that bemiparin provided cost savings of 144.48 EUR per patient compared with enoxaparin. Pharmacy costs per patient were lower for bemiparin during hospital stay (43.34 EUR vs 50.20 EUR; difference, - 6.86 EUR). It was concluded that bemiparin could be more cost effective than enoxaparin for thromboprophylaxis in total knee replacement surgery in the Spanish healthcare setting [98].

2.4. Heparins prescription guidelines review

This review of heparins prescription guidelines contains data collected from three sources, i.e. International Union of Angiology (IUA) recommendations, NICE clinical guideline and American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines.

- *International Union of Angiology (IUA) recommendations* [92].

Venous thromboembolism (VTE) is an important cause of avoidable morbidity and mortality. However, routine prophylaxis for at-risk patients is underused. Recent guidelines issued by an international consensus group, including the International Union of Angiology (IUA), recommend use of low-molecular-weight heparins (LMWHs) for the treatment of acute VTE and prevention of recurrence, and for prophylaxis in surgical and medical patients. This review highlights current inadequacies in the provision of

thromboprophylaxis, and considers the clinical implications of the European guidelines on the prevention and treatment of VTE.

Patients with VTE generally have two or more risk factors, and the effects of multiple risk factors on VTE risk are additive. The type and duration of prophylaxis depends on whether the risk factors are transient (e.g., trauma, surgery, infection, the postpartum period) or persistent (e.g., advanced age, obesity, history of VTE, thrombophilia). Patients admitted to hospital are at particular risk of VTE, and the risk remains elevated after discharge. Patients with VTE receive anticoagulants to treat the acute event and prevent fatal PE, and also to minimize the risks of developing post-thrombotic syndrome and recurrent VTE. For many years, unfractionated heparin (UFH) has been the standard treatment for acute VTE. However, clinical trial data show that LMWHs are more effective than UFH for the initial treatment of VTE and are associated with less major bleeding. As a consequence, LMWHs are replacing UFH in the treatment of acute VTE. The recent European guidelines recommend that LMWH should be used in the initial treatment of VTE, followed by oral anticoagulant therapy for 3 months, or longer in the case of idiopathic VTE. These recommendations are fully consistent with those recently delivered by the American College of Chest Physicians.

- *NICE clinical guideline* – document issue date: January 2010 [93].

The House of Commons Health Committee reported in 2005 that an estimated 25,000 people in the UK die from preventable hospital-acquired venous thromboembolism (VTE) every year. This includes patients admitted to hospital for medical care and surgery. The inconsistent use of prophylactic measures for VTE in hospital patients has been widely reported. A UK survey suggested that 71% of patients assessed to be at medium or high risk of developing deep vein thrombosis did not receive any form of mechanical or pharmacological VTE prophylaxis.

This guideline makes recommendations on assessing and reducing the risk of VTE in patients in hospital. It offers guidance on the most clinically and cost-effective measures for VTE prophylaxis in these patients. The recommendations take into account the potential risks of the various options for prophylaxis and patient preferences.

- *ACCP Evidence-Based Clinical Practice Guidelines* [94].

American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines (8th Edition) recommend to use low-molecular-weight heparins as antithrombotic therapy.

Treatment for venous thromboembolic disease is part of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs. Grade 2 suggests that individual patient values may lead to different choices. Among the key recommendations are the following: for patients with objectively confirmed deep vein thrombosis (DVT) or pulmonary embolism (PE), anticoagulant therapy with subcutaneous (SC) low-molecular-weight heparin (LMWH), monitored IV, or SC unfractionated heparin (UFH), unmonitored weight-based SC UFH, or SC fondaparinux is recommend.

3. RESEARCH DESIGN AND METHODS

3.1. Meta-analysis methodology

3.1.1. Literature search strategy

Meta-analysis was performed to assess low-molecular-weight heparins (i.e. Dalteparin, Enoxaparin, Nadroparin and Tinzaparin) in comparison with un-fractionated heparin in terms of their efficacy and safety parameters along with treatment outcomes.

Meta-analysis was initiated following the hypothesis analysed and published by other authors [61, 62] that low-molecular-weight heparins should be interchangeable due to their similar safety and efficacy parameters in various indications.

The *PubMed.gov* (MedLine) and *Cochrane* databases were used to conduct a comprehensive literature search for randomized controlled trials comparing safety and efficacy values of four different low-molecular-weight heparins with un-fractionated heparin. Literature search was conducted using inclusion / exclusion criteria based on objectives of the research. Key-words for the search were Enoxaparin, Dalteparin, Nadroparin, LMWHs, unfractionated heparin (UFH), e.g. Dalteparin and Nadroparin, Dalteparin and Enoxaparin, Nadroparin and Enoxaparin, etc.. They were defined as keywords and text words.

PRISMA principles which stand for ***P****referred* ***R****eporting* ***I****tems for* ***S****ystematic Reviews and* ***M****eta-****A****nalyses* were used to collect and process data (Figure 3.1.1). PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses [22].

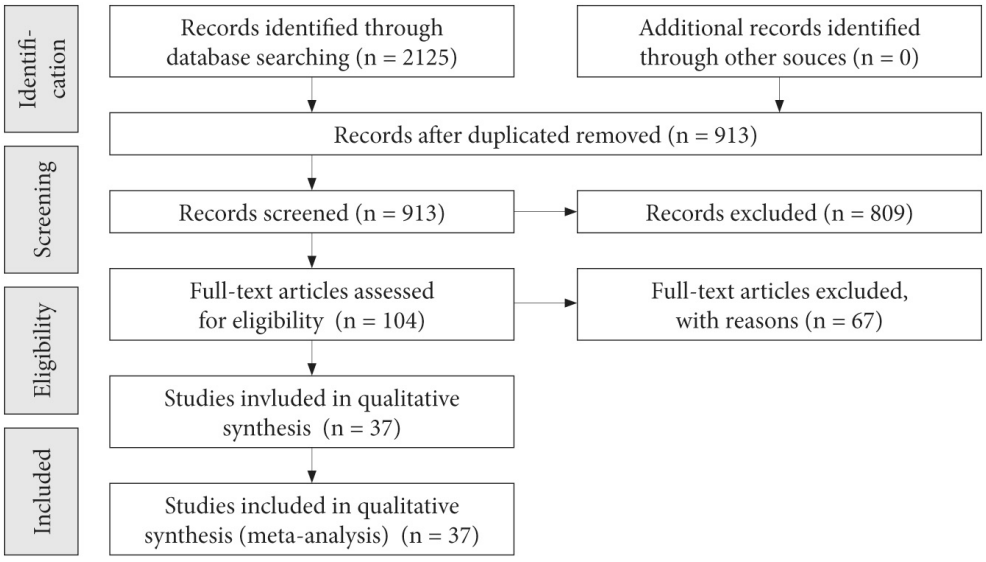

Figure 3.1.1. *PRISMA Flow diagram for the accomplished meta-analysis*

The aim of this meta-analysis was to evaluate the overall superiority of heparins in comparison with each other.

Articles published in English between January 1990 and January 2009 were included in the meta-analysis. Each article had to contain information about randomized control trial methodology and results with direct comparison of two heparins in the treatment of the following conditions or diseases like: deep venous thrombosis (DVT), pulmonary embolism (PE), recurrent angina (RA), myocardial infarction (nonfatal MI, acute MI, and re-infarction). Following treatment end-points were included in this analysis: hemorrhagic complications (e. g. major bleeding), and death. The accomplished meta-analysis involved 37 trials, which provided data of almost 49 thousand patients.

3.1.2. Statistical analysis

All meta-analyses were performed on studies that compared two low-molecular weight heparins or LMWH with un-fractionated heparin. Under the fixed effects model, it was assumed that all studies come from a common population and that the effect size (odds ratio) was not significantly different among the different trials. This assumption was tested by the "Heterogeneity test". If this test yielded a low p value ($p < 0.05$), then the fixed effects model might have been invalid. In this case, the random effects model might have been more appropriate, in which both the random

variation within the studies and the variation between the different studies were incorporated.

A statistical software MedCalc was used for all calculations. MedCalc used the Mantel-Haenszel method for calculating the weighted summary odds ratio under the fixed effects model. Next, the heterogeneity statistic was incorporated to calculate the summary odds ratio under the random effects model. The program listed the results of the individual studies: several positive cases, the total number of cases, and the odds ratio with 95% confidence interval (CI). The total odds ratio with 95% CI was given both for the fixed effects model and the random effects model. If the value 1 was not within the 95% CI, then the odds ratio was statistically significant at the 5 percent level ($p < 0.05$). The random effects model would tend to give a more conservative estimate (i.e., with a wider confidence interval), but the results from the two models usually agreed where there was no heterogeneity. If the test of heterogeneity was statistically significant ($p < 0.05$) then more emphasis should have been placed on the random effects model. Taking into consideration heterogeneity parameter variation, meta-analysis was conducted using both models – fixed effects model and random effects model.

3.2. Drug utilization research methods

3.2.1. Research object and sample size

Heparins sales data in monetary units (wholesale prices) and packaging units from 2003 to 2011 were included in utilization study. Low-molecular-weight heparins (i.e. Bemiparin, Dalteparin, Enoxaparin, Nadroparin and Tinzaparin) together with un-fractionated heparin were included in the analysis. All these compounds are classified to the ATC / DDD drug class B01AB.

Sales data were collected from all licensed pharmaceutical wholesale companies in the country. Data trackers were compiled using monthly sales figures and monthly utilization figures. Single package price reflected the highest acceptable wholesale price of medicine, as approved by Republic of Lithuania Ministry of Health.

All pharmaceutical products of LMWH that were available in Lithuanian market from 2003 to 2011 have been included into pharmacoepidemiological heparins utilization analysis. In total, calculations included six products, i. e. five low-molecular-weight heparins and un-fractionated heparin. Each LMWH was marketed under single trade name only, and UFH was available from three different manufactures during study period,

and therefore three trade names were included into our estimations. Each heparin was available on the market in several dosages and sizes of packages were also different. In total, our drug utilization study involved 24 different pharmaceutical products of heparins and LMWHs.

These estimations included all LMWH used in Lithuania, drug utilization rate 100% (DU100%) during the aforementioned period.

In the Anatomical Therapeutic Chemical (ATC) classification system, the active substances are classified into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Defined daily dose (DDD) definition is: "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults." A DDD will only be assigned for drugs that already have an ATC code. The DDD provide a fixed unit of measurement independent of price and dosage (e.g. tablet strength) enabling the assessment of trends in drug consumption and performing comparisons between population groups.

3.2.2. Drug utilization studies

The need for drug utilization research occurred in the late 70's, when drug utilization research methodology was defined by WHO as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences" (*World Health Organization (WHO) Collaborating Centre. Introduction to Drug Utilization Research.)*. According to the definition, pharmacoepidemiology is a method to study the clinical utilization of medicines in population. Or pharmacoepidemilogy is a study of the use and effects/side effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes [17, 18].

Both drug utilization research and pharmacoepidemiology provide insights into many aspects of drug use and drug prescribing. They describe patterns of drug utilization and identify problems deserving more detailed studies. Drug utilization research can thus help identify health-care budget allocation related issues.

It is essential to identify early signals of irrational use of drugs and to take appropriate actions. Drug utilization research may generate hypotheses that set the agenda for further investigations.

Drug utilization research studies are designed following these objectives: (a) estimate number of patients exposed to specified drugs within a given time period; (b) ddescribe the extent of use at a certain moment and / or

in certain areas, particularly useful to follow trends; (c) estimate the degree of proper use, overuse or underuse; (d) determine the pattern or profile of drug use and the extent to which alternate drugs are being used to treat particular conditions; (e) compare observed patterns of drug use for the treatment of a certain disease with current recommendations or guidelines; (f) use in the application of quality indicators to patterns of drug utilization; (g) case reports of drug problem or adverse effect related to patient exposure to assess the magnitude of the problem [17–19].

There is an increasing interest in the evaluation of the economic impact of clinical care and medical technology. This has evolved into a discipline dedicated to the study of how pharmacotherapeutic methods influence resource utilization in health – pharmacoeconomics. The increasing interest in efficient use of health-care resources has resulted in the establishment of various databases for studies on drug utilization. Raw data required for such research are provided by drug importers, wholesalers or local manufacturers. This information is agreed to be considered as actual utilization data in the country during the pre-defined time period that can be used for further analyses. Clinical drug utilization data obtained from health-care facilities may be used to measure specific aspects of health provision and drug use. Such data may be used to generate indicators that provide information on prescribing habits and aspects of patient care. These indicators can be used to determine where drug use issues exist, provide a mechanism for monitoring and supervision and motivate health-care providers to follow established health-care standards [17–19].

As suggested by WHO, drug utilization data should preferably be presented as numbers of DDDs / 1000 inhabitants / day or, when in-hospital drug use is considered, as DDDs per 100 bed days. Sales or prescription data presented in DDD / 1000 inhabitants / day may provide a rough estimate of the proportion of the population within a defined area treated daily with certain drugs. These utilization data presenting methods are widely used presenting and publishing drug utilization research results worldwide.

Collecting and publishing drug utilization research results are important factors in the process of improving the prescription and dispensing of medicines [9]. As per WHO *Introduction to Drug Utilization Research* instructions, following formulas are recommended to be use for estimations conducting drug utilization research →

- Total drug utilization in DDDs [9]

$$\text{Total drug utilization in DDDs} = \frac{\text{Total amount of compound utilized in the country in mg(s)}}{\text{Standardized DDD of the compound}}$$

- Total drug utilization in DDDs per 1000 hospitalization days (HDs) [9]

$$\text{Utilization in DDD/1000HD} = \frac{\text{Total amount of compound utilized in the country in DDDs}}{\text{Total number of hospitalization days in the country}} \times 1000$$

3.3. Pharmacoeconomic research

3.3.1. Research object and sample size

Pharmacoeconomical research involved evaluation of direct costs of LMWHs and un-fractionated heparin in Lithuania during 9-year period (from 2003 to 2011).

The purpose of this pharmacoeconomic research was to analyze low-molecular-weight heparins utilization trends on the country level. Consequently, pharmacoeconomic decision model was prepared presenting how heparins utilization and expenditures could be rationalized in Lithuania.

This research aimed to develop a pharmacoeconomic decision model based on reference pricing methodology and implementation of cost-minimization analysis.

All heparins that were available in Lithuanian market from 2003 to 2011 have been included into the drug utilization analysis. In total, calculations included six products, eight trade names, and 24 different pharmaceutical forms of heparins. Total costs of heparins were involved in further estimations and were used for cost-minimization analysis and implementation of reference pricing methodology.

Group of low-molecular-weight heparins was suitable for cost-minimization analysis and reference pricing implementation, as LMWHs therapeutic equivalence was demonstrated and scientifically proved using meta-analysis methodology (these meta-analysis results were presented as part of this research) [42].

3.3.2. Cost-minimization analysis

Cost-minimization is a tool used in pharmacoeconomics and applied when comparing multiple drugs or therapies of equal efficacy, equal safety and equal tolerability. Cost-minimization analysis (CMA) is a method of calculating drug costs to project the least costly drug or therapeutic modality. This method of cost evaluation is the one used most often in evaluating the cost of a specific drug. Cost minimization can only be used to compare two products that have been shown to be equivalent in dose and therapeutic effect. Cost minimization analysis (CMA) involves the determination of the

least costly alternative when comparing two or more treatment alternatives. With CMA, the alternatives must have an assumed or demonstrated equivalency in safety and efficacy (i. e., the two alternatives must be therapeutically equivalent). Once this equivalency in outcome is confirmed, the costs can be identified, measured, and compared in monetary units. In many cases, if there is no reliable equivalence between two products and if therapeutic equivalence cannot be demonstrated, and then cost-minimization analysis is inappropriate.

CMA is a frequently used method for comparing competing drugs, programs or treatment alternatives as long as the therapeutic equivalence of the alternatives being compared has been established and / or evident.

Therapeutic equivalence must be referenced by the author conducting the study and should have been done prior to the cost-minimization work [11, 17–19]. Following this requirement, this research was initiated by conducting meta-analysis and proving heparins therapeutic equivalence and then proceeding to cost-minimization analysis

Cost-minimization methodology was selected for this research, as products with the group of low-molecular-weight heparins were identified to be therapeutically equivalent / interchangeable in pre-defined indications. Their therapeutic equivalence was the essential parameter allowing selection of cost-minimization methodology for further investigation. Due to this reason, other methodologies (such as cost-utility analysis, cost-effectiveness analysis, and cost-benefit or cost-utility analysis) were not appropriate. These alternative methodologies have to be selected, when comparing medicines having different safety and efficacy parameters.

3.3.3. Reference pricing methodology

The reference pricing methodology was first implemented in Europe and has driven down pharmaceutical expenditures and prices significantly in countries using this approach, eg. in Germany reference pricing implementation led to a 19 percent decline in pharmaceutical expenditures [63].

Reference pricing method allows limiting expenditure on the reimbursement of drugs by making use of the existence of equivalent drugs on the national market and setting a reimbursement tariff (called reference price) for groups of drugs which are considered to be interchangeable. The prices of the drugs in the interchangeable group may vary greatly. Reference price may be calculated as mean of the various prices, or may reflect the price of one of the lowest-cost items in the class or an average of various low prices; alternatively it may be the price of the product considered to be the most cost-effective in its category [64].

Reference pricing is usually based on a comparison of prices in the home country. There is also an alternative type of reference pricing which can be applied, in which the prices charged for drugs in other countries are also taken into consideration.

In countries where health insurance funds are the largest purchasers of drugs, national reference pricing can have a considerable effect. Setting a reference price system involves four main decisions: (a) defining each class of interchangeable drugs for which a reference price is to be set; (b) determining the way reference reimbursement level is calculated; (c) establishing a procedure for setting acceptable reimbursement levels; (d) setting mechanisms to permit exceptions where these are justified [64].

Reference pricing is extensively in use in many major drug markets; as it continues to evolve, its influence will certainly further expand [39, 46, 64].

Conducting this research, reference price was set, by first determining the group of interchangeable medicines (i.e. low-molecular-weight heparins). Then reference price calculations were performed, based on the least expensive option (Table 3.3.1.3 and Table 3.3.1.4). Further procedures required for setting acceptable reimbursement level and setting mechanisms to permit exceptions were discussed and proposed.

Reference pricing calculations were conducted by first identifying reference drug price and then applying this price to other counterparts. Reference pricing calculations were conducted using two reference price models: (a) reference drug price as the lowest single wholesale package price of the least expensive low-molecular-weight heparin; and (b) reference drug price as the average single wholesale package price of the least expensive low-molecular-weight heparin. Reference drug price represented the highest acceptable wholesale price of medicine, as approved by Republic of Lithuania Ministry of Health.

3.4. Pharmacoepidemiological study design, data collection and statistical analysis

3.4.1. Study Plan

Pharmacoepidemiological study protocol, version 1.0, Final, dated 16 April 2009, was submitted to Kaunas Regional Biomedical Research Ethics Committee on 25 May 2009. Approval for the study conduct was issued on 08 June 2010. In addition, approval to conduct the trial and to collect personal data was obtained from State Data Protection Inspectorate on 19 June 2009.

Study title: *"Prospective observational trial evaluating utilization and safety of heparins in medical in-patients at Kaunas 2nd Clinical Hospital"*. Hospital name changed to Kaunas Clinical Hospital in February 2011, after government initiated reorganization and facilitation were completed.

Study Objectives:

- To evaluate heparins prescription trends at the average secondary level clinical hospital in the country representing the average heparins utilization environment.
- To evaluate the monitoring of treatment efficacy by considering the efficacy parameters (recovered / not recovered / recovered with sequel) reported in medical records.
- To evaluate the monitoring of safety by estimating the incidence of adverse drug reactions induced by heparins and reported in medical records.
- To evaluate the prescription of heparins for patients with relative contraindications.
- To evaluate co-prescription of heparins with drugs that increase the risk of bleeding.

This prospective observational study evaluating utilization and safety patterns of heparins in medical inpatients at the average secondary level clinical hospital was performed at different departments of the aforementioned hospital in order to investigate the main heparins prescription and dispensing patterns. Corresponding secondary level clinical hospital was selected for this research, since it represented average local heparins utilization environment in the country by the means of availability of patients' population, severity of medical conditions treated in a secondary level hospital, qualification of medical staff and access to medicines.

According to the protocol, all patients hospitalized at this hospital and receiving a prescription of un-fractionated heparin or low-molecular-weight heparin from 01 July 2009 to 01 July 2010 were included in the analysis. It was planned to review approximately 250–300 patients' medical records during the aforementioned period, taking into consideration the anticipated patients' admission flow during one-year period.

All patients, admitted to one of the departments of a secondary level clinical hospital and receiving un-fractionated heparin or low-molecular-weight heparin for either treatment of prophylaxis were considered to be suitable for the further evaluations. Patients' medical data were reviewed against study inclusion and exclusion criteria (Table 3.4.1.1). All eligible subjects were allocated to different treatment groups, according to the UFH or LMWH that was prescribed for the treatment / prophylaxis. All patients

were followed-up until their discharge from the hospital. That enabled the collection of data regarding treatment outcomes, and follow-up of adverse drug reactions.

Table 3.4.1.1. *List of pharmacoepidemiological study inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
• Subject was hospitalized at a secondary level clinical hospital. • Subject received anticoagulation therapy during his/her stay at a secondary level clinical hospital. • Subject received at least one prescription of UFH or LMWH during his/her stay at a secondary level clinical hospital. • Subject was male or female, aged over 18 years.	• Subject medical records were illegibly written or incomplete. • Subject medical records did not contain the following information: demographic data, current diagnosis, and description of treatment, duration of hospitalization and duration of treatment, description of treatment outcome. • Subject was hospitalized before 01 July 2009. • The female patient was pregnant or breast feeding. • The clinical data concerning that subject had already been placed into this study.

Medical records of each subject were reviewed, taking into consideration the accuracy and comprehensiveness of data given there. The information which was selected for the further analysis should have been easily understandable and legibly written. The medical records of such patients were reviewed in detail in order to obtain the data necessary for the analysis.

Each subject medical record was cross-checked against the protocol inclusion and exclusion criteria. Only data that met all inclusion criteria and did not meet any of the exclusion criteria of this protocol were considered to be suitable for the further analysis.

The relevant data were collected from hospital medical records using the specific tool *Subject Identification Form* (Supplements Section).

3.4.2. Safety Assessments

Safety assessments were defined as the identification, reporting and follow-up of adverse drug reactions.

According to WHO's Adverse Reaction Terminology, 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, or alteration of the dosage regimen, or withdrawal of the product" [23]. In other words, it is an unexpected or dangerous reaction to a drug or an unwanted effect caused by the administration of a drug.

Following aforementioned ADR definition, adverse drug reactions were expected to be identified and reported in medical record after the treatment with heparins was introduced. If adverse drug reaction occurred, following parameters were expected to be assessed and also reported in the medical records: intensity / severity, duration and possible / probable relation with prescribed treatment. Each adverse drug reaction was expected to be followed-up until the final outcome. Reviewing of ADRs data was needed, as this pharmacoepidemiological study was also designed in order to be able to perform heparins safety analysis.

3.4.3. Statistical Analysis

Microsoft Office Excel 2007 ® was used to arrange data, and *IBM SPSS Statistics* (Statistical Package for the Social Sciences) ® version 18.0 and version 19.0 were used to perform statistical analyses. Descriptive statistics were performed by calculating average / mean / median values of variable (± standard deviation, SD), 95% Confidence Interval CI, statistical significance level was $p < 0.05$. For the comparison of variables Pearson Chi-Square Tests was used. Pearson and Spearman correlation coefficients were used to evaluate correlations between the certain groups of variables.

4. RESULTS

4.1. Meta-analysis results

General review of the accomplished meta-analysis

Meta-analysis of efficacy, safety and treatment outcomes of all LMWHs versus UFH did not demonstrate equivalent efficacy and safety of LMWHs (i.e. Dalteparin, Nadroparin, Enoxaparin and Tinnzaparin) in comparison with UFH. All LMWHs which were taken into consideration manifested superiority against UFH.

Dalteparin vs. UFH. Twelve studies involving 3,993 patients were included. There were no statistically significant differences in the efficacy values of those two medicines, fixed effects odds ratio 1.024 [95% CI, 0.750–1.397]; random effects odds ratio 1.141 [95% CI 0.952–1.368]. Test for heterogeneity (Q = 23.2064; DF = 11; $p = 0.0165$).

UFH vs. Nadroparin. Nine studies involving the total of 8,283 patients were included. There was a statistically significant difference in the efficacy values of those two medicines, fixed effects odds ratio 0.481 [95% CI, 0.252–0.812]; random effects odds ratio 0.487 [95% CI 0.393–0.604]. Test for heterogeneity (Q = 34.6006; DF = 8; $p < 0.0001$).

UFH vs. Enoxaparin. Seventeen studies involving the total of 34,801 patients were included. There was a statistically significant difference in the efficacy values that were estimated, fixed effects odds ratio 0.696 [95% CI, 0.591–0.821]; random effects odds ratio 0.753 [95% CI 0.713–0.796]. Test for heterogeneity (Q = 53.7578; DF = 16; $p < 0.0001$).

Tinzaparin vs. UFH. Four studies involving the total of 1,783 patients were included. There was a statistically significant difference in the efficacy values that were estimated, fixed effects odds ratio 2.286 [95% CI, 1.480–3.533]; random effects odds ratio 2.240 [95% CI 1.446–3.471]. Test for heterogeneity (Q = 1.6350; DF = 3; $p < 0.6515$) (Table 4.1.1.1).

Additional direct comparison was also accomplished with the group of low-molecular-heparins alone.

Enoxaparin vs. Dalteparin. Four studies involving 471 patients were include. There were no statistically significant differences in the efficacy values that were estimated, fixed effects odds ratio 1.447 [95% CI, 0.957–2.281]; random effects odds ratio 1.470 [95% CI 0.949–2.277]. Test for heterogeneity (Q = 1.4669; DF = 3; $p = 0.6899$).

Nadroparin vs. Enoxaparin. Three studies involving 1,118 patients were included. There were no statistically significant differences in the efficacy values that were estimated, fixed effects odds ratio 1.360 [95% CI,

1.050–1.762]; random effects odds ratio 1.352 [95%ercent CI 1.028–1.779]. Test for heterogeneity (Q = 2.0356; DF = 2; $p = 0.3614$).

Tinzaparin vs. Enoxaparin. Three studies involving 557 patients were included. There were no statistically significant differences in the efficacy values that were estimated, fixed effects odds ratio 2.094 [95% CI, 1.437–3.050]; random effects odds ratio 1.931 [95% CI 1.086–3.434]. Test for heterogeneity (Q = 2.4327; DF = 2; $p = 0.2963$).

Dalteparin vs. Nadroparin. Two studies involving 294 patients were included. There were significant differences in the efficacy values, fixed effects odds ratio 0.577 [95% CI, 0.337–0.988]; random effects odds ratio 0.626 [95% CI 0.219–1.789]. Test for heterogeneity Q = 3.5333; DF = 1; $p = 0.0601$ (Table 4.1.1)

Independent comparison of Tinzaparin *vs.* Dalteparin and Tinzaparin *vs.* Nadroparin has not been accomplished due to the limited number of studies, directly comparing safety and efficacy parameters and treatment outcomes of these LMWHs. Limited number of studies refers to less than two published clinical research articles directly comparing aforementioned parameters of these heparins.

Bemiparin was another heparin that has not been involved in the meta-analysis due to the fact that insufficient data comparing Bemiparin with UFH and other LMWHs were available in reviewed scientific databases.

Table 4.1.1. *Data from the accomplished meta-analysis of UFH and LMWHs*

Compared compounds	No. of studies	No. of subjects involved	End points occurred to the no. of subjects involved	Fixed effects and random effects odds ratio [95% CI]	*P* value
Dalteparin *vs.* UFH	12	3,993	547/1,846 (29.63%) *vs.* 603/2,147 (28.09%)	1.024 [0.750–1.397] 1.141 [0.952–1.368]	0.0165
UFH *vs.* Nadroparin	9	8,273	269/4,123 (6.52%) *vs.* 154/4,150 (3.71%)	0.481 [0.285–0.812] 0.487 [0.393–0.604]	<0.0001
UFH *vs.* Enoxaparin	17	34,801	4,867/17,454 (27.88%) *vs.* 3,238/17,347 (18.67%)	0.696 [0.591–0.821] 0.753 [0.713–0.796]	<0.0001
Tinzaparin *vs.* UFH	4	1,783	72/934 (7.71%) *vs.* 31/849 (3.65%)	2.286 [1.480–3.533] 2.240 [1.446–3.471]	<0.6515
Enoxaparin *vs.* Dalteparin	4	471	130/228 (52.02%) *vs.* 119/243 (48.97%)	1.447 [0.957–2.281] 1.470 [0.949–2.277]	0.6899

Table 4.1.1. *Continued*

Compared compounds	No. of studies	No. of subjects involved	End points occurred to the no. of subjects involved	Fixed effects and random effects odds ratio [95% CI]	*P* value
Nadroparin *vs.* Enoxaparin	3	1,118	402/546 (73.63%) *vs.* 385/572 (67.31%)	1.360 [1.050–1.762] 1.352 [1.028–1.779]	0.3614
Tinzaparin *vs.* Enoxaparin	3	577	63/274 (22.99%) *vs.* 106/273 (38.83%)	2.094 [1.437–3.050] 1.931 [1.086–3.434]	0.2963
Dalteparin *vs.* Nadroparin	2	294	103/147 (70.07%) *vs.* 118/147 (80.27%)	0.577 [0.337–0.988] 0.626 [0.219–1.789]	0.0601

All compared low-molecular-weight heparins have independently shown to be more safe and effective than UFH. None of low-molecular-weight heparins demonstrated significant superiority in terms of safety and efficacy parameters and treatment outcomes when compared with each other. Meta-analysis results supported the hypothesis that LMWHs had very similar therapeutic profiles and could be considered interchangeable in some indications, i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE) treatment and prophylaxis, recurrent angina (RA), myocardial infarction (nonfatal MI, acute MI, and re-infarction), prophylaxis during surgical interventions, prophylaxis for bed-ridden patients (Table 4.1.1 and Supplements Section).

4.2. Utilization trends of heparins

General utilization and sales trends of heparins in Lithuania

Total costs of heparins in Lithuania increased almost nine-fold during the 9-year period, from 1,088 thousand LTL in 2003 up to 10,284 thousand LTL in 2011. The most significant growth was reported in 2007 when total heparins expenditures reached 6,406 thousand LTL, increasing by 178% compared to the previous year. In 2008 and 2009 total yearly expenditures on heparins remained relatively stable (corresponded to 8,356 thousand LTL and 8,858 thousand LTL respectively). That was the period when global economic recession began; therefore governmental restrictions we applied on public expenditures and that did not allow the increase of health care budgets in the country. In 2010 the total costs of heparins were 9,395 thousand LTL – more than 6 percent higher compared to 2009 (Figure 4.2.1).

Utilization of heparins also increased dramatically, from 322 thousand DDDs in 2003 to 2,307 thousand DDDs in 2011, which is more than seven fold. Converted to the value of DDDs / 1000 hospitalization days this growth was the following – from 40.12 DDDs / 1000 HD in 2003 up to 309.60 DDDs / 1000 HD in 2011 (Table 4.2.1 and Table 4.2.2). The most significant increase was reported in 2007 when the utilization of heparins reached 171.82 DDDs / 1000 HD. That was a 380% increase compared to 2006 (Figure 4.2.1 and Figure 4.2.2).

The growth of utilization could be justified by the increased number of indications of heparins, increased need for anticoagulation therapies in many areas along with the higher awareness and higher accessibility of these medicines. During this period there were no significant changes in costs of single DDD price of heparins, just the opposite – singe DDD price for all low-molecular-weight heparins decreased during this 9-year period. Therefore it was important to indentify the coherence between these two opposite tendencies – increase of utilization rates and decrease of heparins single DDD price. In practice the growth of total expenditures was three-fold faster than the growth of utilization during the period of interest. This research was designed to identify possible background justifying this growth and to suggest possible solutions allowing controlling this type of growth of expenditures in the future.

The heparins utilization trends at hospitals reflect the global tendencies of utilization, since these medicines are primarily used at the in-patient settings. In general heparins are calculated to consume up to 10 percent of total medication costs in hospitals. It is expected that implementation of pharmacoeconomic models could become a powerful tools enabling health care institutions manage the growth of expenditures and consequently balance their limited budgets. As a result implementation of pharmacoeconomic models on the country level and at health-care institutions could determine the overall decrease of expenditures on heparins in Lithuania.

Therefore certain measures have to be taken aiming to balance limited budgets of health care institutions. Such a situation should become a subject for further investigations and implementation of pharmacoeconomic analysis.

Table 4.2.1. *Distribution of UFH and LMWHs costs and utilization in Lithuania from 2003 and 2011 (9-year period)*

		Bemiparin*	Dalteparin	Enoxaparin	Nadroparin	Tinzaparin	Heparin	TOTAL
2003	Expenditures (Lt)	–	41,620.00	260,514.00	483,729.00	75,544.00	226,869.00	**1,088,276,00**
	Utilization (DDDs)	–	5649	31034	53811	7620	233975	**332089**
2004	Expenditures (Lt)	–	52,826.00	142,037.00	581,020.00	50,966.00	201,024.00	**1,027,873,00**
	Utilization (DDDs)	–	4983	16490	64714	3680	235282	**325149**
2005	Expenditures (Lt)	–	79,384.00	109,538.00	857,335.00	–	90,655.00	**1,136,912,00**
	Utilization (DDDs)	–	10160	11908	80105	0	108755	**210928**
2006	Expenditures (Lt)	–	171,366.00	114,678.00	1,839,660.00	–	178,232.00	**2,303,936,00**
	Utilization (DDDs)	–	21740	12260	168440	0	81050	**283490**
2007	Expenditures (Lt)	–	486,041.05	2,099,463.36	3,137,551.37	–	681,834.90	**6,404,890,68**
	Utilization (DDDs)	–	98620	330850	359650	0	584661	**1373781**
2008	Expenditures (Lt)	511,639.72	769,864.83	3,010,702.10	3,291,548.69	–	772,147.02	**8,355,902,36**
	Utilization (DDDs)	58760	157920	476198	395657	0	749958	**1838493**
2009	Expenditures (Lt)	1,087,386.00	898,817.00	4,045,505.00	2,206,068.00	–	619,989.75	**8,857,765,75**
	Utilization (DDDs)	141795	201840	663436	287080	0	612940	**1907091**
2010	Expenditures (Lt)	933,055.00	1,586,553.00	2,952,496.00	2,189,751.00	–	1,733,442.94	**9,395,297,94**
	Utilization (DDDs)	148630	576500	492204	398040	0	458463	**2073837**
2011	Expenditures (Lt)	1,1195,621.47	2,514,636.70	3,055,190.91	2,288,855.52	–	1,229,159.63	**10,283,464,23**
	Utilization (DDDs)	231395	899480	504614	449590	0	221450	**2306529**

* Marketing Authorization in Lithuania obtained late in 2008.

Table 4.2.2. *Alteration of heparins utilization (in DDDs / 1000 HDs) and costs (single DDD price) in Lithuania from 2003 and 2011*

		Bemiparin	Dalteparin	Enoxaparin	Nadroparin	Tinzaparin	Heparin	TOTAL
2003	DDDs / 1000 HDs	–	0.68	3.75	6.50	0.92	28.27	**40.12**
	Single DDD price	– Lt	7.37 Lt	8.39 Lt	8.99 Lt	9.91 Lt	0.97 Lt	**3.28 Lt**
2004	DDDs / 1000 HDs	–	0.60	1.98	7.76	0.44	28.20	**38.97**
	Single DDD price	– Lt	10.60 Lt	8.61 Lt	8.98 Lt	13.85 Lt	0.85 Lt	**3.16 Lt**
2005	DDDs / 1000 HDs	–	1.24	1.45	9.76	----	13.25	**25.70**
	Single DDD price	– Lt	7.81 Lt	9.20 Lt	10.70 Lt	- Lt	0.83 Lt	**5.39 Lt**
2006	DDDs / 1000 HDs	–	2.75	1.55	21.27	----	10.24	**35.81**
	Single DDD price	– Lt	7.88 Lt	9.35 Lt	10.92 Lt	- Lt	2.20 Lt	**8.13 Lt**
2007	DDDs / 1000 HDs	–	12.33	41.38	44.98	----	73.12	**171.82**
	Single DDD price	– Lt	4.93 Lt	6.35 Lt	8.72 Lt	- Lt	1.17 Lt	**4.66 Lt**
2008	DDDs / 1000 HDs	7.54	20.25	61.07	50.74	----	96.19	**235.79**
	Single DDD price	8.71 Lt	4.88 Lt	6.32 Lt	8.32 Lt	- Lt	1.03 Lt	**4.54 Lt**
2009	DDDs / 1000 HDs	18.65	26.55	87.26	37.76	----	80.61	**250.82**
	Single DDD price	7.67 Lt	4.45 Lt	6.10 Lt	7.68 Lt	- Lt	1.01 Lt	**4.64 Lt**
2010	DDDs / 1000 HDs**	19.55	75.82	64.73	52.35	----	60.30	**272.75**
	Single DDD price	6.28 Lt	2.75 Lt	6.00 Lt	5.50 Lt	- Lt	3.78 Lt	**4.53 Lt**
2011	DDDs / 1000 HDs**	31.06	120.74	67.73	60.35	----	29.72	**309.60**
	Single DDD price	5.17 Lt	2.80 Lt	6.05 Lt	5.09 Lt	- Lt	5.55 Lt	**4.46 Lt**

** Planned number of hospitalization days was used for estimations.

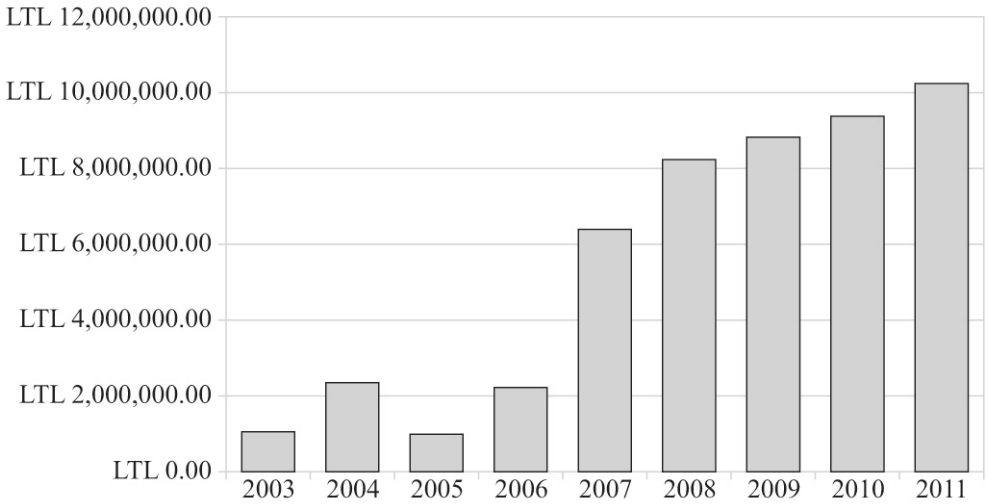

Figure 4.2.1. *Dynamics of total heparins expenditures in Lithuania 2003–2011 (9-year period)*

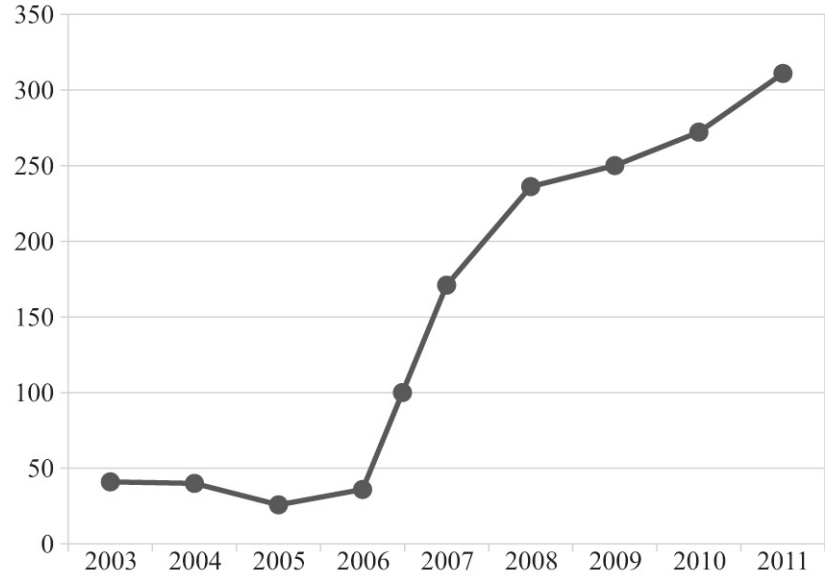

Figure 4.2.2 *Dynamics of heparins utilization rate in DDDs / 1000 hospitalization days*

Low-molecular-weight heparins are primarily administered at the in-patient settings. These health care providers are in particularly sensitive for the increase of expenditures and utilization of drugs. Implementation and

further use of pharmacoeconomic decision modelling is expected to allow hospitals better control their expenditures on medicines.

Heparins utilization trends have been recently analysed and published by Regulatory Authorities in Estonia, Latvia and Lithuania taking into consideration their DDD / 1000 / day parameters and assessing the relative change in use from 2010 to 2012 (Table 4.2.3). Results of this analysis reported gradual increase of heparins utilization during this 3-year period in all countries (total value for Lithuania was highly impacted by the dramatic drop of UFH utilization). Low-molecular-weight heparins utilization figures either remained relatively stable or increased during the period of analysis. It would be beneficial for responsible Regulatory authorities in all Baltic countries to provide data representing long-term utilization trends (eg. 10 years), which could be more informative and allowing in-depth analysis and further decision making.

Table 4.2.3. *Heparins utilization trends in DDD/1000/day in Estonia, Latvia and Lithuania (2010–2012)*

Country name	DDD/1000/day			Relative change %
	2010	2011	2012	
	B01AB Heparin Group			
Estonia	2.04	1.78	2.03	14
Latvia	1.41	1.29	1.56	21
Lithuania	3.73	2.05	1.69	-18
	B01AB01 Heparin			
Estonia	0.12	0.1	0.09	-10
Latvia	0.39	0.23	0.23	0
Lithuania	2.63	0.38	0.34	-11
	B01AB04 Dalteparin			
Estonia	0.04	0.05	0.07	40
Latvia	0.19	0.24	0.46	94
Lithuania	0.48	0.76	0.38	-50
	B01AB05 Enoxaparin			
Estonia	1.63	1.38	1.58	14
Latvia	0.50	0.46	0.45	-2
Lithuania	0.18	0.35	0.28	-20

Table 4.2.3. *Continued*

Country name	DDD/1000/day			Relative change %
	2010	2011	2012	
	B01AB06 Nadroparin			
Estonia	0.11	0.06	0.07	17
Latvia	0.29	0.33	0.39	21
Lithuania	0.32	0.36	0.47	31
	B01AB12 Bemiparin			
Estonia	0.14	0.19	0.23	21
Latvia	0.04	0.04	0.04	-2
Lithuania	0.12	0.19	0.22	16

4.3. Pharmacoeconomic evaluation of heparins costs and utilization

Pharmacoeconomic decision modelling based on cost-minimization analysis

A number of published reviews demonstrated that reference pricing resulted in decreased use of the expensive drugs and stimulate the use of reference drugs [6]. This generally decreased the expenditures on drugs by third party payers. Reference pricing was found to have no adverse effects on health, nor did it increase the use of health services [8]. These arguments supported the decision to select and implement reference pricing methodology in further analysis.

Pharmacoeconomic decision modelling and reference price implementation within the group of heparins were based on the results of the accomplished heparins meta-analysis. In general, systematic reviews and meta-analysis can be powerful tools used to support clinical decision-making, as well as summarize current knowledge in relation to an area of research interest [7].

After meta-analysis of heparins was completed, the decision was made to perform cost-minimization analysis considering them as having similar therapeutic effect and safety parameters. Cost-minimization estimations were performed using the data of heparins sales in Lithuania from the 9-year period (from 2003 to 2011). These estimations included all LMWH used in Lithuania (DU100%) during the aforementioned period. The last 4-year period (from 2008 to 2011) was selected as the most appropriate one for implementation of reference pricing methodology. During this period, extra-

ordinary fluctuation neither in utilization rates nor in expenditures was reported. Consequently, this relatively stable period could adequately reflect the benefits of reference pricing.

Following the guidelines of reference pricing implementation, the lowest single DDD price within the selected group low-molecular-weight heparin had to be set as reference. According to pharmacoeconomic estimations, single DDD price of Dalteparin was identified to be the lowest in the period from 2008 to 2011 within the group of LMWHs. It has to be noted that Dalteparin single DDD price was approximately 50% lower than the price of the next cheapest counterpart and approximately two-fold lower the price of the most expensive heparin. Taking into account the fluctuation of singe DDD prices during the 4-year period, average Dalteparin single DDD price was used for cost minimization estimations. In addition, the lowest Dalteparin single DDD price was reported in 2010; therefore, the second step of cost-minimization analysis was based on this single DDD price value.

As suggested by the cost-minimization model for 2008–2011, the implementation of reference pricing methodology would significantly contribute to the effective management of costs of low-molecular weight heparins by substantially decreasing expenditures on this group of medicines.

According to the estimations, setting the reference price of 4.02 LTL (average single DDD price for the least expensive counterpart Delteparin) for the group of low-molecular-weight heparins would result in total savings of 1,899–3,208 thousand LTL in Lithuania yearly (as per 2008–2011 data). Based on cost-minimization model for 2008–2011, the implementation of reference pricing would enable to decrease the total expenditures on LMWHs heparins by 38.66–47.63% (Table 4.3.3). This potential decrease of expenditures would be significant, since actual costs of heparins could be decreased by nearly two-fold, if reference pricing methodology was implemented in practice.

According to the estimations, setting the reference price of 2.75 LTL (lowest single DDD price for the least expensive counterpart Delteparin) for the group of low-molecular-weight heparins would result in total savings of 3,218–4,679 thousand LTL in Lithuania yearly (as per 2008–2011 data). Based on cost-minimization model for 2008–2011.

The implementation of reference pricing would enable to decrease the total expenditures on LMWHs heparins by 59.82–69.59% (Table 4.3.4). This potential decrease of expenditures would be significant as well, since actual costs of heparins could be reduced more than two-fold, if reference pricing methodology was implemented in practice.

Table 4.3.3. *Cost-minimization model for 2008–2011 period, suggesting singe DDD price – 4.02 Lt as reference*

		Bemiparin	Dalteparin	Enoxaparin	Nadroparin	TOTAL
Suggested single DDD price – 4.02 Lt						
2008	Counted expenditures (Lt)	236,215.20 Lt	634,838.40 Lt	1,914,315.96 Lt	1,590,541.14 Lt	**4,375,910.70 Lt**
	Potential savings (Lt)	275,424.52 Lt	135,026.43 Lt	1,096,386.14 Lt	1,701,007.55 Lt	**3,207,844.64 Lt**
2009	Counted expenditures (Lt)	570,015.90 Lt	811,396.80 Lt	2,667,012.72 Lt	1,154,061.60 Lt	**5,202,487.02 Lt**
	Potential savings (Lt)	517,370.10 Lt	87,420.20 Lt	1,378,492.28 Lt	1,052,006.40 Lt	**3,035,288.98 Lt**
2010	Counted expenditures (Lt)	597,492.60 Lt	1,586,553.00 Lt	1,978,660.08 Lt	1,600,120.80 Lt	**5,762,826.48 Lt**
	Potential savings (Lt)	335,562.40 Lt	– Lt	973,835.92 Lt	589,630.20 Lt	**1,899,028.52 Lt**
2011	Counted expenditures (Lt)	930,207.90 Lt	3,615,909.60 Lt	2,028,548.28 Lt	1,807,351.80 Lt	**9,272,246.58 Lt**
	Potential savings (Lt)	265,413.57 Lt	– Lt	1,026,642.63 Lt	481,503.72 Lt	**1,011,217.65 Lt**

Table 4.3.4. *Cost-minimization model for 2008–2011 period, suggesting singe DDD price – 2.75 Lt as reference*

		Bemiparin	Dalteparin	Enoxaparin	Nadroparin	TOTAL
Suggested single DDD price – 2.75 Lt						
2008	Counted expenditures (Lt)	161,590.00 Lt	434,280.00 Lt	1,309,544.50 Lt	1,088,056.75 Lt	**2,993,471.25 Lt**
	Potential savings (Lt)	350,049.72 Lt	335,584.83 Lt	1,701,157.60 Lt	2,203,491.94 Lt	**4,590,284.09 Lt**
2009	Counted expenditures (Lt)	389,936.25 Lt	555,060.00 Lt	1,824,449.00 Lt	789,470.00 Lt	**3,558,915.25 Lt**
	Potential savings (Lt)	697,449.75 Lt	343,757.00 Lt	2,221,056.00 Lt	1,416,598.00 Lt	**4,678,860.75 Lt**
2010	Counted expenditures (Lt)	408,732.50 Lt	– Lt	1,353,561.00 Lt	1,094,610.00 Lt	**2,856,903.50 Lt**
	Potential savings (Lt)	524,322.50 Lt	– Lt	1,598,935.00 Lt	1,095,141.00 Lt	**3,218,398.50 Lt**
2011	Counted expenditures (Lt)	636,336.25Lt	2,473,570.00 Lt	1,387,688.50 Lt	1,236,372.50 Lt	**5,733,967.25 Lt**
	Potential savings (Lt)	559,285.22 Lt	41,066.70 Lt	1,667,502.41 Lt	1,052,483.02 Lt	**4,549,496.98 Lt**

4.4. Results of pharmacoepidemiological study evaluating conducted at a secondary level clinical hospital

4.4.1. Demographic data and general trends

A pharmacoepidemiological study of 339 patients who were admitted to a secondary level clinical hospital from 01 July 2009 to 01 July 2010 was conducted to investigate heparins prescription patterns at this setting.

This study was carried out in the same clinical context, in the Emergency Room, Cardiology, Urology, Internal Medicine, Surgery and Infectious Diseases Departments, where LMWHs were principally prescribed for treatment and prophylaxis (as preventive treatment for deep venous thrombosis and pulmonary embolism). Most data were collected from Cardiology Department, 35.4%, followed by Surgery Department with 24.8% and Internal Medicine Department – 22.7%.

Characteristics of patients who were treated with LMWHs: 177 males (52.2%) against 162 females (47.8%), elderly population, i.e. mean age 69.6 years, minimum age 21 years, maximum age 101 years, and mean duration of hospitalization did not exceed 10 days, i. e. mean duration was 9.6 days, minimal duration was 1 day and maximal duration was 87 days. Mean duration of anticoagulation therapy was slightly longer than 4 days; minimal duration was also 1 day and maximal duration was 53 days (Table 4.4.1.1.).

All these subjects were identified to be eligible for this study and their medical data were used for further analysis.

Table 4.4.1.1. *Baseline characteristics of pharmacoepidemiological study subjects*

Baseline characteristic	**Value**			
Number of subjects involved	339			
Gender				
Female (n and %)	162 (47.8%)			
Male (n and %)	177 (52.2%)			
General characteristics	**Mean , SD**	**Median**	**Minimum**	**Maximum**
Age in years	69.6 (13.3)	72.0	21	101
Duration of hospitalization in days	9.6 (9.1)	8.0	1	87
Duration of heparins therapy in days	4.3 (4.4)	3.0	1	53

General baseline characteristics of the accomplished review of pharmacoepidemiological study data involved the division of variables of interest into the groups by the department they were reported at (Table 4.4.1.2 and Table 4.4.1.3).

As confirmed by statistical analysis, significant variability regarding prescription of heparins at different departments of a second level clinical hospital was identified. The most frequently prescribed LMWH was Dalteparin, which was administered in 70.2% of cases. This leadership was determined by the extensive use of this low-molecular-weight heparin at Cardiology Department – 111 patients, Internal Medicine and Surgery Departments – with over 50 patients in each. Though, Dalteparin was not that popular at Urology Department, where administration of this heparin was fairly limited, just 8 prescriptions were given during the study period.

On the contrary, at Urology Department Nadroparin was the most frequently prescribed LMWH, administered by 31 subjects, followed by the second counterparts Enoxaparin given to 10 patients in total. It is important to note, that Urology Department was almost the only one to use Enoxaparin for medical in-patients at their facility. Only single prescriptions of Enoxaparin were recorded at Internal Medicine and Surgery Departments that might be considered as not significant compared to general trend.

Bemiparin a heparin with the newly obtained Marketing Authorization has been prescribed exceptionally at Surgery Department, 95.8% of cases. During the study period, 24 patients were exposed to this LMWH at aforementioned department, representing 7.1% sample size in the general pool of heparins prescriptions.

In addition, un-fractionated heparin was identified to be used at the research facility, primarily at Cardiology Department, where it was administered by 9 patients in total. The use of un-fractionated heparin was considered and significantly decreasing, as the number of prescriptions was very limited and the total utilization share did not exceed 3%.

These results demonstrated significant variability of heparins' prescription practices at different departments of the clinical hospital. These finding justified the decision to investigate further heparins utilization patterns in order to identify possible deficiencies leading to potential misuse of these medicines consequently resulting in financial losses.

Table 4.4.1.2. *Baseline pharmacoepidemiological study subjects' characteristics clustered by the department name (Part 1)*

			Cardiology	Internal Medicine	Surgery	Urology	Other	Total
Gender	Male	n	53	42	34	41	7	**177**
		%	29.9%	23.7%	19.2%	23.2%	4.0%	**100.0%**
	Female	n	67	35	50	8	2	**162**
		%	41.4%	21.6%	30.9%	4.9%	1.2%	**100.0%**
Age (years)	1–65	n	37	28	26	22	3	**116**
		%	31.9%	24.1%	22.4%	19.0%	2.6%	**100.0%**
	> 65	n	83	49	58	27	6	**223**
		%	37.2%	22.0%	26.0%	12.1%	2.7%	**100.0%**
Duration of Hospitalization (days)	< 6	n	55	7	29	5	5	**101**
		%	54.5%	6.9%	28.7%	5.0	5.0	**100.0%**
	6–10	n	40	45	25	35	2	**147**
		%	27.2%	30.6%	17.0%	23.8%	1.4%	**100.0%**
	11–15	n	14	18	12	8	0	**52**
		%	0.3%	0.3%	0.2%	0.2%	0.0%	**100.0%**
	> 15	n	11	7	18	1	2	**39**
		%	28.2%	17.9%	46.2%	2.6%	5.1%	**100.0%**
Heparin Name	Clexane	n	0	1	1	10	0	**12**
		%	0.0%	8.3%	8.3%	83.3%	0.0%	**100.0%**
	Fragmin	n	111	59	53	8	7	**238**
		%	46.6%	24.8%	22.3%	3.4%	2.9%	**100.0%**
	Fraxiparin	n	0	17	6	31	1	**55**
		%	0.0%	30.9%	10.9%	56.4%	1.8%	**100.0%**
	Heparin	n	9	0	1	0	0	**10**
		%	90.0%	0.0%	10.0%	0.0%	0.0%	**100.0%**
	Zibor	n	0	0	23	0	1	**24**
		%	0.0%	0.0%	95.8%	0.0%	4.2%	**100.0%**

Table 4.4.1.3. *Baseline pharmacoepidemiological study subjects' characteristics clustered by the department name (Part 2)*

			Cardiology	Internal Medicine	Surgery	Urology	Other	Total
Duration of Treatment (days)	< 5	n	99	43	48	34	4	**228**
		%	43.4%	18.9%	21.1%	14.9%	1.8%	**100.0%**
	5–7	n	18	21	21	12	1	**229**
		%	24.7%	28.8%	28.8%	16.4%	1.4%	**100.0%**
	> 7	n	3	13	15	3	4	**38**
		%	7.9%	34.2%	39.5%	7.9%	10.5%	**100.0%**
Contraindications	No	n	35	26	22	18	3	**104**
		%	33.7%	25.0%	21.2%	17.3%	2.9%	**100.0%**
	Yes	n	85	51	62	31	6	**235**
		%	36.2%	21.7%	26.4%	13.2%	2.6%	**100.0%**
Safety Monitoring	No	n	26	0	17	4	0	**47**
		%	55.3%	0.0%	36.2%	8.5%	0.0%	**100.0%**
	Yes, ADRs not reported	n	87	58	51	44	6	**246**
		%	35.4%	23.6%	20.7%	17.9%	2.4%	**100.0%**
	Yes, ADRs	n	7	19	16	1	3	**46**
		%	15.2%	41.3%	34.8%	2.2%	6.5%	**100.0%**
Treatment outcomes	Recovered	n	114	66	74	49	3	**306**
		%	37.3%	21.6%	24.2%	16.0%	1.0%	**100.0%**
	Not recovered	n	6	11	10	0	6	**33**
		%	18.2%	33.3%	30.3%	0.0%	18.2%	**100.0%**

Following heparins were available at a secondary level clinical hospital during the course of the study: Enoxaparin (*Clexane*), Nadroparin (*Fraxiparin*), Dalteparin (*Fragmin*), Bemiparin (*Zibor*) which has been introduced into Lithuanian market late in 2008, and unfractionated heparin. The most frequently prescribed counterpart was Dalteparin, with the prescription rate above 69% (n=236), the second and third mostly prescribed LMWHs were Nadroparin (16.2%, n=55) and Bemiparin (7.1%, n=24). Prescription of the other heparins did not exceed 4% rate, as it was investigated during this research study (Table 4.4.1.4).

As it was identified from patients' medical records, the most frequent indication for heparins prescription were prophylaxis of VT in surgery, 39.8% (n=135) and treatment of unstable coronary artery disease or myocar-

dial infarction, 49.0% (n=166). Other indications were represented by significantly lower number of patients, DVT – 4.1% (n=14) and bedridden patients prophylaxis – 6.5% (n=22) respectively (Table 4.4.1.4).

Table 4.4.1.4. *General heparins prescription trends at the secondary level clinical hospital clustered by the treatment indication name*

			Treatment indications				
			DVT	**Prophylaxis of VT in surgery**	**Prophylaxis for bedridden patients**	**Treatment of UCAD or MI**	**Other**
Depart-ment	Cardiology	n	0	1	0	119	0
		%	0.0%	0.8%	0.0%	99.2%	0.0%
	Internal Medicine	n	12	5	18	40	2
		%	15.6%	6.5%	23.4%	51.9%	2.6%
	Surgery	n	2	80	0	2	0
		%	2.4%	95.2%	0.0%	2.4%	0.0%
	Urology	n	0	49	0	0	0
		%	0.0%	100.0%	0.0%	0.0%	0.0%
	Other	n	0	0	4	5	0
		%	0.0%	0.0%	44.4%	55.6%	0.0%
Total		**n**	**14**	**135**	**22**	**166**	**2**
		%	**4.1%**	**39.8%**	**6.5%**	**49.0%**	**0.6%**
Heparin Name	Enoxaparin	n	0	12	0	0	0
		%	0.0%	100.0%	0.0%	0.0%	0.0%
	Dalteparin	n	11	61	20	144	2
		%	4.6%	25.6%	8.4%	60.5%	0.8%
	Nadroparin	n	2	39	2	12	0
		%	3.6%	70.9%	3.6%	21.8%	0.0%
	Heparin	n	1	0	0	9	0
		%	10.0%	0.0%	0.0%	90.0%	0.0%
	Bamiparin	n	0	23	0	1	0
		%	0.0%	95.8%	0.0%	4.2%	0.0%
Total		**n**	**14**	**135**	**22**	**166**	**2**
		%	**4.1%**	**39.8%**	**6.5%**	**49.0%**	**0.6%**

4.4.2. Treatment outcomes

90.27% of all treatment outcomes were assessed as positive, as these patient (n=306) were considered as recovered after their treatment course at the in-patient setting.

In total, 9.14 percent of treatment outcomes were negative, composite end-points:

- Death, 6.49%, n=22
- Not recovered, 1.77%, n=6
- Recovered with sequel, 1.47%, n=5

The major cause for death was the fatal diagnosis of DVT or PE and various cardiovascular events. All patients who did not recover were transferred to another treatment facility during their hospitalization period due to the need for additional medical services, which were not available at a secondary level clinical hospital during the course of the research study. After this transfer, the possibilities to identify their final treatment outcomes were very limited, as no relevant data were reported in their in-patient medical records archived at the hospital where the research took place.

Heparins treatment outcomes were statistically significantly linked to the treatment duration. As reported, the prolonged treatment duration was associated with the increased risk for the negative treatment outcomes. When the treatment was shorter than 5 days, the probability of the negative treatment outcomes (noted as not recovered) was 6.6%. When heparin treatment duration was between 5 and 7 days, the percentage of not recovered patients increased up to 12.3%. And if treatment duration was longer than 8 days, then negative treatment outcomes frequency peaked 23.7% (r_s = 0.169, Pearson χ^2 = 11.6, $p < 0.003$). This tendency might be reported as increased probability of a negative treatment outcome to be related with the longer heparins treatment duration.

Statistical analysis did not show any relation between prescribed heparin compound name and treatment outcomes (r_s = -0.043, Pearson χ^2 = 0.158, $p < 0.663$). It had to be concluded that heparin name was not among the variables that had possible direct impact on treatment outcomes.

The frequency of adverse drug reactions (ADRs) was dependent upon the treatment duration. The longer the treatment was, the more frequently adverse reactions were reported. When the treatment was shorter than 5 days, ADRs frequency was 9.2%. When heparin treatment duration was between 5 and 7 days, ADRs frequency was reported as 15.1%. In case, treatment duration was longer than 8 days, ADRs frequency was significantly higher, i.e. 36.8% (r_s = 0.270, Pearson χ^2 = 33.2, $p < 0.0005$). This tendency was

summarized as increased probability of ADRs was significantly related with the treatment duration of heparins.

4.4.3. Safety measures

A number of adverse reactions were reported in patients medical records, resulting in the total incidence rate of 13.57% (n=46). Primarily reported adverse drug reactions were thrombocytopenia (which was identified as a result of laboratory result monitoring during treatment period), bleeding and dizziness / headache. Thrombocytopenia was the primary adverse reaction of interest, with the total count of 15 events (frequency 4.42%). Though the figure did not differ from this adverse reaction incidence rate stated in manufacturers' instructions (Summary of Product Characteristics, SmPC) and reported in a number of clinical trials. There were several other adverse reactions reported, but their possible relationship with heparins treatment was difficult to prove. One anaphylactic reaction was recorded; though it was related to the treatment with antibiotic (relevant explanation was present in medical records).

The incidence of adverse drug reactions differed significantly among the departments of the secondary level clinical hospital. The majority of all ADRs were reported at Internal Medicine and Surgery departments, corresponding to 41.3% and 34.8% of all cases. ADRs incidence rate at Urology department was particularly low, just 2.2%. The timely, adequate and comprehensive reporting of adverse drug reactions is an essential part of patients' medical care, allowing to justify future therapy alterations and to prevent patient from repeated adverse drug reactions during their hospital stay. Probable underreporting of adverse drug reactions was detected in patients' medical records. This finding was based on the fact that the number of reported ADRs in corresponding patient's medical records was significantly lower compared to standard ADRs rates defined in manufacturers' instructions.

The following variables were taken into considerations assessing heparins safety measures: gender and age of subjects, hospital department and duration of hospitalization, treatment duration and name of heparin used for treatment, relative contraindications and treatment outcomes. Three-step safety data review was conducted in order to evaluate heparins safety monitoring patterns at the in-patient setting. Initially, all patients for whom there was no evidence in medical records about performed safety monitoring during the hospitalization period were separated from the whole sample. Later on, all subjects for whom safety monitoring had been performed were divided into two groups. Safety monitoring was performed for the first

groups of patients, though no discrepancies were identified and reported. For the second group of patients, safety monitoring was performed either, as a result, various discrepancies or adverse drug reactions (ADRs) were detected and recorded.

Statistical analysis methods (Spearman correlation, Pearson χ^2 test, significance level <0.005) were used to assess the correlation between safety measures and other variables.

Statistically significant difference was observed comparing safety monitoring trends at various departments at the in-patient setting (r_s = 0.113, Pearson χ^2 = 46.1, $p < 0.005$). At Surgery and Cardiology departments there were no evidence in source documents about performed safety monitoring in 36.2 and 55.3% of cases respectively. On the contrary, at the department of Internal Medicine safety was monitored for all patients, consequently the highest number of discrepancies and adverse drug reactions (ADRs) were identified at this department. Even though safety was extensively monitored at Urology department, very few ADRs were reported in medical records. It might be concluded that there was a lack of consistency in safety monitoring practices followed at the in-patient setting. Safety follow-up and reporting of ADRs are essential parts of diseases management, therefore, additional efforts have to be taken to establish more firmly the importance of safety monitoring in patients daily follow-up practice.

Statistical analysis did not show any relation between different heparin compounds and safety measures (r_s = -0.007, Pearson χ^2 = 7.96, $p < 0.437$). This trend corresponded to the results of the accomplished meta-analysis, where it was demonstrated that different low-molecular weight heparins were interchangeable and did not differ in terms of their safety parameters. The average ADRs rate in the group of LMWHs at the in-patient setting varied around 13.57%.

Duration of exposure to heparins was also considered as the important factor, having a direct impact of the ADRs rate (r_s = 0.270, Pearson χ^2 = 33.2, $p < 0.005$). In total, 36.8% of patients experienced ADRs, in cases when heparins were administered for a longer period of time, i.e. 8 days and above. The ADRs rate was 15.1% in the subjects' sample, where duration of heparins administration was 5–7 days. This figure was more than two-fold lower than the ADRs rate in the initially described group of patients. According to the general trend, when heparins were prescribed for the short term use, the reported rate of ADRs was 9.2%. This important safety reference has to be considered, before making the decision to prolong the administration of heparins in the in-patient settings. In case, it is determined to prescribe heparins for the long term use, additional measures have to be taken to ensure proper safety monitoring and adequate follow-up / review of relevant laboratory

parameters. Permanent compliance with standard heparins safety monitoring requirements is essential aiming to ensure that patients' needs are met.

Duration of hospital stay was another variable that statistically significantly correlated with ADRs (r_s = 0.282, Pearson χ^2 = 48.3, $p < 0.005$). Prolonged hospitalization (duration 11–15 days) or significantly prolonged hospitalization (duration more than 15 days) were related with the increased ADRs rate. This correlation might have been influenced by the severe medical conditions, which required longer in-patient stay. Though it would be important to emphasize that extensive and close safety monitoring would be a critical part of patient's management, in case significantly prolonger hospitalization is required. Longer hospitalization is definitely related to the significant increase of ADRs rate and possibly more complicated medical conditions that required adequate follow-up of each individual patient in all cases.

Statistical analysis demonstrated the significant correlation between treatment outcomes and ADRs (r_s = 0.247, Pearson χ^2 = 27.2, $p < 0.005$). Significantly higher rate of ADRs was detected in the sample of patient who did not recover (42.4% ADRs rate), compared to the sample of patients who recovered (10.5% ADRs rate). This result strongly supports the importance of safety monitoring in the disease management at the in-patient setting. Additional actions have to be taken in order to increase the level of safety monitoring in particularly for patients for who due to severe medical condition treatment outcomes might be foreseen to be negative.

Statistical analysis did not show any relation between reported / not reported contraindications and ADRs (r_s = -0.004, Pearson χ^2 = 0.024, $p < 0.988$). The rate of ADRs did not differ significantly in both patient samples. It might be concluded that this variable was not among the ones that significantly influenced the increase of ADRs rate among the patients.

It is essential to emphasize the importance of safety monitoring in patients administering heparins. In particularly, it is necessary to monitor closely the patients, for whom heparins are prescribed for the long-term treatment, for patients with prolonged hospital stay, and for patients with complicated concomitant medical conditions. Thus, low-molecular weight heparins did not differ in terms of their safety parameters; therefore, requirement for additional follow-up is not affected by the heparin name prescribed for the particular patient.

According to *NHS Devon* Clinical Guideline for the use and monitoring of Low Molecular Weight Heparins (LMWHs) in community hospitals and community settings v1.0 January 2011, following investigations have to be conducted prior to use of LMWHs aiming to ensure adequate safety and efficacy monitoring for patients [10]. Taking into consideration these requirements, the data of pharmacoepidemiological study were re-assessed to

evaluate the monitoring compliance at the secondary level clinical hospital with these international guidelines. The results of this analysis were summarized in Table 4.4.3.1. Local guidelines on heparins orders that could be followed by clinicians were not available at the clinical hospital.

Table 4.4.3.1. *List of parameters that have to be checked and/or assessed before prescribing LMWHs to patients*

Laboratory results monitoring	Other
Full blood count (FBC) INR & APTR Liver function tests (LFTs) Renal function Urea & Electrolytes (U&Es)	History of bleeding risk, acute peptic symptoms or other contraindications have to be checked Drugs that may prolong bleeding time or affect platelet function (e.g. aspirin, NSAIDs, clopidogrel) have to be checked Patient‘s weight has to be monitored VTE risk assessment has to be conducted

As per pharmacoepidemiological study data, no information was indentified in patient's medical records concerning VTE risk assessment, evaluation of concomitant medicines that could increase the risk of bleeding and evaluation of contraindications. Due to this reason, daily medical practice might be considered as non-compliant with the requirements of available international guidelines. At the time of admission to hospital, the weight of each patient was reported in their medical records. It was considered that a requirement for weight monitoring was fully implemented in practice at the secondary level clinical hospital. There were no evidence available in medical records of pharmacoepidemiological study patients about VTE risk assessment conducted during their stay at the clinical hospital; therefore it was considered that this assessment has not been performed for any patient out of 339 (Table 4.4.3.2).

It is important to emphasize that laboratory results monitoring should be performed before prescribing heparins and during heparins treatment course. Laboratory results monitoring is essential in order to ensure appropriate observation of safety and efficacy parameters during the treatment period. As confirmed by study data, laboratory testing was identified to be limited and requiring further increase of testing rates to meet the requirements of international guidelines.

According to pharmacoepidemiological study data no laboratory tests were performed in 60.77% of all cases (n=206) at the secondary level clinical hospital before prescribing heparins to patients. According to the study results, laboratory testing was performed in 39.23% of all case (n=133). The number of laboratory tests performed for each individual pa-

tient differed significantly, therefore all required laboratory tests were performed for a small sample of patients only. For example, electrolytes might be considered as the most frequently monitored laboratory parameters, as these test were performed for 33.33% of patient (n=113). Following laboratory tests were performed for the limited sample of patients even though according to international guidelines they should have been performed for each patient administering heparin, eg. liver function test were performed for 65 patients only (19.17%); renal function tests and urea were monitored for 89 patient (26.25%) and full blood count together with INR and APTR were monitored in 27.43% of cases, n=93 (Table 4.4.3.3).

According to pharmacoepidemiological study data no laboratory tests were performed in 46.02% of all cases (n=156) at the secondary level clinical hospital during the treatment period. According to the study results, laboratory testing was performed in 53.98% of all case (n=183). The number of laboratory tests performed for each individual patient differed significantly, therefore all required laboratory tests were performed for a small sample of patients only. For example, electrolytes testing were performed for 25.96% of patient (n=88); and liver function test were performed for 60 patients only (17.70%). Renal function tests and urea were monitored for 66 patient (19.47%) and full blood count was monitored in 19.17% of cases, n=65 (Table 4.4.3.4).

Certain measures have to be taken to establish more firmly the importance of laboratory results monitoring for patients receiving heparins for treatment and/or prophylaxis. It is critical to implement comprehensive and consistent laboratory parameters monitoring practice, based on available international clinical guidelines – it would be advisable to follow recommendations outlined in Table 4.4.3.1. Having this practice in place would ensure the adequate safety monitoring of individual patients and would allow adequate safety follow-up of their medical conditions.

Table 4.4.3.2. *Compliance of daily medical practice applied at a secondary level clinical hospital with international clinical guidelines*

General patients monitoring requirement	Concordance of daily medical practice
History of bleeding risk, acute peptic symptoms or other contraindications have been checked	0 out of 339
Drugs that may prolong bleeding time or affect platelet function have been checked	0 out of 339
Patient‘s weight has been monitored	339 out of 339
VTE risk assessment has been conducted	0 out of 339

Table 4.4.3.3. *Compliance of daily medical practice applied at a secondary level clinical hospital with international clinical guidelines (laboratory results monitoring before prescription of heparins)*

Laboratory results monitoring		**Concordance of daily medical practice**
Laboratory results were not monitored at the time of admission		206 out of 339 (60.77%)
Laboratory results were monitored at the time of admission		133 out of 339 (39.23%)
Laboratory tests	Full blood count	93 out of 339 (27.43%)
	INR	93 out of 339 (27.43%)
	APTR	93 out of 339 (27.43%)
	Liver function tests	65 out of 339 (19.17%)
	Renal function	89 out of 339 (26.25%)
	Urea	89 out of 339 (26.25%)
	Electrolytes	113 out of 339 (33.33%)

Table 4.4.3.4. *Compliance of daily medical practice applied at a secondary level clinical hospital with international clinical guidelines (laboratory results monitoring during heparins administration)*

Laboratory results monitoring		**Concordance of daily medical practice**
Laboratory results were not monitored during treatment course		156 out of 339 (46.02%)
Laboratory results were monitored during treatment course		183 out of 339 (53.98%)
Laboratory tests	Full blood count	65 out of 339 (19.17%)
	INR	50 out of 339 (14.75%)
	APTR	59 out of 339 (17.40%)
	Liver function tests	60 out of 339 (17.70%)
	Renal function	66 out of 339 (19.47%)
	Urea	49 out of 339 (14.45%)
	Electrolytes	88 out of 339 (25.96%)

4.4.4. Financial considerations

The cost-minimization model used in Lithuania was extrapolated and applied on low-molecular-weight heparins utilization data at a secondary level clinical hospital. These calculations were based on heparins utilization data collected during the pharmacoepidemiological study conduct at this facility.

According to the estimations, setting the reference price of 2.75 LTL (lowest Dalteparin single DDD price) for low-molecular-weight heparins

group would result in total savings of 2,156 LTL at the secondary level clinical hospital during the research period. Based on the suggested cost-minimization model, the implementation of reference pricing would enable to decrease the total expenditures on LMWHs by 29.2% (Table 4.4.4.1). This potential decrease of expenditures could be considered as significant. As suggested by the cost-minimization model, the implementation of reference pricing methodology at a secondary level clinical hospital would significantly contribute to the proper and effective management of treatment costs in the group of low-molecular weight heparins.

Table 4.4.4.1. *Cost-minimization model for secondary level clinical hospital, suggesting singe DDD price – 2.75 Lt as reference*

	Bemiparin	**Dalteparin**	**Enoxaparin**	**Nadroparin**	**TOTAL**
Hospital expenditures (Lt)	1,526.04 Lt	3,300.00 Lt	462.00 Lt	2,095.50 Lt	**7,383.54 Lt**
Hospital utilization (DDDs)	243	1200	77	381	**1901**
Suggested singe DDD price – 2.75 Lt					
Counted expenditures (Lt)	668.25 Lt	3,300.00 Lt	211.75 Lt	1,047.75 Lt	**5,227.75 Lt**
Potential savings (Lt)	857.79 Lt	0	250.25 Lt	1,047.75 Lt	**2,155.79 Lt**

5. DISCUSSION

There are several factors that determine the rapid growth of expenditures on pharmaceuticals worldwide. These factors have already been discussed widely for more than decade by many interested parties. A lot of important reasons have been mentioned in this discussion, such as ageing population, increased number of chronic diseases, and increased number of prescriptions for medicines for the long-term use, development of new medicines, new and extraordinary expensive medicines for end-stage diseases, increased number of prescriptions per patient, increased overall volume of prescriptions, primary care – hospital – primary care shifts, etc. [24, 65, 66].

Having in mind this extensive list, it is essential to reveal if anything could be done to limit and / or control the growth of expenditures on medicines globally.

Pharmaceutical industry is one of the constantly growing and complex industries in the world. The aggressive development and extraordinary growth of revenue of this industry started in the middle of the last century and it still hits new peaks every year. The global pharmaceutical market in 2010 exceeded 825 billion USD and increased by 5% compared to previous year. Moreover, it is expected to exceed 975 billion USD by 2013. The global pharmaceutical market sales are expected to rise by 4–7% annually (by 3–6% or by 5–8%, as noted by a number of authors in various forecasts) through 2013 and / or 2014 [14–16].

Global heparins market has been dominated by low-molecular-weight heparins. The annual global market of anticoagulants is approximately 6 billion USD, though worldwide heparins sales exceed 4 billion USD and 15% yearly growth rate is anticipated in the next years. The US pharmaceutical market accounts for more than 50% of all global sales of heparins.

The US sales of Enoxaparin alone reached 2.7 billion USD in 2009. Consequently, Enoxaparin was reported to be the best-selling hospital medicine in the US in the same year. Since the launch of this medicine in the last decade of the 20th century, it has been prescribed for more than 200 million patients. The first generic version of this molecule has already been released in the US, which happened in 2010.

Sales of other low-molecular-weight heparins also contributed to impressive figures worldwide. For example, Nadroparin global sales were 319 million USD in 2003 and were increasing gradually since that time, until reached 368 million in 2007 and 418 million in 2008. In 2001 Tinzapatin global sales were 100 million USD. And global sales of Nadroparin grew from 335 million USD in 2007 up to more than 360 million USD in 2008.

Yet Enoxaparin sales remain in the leading position within the group of low-molecular-weight heparins worldwide, which contributes to the total market share of more than 60%.

5.1. Policy implications

Due to the fact that pharmaceutical costs are increasing worldwide, a number of international organizations have established pharmacoeconomic guidelines and recommendations that should be used conducting various types of pharamacoeconomic analyses and assessments.

ISPOR (International Society for Pharmacoeconomics and Outcomes Research) has demonstrated a pro-active approach encouraging all countries to prepare and regularly review country specific pharmacoeconomic guidelines and recommendations. It is also recommended by the organization to review and up-dated country specific guidelines on the regular basis in order to meet the recent requirements and needs of the changing pharmaceutical environment. Large international organizations also publish global recommendations, though in the majority of cases several country specific alterations should be made. That is mainly a result of significant differences in the health-care structures in the countries, also various reimbursement rules and restrictions, as well as different roles of payees in a decision making pathway, etc. Many countries have prepared comprehensive guidance documents providing recommendations on the implementation of health technology assessment (HTA) and other relevant pharmacoeconomic methodologies, e. g. Guidelines for the Economic Evaluation of Health Technologies in Ireland, 2010; Guidelines for Conducting Health Technology Assessment (HTA), Poland 2009; Guidelines for Pharmacoeconomic Evaluations in Belgium, 2008; General Methods for the Assessment of the Relation of Benefits to Costs, Germany 2009; etc. [11].

According to the evidence-based approach it is really critical to consider costs of treatment as a part of the health care decision making in all countries. Following this approach, it is essential to select and justify the appropriate type of analysis that would be implemented conducting pharmacoeconomic evaluations.

Cost-minimization analysis is assuming that the treatment outcomes of compared therapies are equal therefore only direct costs are compared. Cost-minimization analysis is mentioned in all country specific guidelines as an acceptable method of pharmacoeconimic evaluations and is defined as the most appropriate method in case similar therapies are compared.

NICE (National Institute of Heath and Clinical Excellence) has also published a number of papers defining the role of pharmacoeconomics in the decision making strategy. According to NICE experts, expenditures on medicines exceed 13 billion GBP per annum, and these expenditures are constantly growing. Aging populations and technological advancement are the factors that are complicated to influence, yet budgetary cuts are necessary in today's economic environment. There are also several bodies within NHS that are in charge of making decisions on whether particular drugs have to be available for the patients in the UK and at what price [13]. The importance of pharmacoeconomics is highly recognized in this area, therefore health economic evidences are considered to be the essential components of health care decision making.

All these theoretical considerations have been widely implemented in practice, providing justifications for numerous decisions. NICE approach towards decision making and pharmacoeconomic analysis implementation has been widely discussed in scientific publications [67]. A number of decision making strategies are suggested there for health-care decision makers along with pharmaceutical industry. Some practical examples also deserve to be mentioned, such as implementation of reference pricing methodology in the group asthma medicines and insulins (different insulin analogs used for type 1 diabetes and type 2 diabetes treatments). Implementation of respective methodologies resulted in significant savings in the country. Rationalized use of financial recourses obviously has a very positive impact on the whole NHS budget [67].

Following the recent independent report prepared and published by the European Parliament (EP), reference pricing is used in several European Union (EU) countries to control drug prices. According to latest data, reference pricing was proved to be leading to price convergence for some drugs and, in general, to lower prices in the countries [12].

Price regulations based on reference pricing methodology are considered to be powerful financial measures. Consequently implementation of national guidelines and use of pharmacoeconomics in pricing decisions are strongly recommended, as that would enable each individual member country rationalize and / or control their pharmaceutical expenditures.

5.2. Purpose of this research

Unfractioned heparin and low molecular weight heparins are cbeoming one of the most prescribed medicines in hospitals. Thus it is very important to promote its rational use taking into consideration: (a) effectiveness, (b) safety and outcoumes profile, and (c) costs of medicines. The task of our reseach work was to develop an optimal decision making model for heparins therapy, based on the main principles of pharmacoeconomics – to keep balance between clinical outcomes, economic outcomes and humanistic / social outcomes – basic components of the contemprorary clinical decision making. Traditional medical evaluation focused only on the evaluation of benefics (clinical effectiveness) while modern pharmacoeconomics concept is to determine the most efficient way to use our health care resources or to buy the greatest amount of benefits from the new drugs for a given resource used. This is a modern approach to assess new drugs or new health care technologies, based on evaluation of effectiveness, safety, outcomes and costs; and the main task of pharmacoeconomic research is to promote rational use of drugs in order to achieve the best value for the money spent on drugs and the whole therapy [20].

Pharmacoeconomic evaluation is mostly addressed for the evaluation of a new drugs in comparison it with the already authorized and used over the time. Such type of the evaluation is mainly of interest of clinical pharmacologists and clinical pharmacist due to their roles in conducting clinical trials and interpretation of trials results. Modern clinical trials also include economic component of the therapy in order to be attractive for the reimbursement system, consequently the role of clinical pharmacologists and pharmacists becoming more important and needs more knowledges and experience in the assessment of new drugs.

This research was conducted aiming to demonstrate the potential benefits of pharmacoeconomic decisions modeling on the country level and to establish more firmly the place of pharmacoeconomic analyses among the decision makers at the in-patient settings.

A number of various reviews and recommendations published and available worldwide [3, 68–70] emphasized that reference pricing resulted in less use of the more expensive drugs and more use of reference drugs. That generally resulted in the decreased of the expenditures on medicines and affected all payers (governments, private health insurance funds and patients). Reference pricing was not found to have adverse effects on health, nor did it increase the utilization of health services / resources.

Low-molecular-weights heparins were considered to be interchangeable in terms of their efficacy and safety parameters, as well as treatment outco-

mes after meta-analysis results were summarized. Therefore this group of medicines was suitable for further investigations and implementation of cost-minimization analysis based on reference pricing methodology. Cost-minimization analysis is one of pharmacoeconomic decision modeling tools widely recognized and implemented globally.

The utilization of heparins in the outpatient environment is limited due to the method of administration, approved indications and other restrictions. As a result, LMWHs are most frequently used at the in-patient settings. Therefore it was scientifically justifyable to investigate LMWHs utilization patters in the in-patient environment on the country level. Following this workflow, the pharmacoepidemiological study (study title: *"Prospective observational trial evaluating utilization and safety of heparins in medical in-patients at the medium size secondary level clinical hospital"*) was initiated.

Observational research study report demonstrated general heparins utilization tendencies on the country level. Total costs of heparins in Lithuania increased almost ten-fold during the 9-year period, i.e. from 1,088 thousand LTL in 2003 up to 10,284 thousand LTL in 2011. Utilization of heparins also increased dramatically, from 322 thousand DDDs in 2003 to 2,307 thousand DDDs in 2011, which is almost seven-fold. Taking into consideration the value of DDDs / 1000 hospitalization days, a significant increase was also noted. According to estimations the growth from 40.12 DDDs / 1000 HD in 2003 up to 309.60 DDDs / 1000 HDs in 2011 was reported.

It is important to note that the expenditures demonstrated the tendency of markedly faster growth which could not be equally covered by the increased heparins utilization rates in the country. Therefore, it was important to identify the reasons behind that disproportional growth and to anticipate relevant actions that would have to be taken in order to control / restrict the increase of costs in the future. The dramatic increase of expenditures was the point of interest of the pharmacoeconomic research.

Consequently, cost-minimization estimations were performed using the data of heparins sales in Lithuania from 2003 to 2010. The estimations included all LMWH used in Lithuania (DU100%) during the aforementioned period. The last three year period (2008–2010) was selected as the most appropriate one for implementation of reference pricing methodology. During this period, extraordinary fluctuation neither in utilization rates nor in costs was noted.

Following reference pricing implementation guidelines, the lowest single DDD price within the selected group of low-molecular-weight heparin had to be set as reference. According to pharmacoeconomic estimations, single DDD price of Dalteparin was identified to be the lowest in the period

from 2008 to 2011 within the group of LMWHs. Setting the reference price of 4.02 LTL (average Dalteparin single DDD price) for low-molecular-weight heparins group would result in total savings of 1,899–3,208 thousand LTL in Lithuania yearly. Based on cost-minimization model for 2008–2011, the implementation of reference pricing would enable to decrease the total expenditures on LMWHs by 38.66–47.63%. Setting the reference price of 2.75 LTL (lowest Dalteparin single DDD price) for low-molecular-weight heparins group would result in total savings of 3,218–4,679 thousand LTL in Lithuania. That would enable to decrease the total expenditures on LMWHs by 59.82–69.59%. This potential decrease of expenditures should be considered as significant, due to the fact that actual costs of heparins could be reduced more than two-fold, if reference pricing methodology was implemented on the country level.

As suggested by the cost-minimization country model for 2008–2011, the implementation of reference pricing methodology would significantly contribute to the proper and effective management of expenditures in the group of low-molecular-weight heparins.

LMWHs could be interchangeable in terms of their health benefits; that is the idea behind reference pricing, in which reimbursement of a drug is based on the least expensive option.

The heparins utilization trends at hospitals reflected the global tendencies of utilization, as these medicines were primarily used at the in-patient settings and in total contribute from 8 to 10% of expenditures. That is why it would be extremely important to start implementing the reference pricing methodology at the largest healthcare institutions as that would result in a significant decrease of expenditures on the country level. As a result, voluntary introduction of cost-minimization policies could become a useful tool enabling healthcare providers and in-patient settings balance their budgets and rationalize expenditures on anticoagulation therapies.

5.3. Towards a rational use of low-molecular-weight heparins

One of the primary objectives of drug utilization research is to provide background for rational use of medicines. Design of this research was aiming to demonstrate potential benefits that pharmacoeconomic decisions modelling could suggest for all involved countries and institutions, decision makers and payees, as well as clinicians and pharmacists. Rational utilization of drugs has become a complex process, and this type of research could promote the use of different type of pharmacoeconomic analyses by decision makers working with the vast information making their informed

decision on rational use of drugs [71–73]. Rational utilization of low-molecular-weight heparins could be facilitated and implemented by promoting high quality, financially justifiable prescribing through coordinated programs and activities involving health authorities as well as medical and pharmaceutical professionals.

This research was concluded by making further recommendations to enable rational use of low-molecular-weight heparins:

(a) Country perspective

Evidences demonstrate that little is done to monitor and evaluate prescribing as well as promote rational drug use on the country level in Lithuania. Drug utilization data on dispensing collected by local authorities from various sources could be used to conduct complex pharmacoepidemiological analyses.

It is important to develop a comprehensive medicines policy with clear objectives addressing financing issues, also aiming for improvement in rational drug use and better economic efficiency. Following recommendations could be made for further discussion and considerations: (i) developing a comprehensive medicines policy to include all important areas; (ii) implementing a national program to improve prescribing and use of medicines; (iii) monitoring the implementation of newly developed policies at different levels; (iv) analyzing further concerns over significantly increasing expenses for medicines; (v) establishing requirements and processes for drug utilization research in the country.

(b) Institution perspective

An integrated system of monitoring and evaluation would provide accurate information on prescribing and would guarantee continuous flow of information at the clinical hospital in real time rather than on retrospective basis. Reviewing heparins utilization data at the clinical hospital there were major deficiencies identified in terms of safety and efficacy monitoring compared with the international heparins treatment guidelines. Those monitoring processes have to be improved aiming to ensure better treatment results. Therefore it would be highly recommended to issue local guidelines on heparins use and to review them regularly to meet local needs. Additional efforts should be taken to ensure proper supervision and follow-up on the implementation of these guidelines in daily medical practice.

(c) Clinician perspective

While it is important to understand the principles of rational drug use, these principles must be reinforced through adequate training schemes for clinicians as well as timely information on new technologies and rational prescribing. The objective would be to develop and deliver training and education services to health care professionals / clinicians about the rational

prescribing; to ensure clinicians have accurate and correct information available; and to help design and develop a prescribing information system, including timely monitoring and feedback on prescription patterns.

These practical recommendations would be useful, as according to research data there were major gaps identified analyzing low-molecular-weight heparins utilization patterns in Lithuania.

CONCLUSIONS

1. Meta-analysis study, which directly compared low-molecular-weight heparins (LMWH) in terms of safety, efficacy parameters and treatment outcomes in certain indications, was unique. None of low-molecular-weight heparins demonstrated statistically significant superiority in terms of safety and efficacy parameters as well as treatment outcomes when compared with each other. All LMWHs demonstrated superiority against un-fractionated heparin. LMWHs could be considered inter-changeable due to similar therapeutic profiles in some indications.
2. Heparins utilization study reported that in Lithuania consumption of heparins and corresponding costs were constantly increasing during the period of investigation; therefore it would be relevant to implement modern pharmacoeconomic methodologies to control / regulate costs. In order to control the future costs of heparins, it would be highly recommended to apply reference pricing methodology for this group of medicines.
3. Meta-analysis confirmed the hypothesis that low-molecular-weight heparins could be interchangeable in some treatment regimens; therefore cost-minimization methodology was selected to develop pharmaco-economic decision model. Cost-minimization model suggested that expenditures on this group of medicines could be decreased by nearly 70 percent. This model could be versatile and implemented in practice conducting pharmacoeconomic analyses for other classes of medicinal products, when similar assessment criteria are selected.
4. Analysis of pharmacoepidemiological study data confirmed that heparins prescription practices at the clinical hospital were inconsistent and insufficiently regulated. The frequency of adverse drug reactions (ADRs) was reported to dependent upon the treatment duration, thus at some instances treatment duration could be re-considered. Statistical analysis demonstrated significant correlation between treatment outcomes and ADRs, therefore implementation of consistent safety monitoring practice would be highly recommended. Pharmacoepidemiological study demonstrated current problematic situation at the clinical hospital and indicated the prospects for further research activities in this direction. Following studies could investigate the alteration of heparins prescription practices at the clinical hospital.
5. Pharmacoepidemiological study conducted at the clinical hospital revealed non-compliance of heparins safety monitoring practices with international clinical guidelines. No information was reported in pa-

tients' medical records concerning VTE risk assessment, evaluation of concomitant medications increasing the risk of bleeding and evaluation of contraindications. Safety monitoring of laboratory parameters was insufficient. Lack of local clinical guidelines was a limiting factor that had a negative impact on patients' safety monitoring and treatment outcomes.

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SUMMARY IN LITHUANIAN

ĮVADAS

Pastaraisiais metais daugelyje šalių sveikatos priežiūros išlaidos augo daug greičiau nei bendras gerovės lygis, todėl yra nuolat diskutuojama, kaip šį išlaidų augimą reikėtų kontroliuoti. Sveikatos priežiūros sistemos daugelyje šalių susiduria su panašiais sunkumais, t. y. riboti ištekliai, nuolat didėjantis lėtinėmis ligomis sergančių gyventojų skaičius, aukštos kokybės sveikatos priežiūros paslaugų paklausa. Pateikiamos kelios pagrindinės priežastys, lemiančios nuolatinį išlaidų augimą: bendras gyventojų senėjimas, brangių sveikatos priežiūros technologijų naudojimas, didėjantys gyventojų lūkesčiai dėl geresnės sveikatos priežiūros ir kt.

Sveikatos priežiūros programų ekonominis įvertinimas yra nauja disciplina, kuria susidomėjimas pastaraisiais metais gerokai išaugo. Sveikatos priežiūros ekonomikos vertinimas yra apibrėžiamas kaip lyginamosios analizės metodas, tiriantis išlaidas ir dviejų ar daugiau alternatyvių intervencijų poveikį sveikatai. Šiame apibrėžime yra svarbūs du elementai – gydymo alternatyvų palyginimas ir dviejų matmenų – išlaidų ir poveikio sveikatai palyginimas.

Darbo tikslas

Ištirti bendras mažos molekulinės masės heparinų preparatų vartojimo tendencijas Lietuvoje ir suformuluoti farmakoekonominių sprendimų modelį mokėtojams, kuris padėtų racionaliau naudoti lėšas šios grupės vaistiniams preparatams.

Darbo uždaviniai

- atlikti heparinų preparatų meta-analizę, palyginant jų efektyvumo ir saugumo parametrus bei gydymo baigtis;
- atlikti heparinų preparatų ilgalaikio suvartojimo Lietuvoje farmakoepidemiologinį tyrimą;
- suformuluoti farmakoekonominį kaštų mažinimo sprendimų modelį mažos molekulinės masės heparinų preparatų grupei, remiantis referentinės kainos metodika;
- ištirti heparinų preparatų skyrimo tendencijas antrinio lygio klinikinėje ligoninėje ir palyginti heparinų preparatų skyrimo atitikimą tarptautinėms gairėms.

Darbo svarba ir naujumas

Farmakoekonominių sprendimų modeliavimas yra naujas ir efektyvus įrankis, plačiai naudojamas įvairių šalių sprendimus priimančių asmenų ir atitinkamų sveikatos priežiūros institucijų, priimant sprendimus dėl naujų ir esamų gydymo būdų.

Farmakoekonominių sprendimų modeliai gali būti naudingi įrankiai, atliekant išlaidų mažinimo, išlaidų efektyvumo ir kaštų naudingumo analizes bet kuriame vaistinio preparato tyrimo, vystymo ir prekybos etape.

Finansiniai sprendimai yra reikšmingi šiuolaikinės medicinos ir farmacijos aplinkoje. Todėl farmakoekonominės metodikos, leidžiančios pasirinkti racionaliausią sprendimą medicininiu ir finansiniu aspektu, turėtų būti plačiai naudojamos, siekiant subalansuoti sveikatos priežiūros biudžetus šalyse.

Vaistinių preparatų suvartojimo mokslinių tyrimų pagrindinis tikslas yra skatinti racionalų vaistų vartojimą populiacijoje / visuomenėje. Pirmiausia reikia išsiaiškinti, kaip vaistiniai preparatai yra skiriami ir naudojami. Po to, surikus ir apibendrinus šią informaciją, svarbu inicijuoti diskusiją apie racionalų vaistų vartojimą, o vėliau pasiūlyti priemonių, kurios galėtų pakeisti vaistinių preparatų skyrimo įpročius. Informacija apie praeityje fiksuotus paskyrimus yra labai svarbi atliekant tolesnius tyrimus ir taikant farkamoekonominių sprendimų metodikas.

Heparinų preparatai yra dažnai skiriami hospitalizuotiems pacientams, esant įvairioms indikacijoms, profilaktikos ir gydymo tikslais, jiems taip pat yra numatytas svarbus vaidmuo daugelyje gydymo schemų. Dėl šių priežasčių racionalus heparinų preparatų skyrimas tapo svarbia daugelio sveikatos sutrikimų valdymo dalimi. Tinkamas ir racionalus heparinų preparatų skyrimas, turėtų teigiamos įtakos gydymo rezultatams, taip pat sumažintų nepageidaujamų reakcijų dažnį. Todėl galimai sumažėtų tiesioginiai heparinų preparatų kaštai, ir atitinkamai mažėtų išlaidos susijusios su pacientų hospitalizavimu sveikatos priežiūros įstaigose.

Šiuo metu farmakoekonominių sprendimų modeliavimas nėra naudojamas sveikatos priežiūros institucijose Lietuvoje. Šio darbo pasiūlyti modeliai galėtų būti taikomi praktikoje, norint geriau kontroliuoti sveikatos priežiūros įstaigų išlaidas mažos molekulinės masės heparinų preparatams.

Darbo naujumas – pasiūlyti farmakoekonominių sprendimų modeliai yra nauji ir dar nėra plačiai taikomi sveikatos priežiūros institucijose sprendimams dėl išlaidų vaistiniams preparatams pagrįsti.

Darbo svarba – pasinaudojus siūlomais metodais būtų galima racionaliau ir efektyviau panaudoti lėšas, skirtas vaistinių preparatų įsigijimui sveikatos priežiūros įstaigose.

REZULTATAI

Heparinų preparatų meta-analizės rezultatai

Atliekant meta-analizę buvo vertinamas mažos molekulinės masės heparinų preparatų (Bemiparino, Enoksaparino, Dalteparino, Nadroparino, Tinzaparino) ir nefrakcionuoto heparino efektyvumas ir saugumas bei gydymo baigtys. Pagal šiuos parametrus, visi MMMH (mažos molekulinės masės heparinų preparatai) buvo pranašesni prieš NFH. Atlikus mažos molekulinės masės heparinų preparatų palyginimą, nebuvo nustatytas vienas preparatas, kuris būtų statistiškai reikšmingai pranašesnis prieš kitus tos grupės preparatus. Atsižvelgiant į atliktos meta-analizės rezultatus, mažos molekulinės masės heparinų preparatai gali būti laikomi tarpusavyje pakeičiamais preparatais dėl jų farmakologinių savybių ir analogiškų efektyvumo, saugumo rodiklių bei tikėtinų gydymo baigčių. Atliktos meta-analizės rezultatais buvo remiamasi, pasirenkant atitinkamą farmakoekonominio modeliavimo metodiką.

Heparinų preparatų panaudojimo tyrimas Lietuvoje

Heparinų preparatų panaudojimas Lietuvoje didėjo nuo 40,12 ADD / 1000 lovadienių 2003 m. iki 309,60 ADD / 1000 lovadienių 2011 m. Bendri heparinų preparatų kaštai Lietuvoje didėjo nuo 1088 tūkst. LTL 2003 m. iki 10284 tūkst. LTL 2011 m., t. y. daugiau nei dešimt kartų per devynerių metų laikotarpį. Heparinų preparatų kaštai šalyje augo reikšmingai greičiau nei suvartojimo rodikliai, todėl buvo svarbu nustatyti faktorius, kurie lėmė tokį greitą kaštų augimą, pralenkusį suvartojimo rodiklius.

Manoma, kad heparinų preparatų panaudojimo augimą lėmė kelios priežastys, t. y. platesnis heparinų preparatų indikacijų spektras, dažnesnis skyrimas pacientams profilaktikos ir gydymo tikslais, ilgėjantis heparinų preparatų sąrašas ir didėjantis jų pasirinkimas, informacijos sklaida apie heparinų preparatų naudą ir kt.

Heparinų preparatų farmakoekonominis tyrimas

Atlikus farmakoekonominius skaičiavimus buvo nustatyta, jog Dalteparino ADD kaina buvo mažiausias heparinų preparatų grupėje. Pasirenkant referentinę kainą 2,75 Lt (mažiausia Dalteparino vienos ADD kaina), iš viso būtų galima racionaliau panaudoti 3,218–4,679 tūkst. Lt kasmet (pagal 2008–2011 m. duomenis). 2008–2011 metais išlaidos heparinų grupės preparatams būtų sumažintos 59,82–69,59 proc., jei būtų buvęs pritaikytas kaštų mažinimo modelis. Kaštų mažinimo metodikos taikymas reikšmingai

prisidėtų prie tinkamo ir efektyvaus išlaidų mažos molekulinės masės heparinų grupės preparatams valdymo.

Farmakoepidemiologinio tyrimo rezultatai

Atliekant farmakoepidemiologinį tyrimą vidutinėje antrinio lygio ligoninėje šalyje, buvo įvertintos 339 pacientų ligos istorijos. Tyrimas buvo atliekamas siekiant ištirti heparinų preparatų skyrimo tendencijas vidutinėje antrinio lygio klinikinėje ligoninėje šalyje.

Šie heparinų preparatai buvo panaudoti antrinio lygio klinikinėje ligoninėje tyrimo metu: Enoksaparinas (*Clexane*), Nadroparinas (*Fraxiparin*), Dalteparinas (*Fragmin*) ir Bemiparinas (*Zibor*). Dažniausiai buvo skiriamas Dalteparinas, (69,0 proc., n = 236), antroje ir trečioje vietose buvo Nadroparinas (16,2 proc, n = 55) ir Bemiparinas (7,1 proc, n = 24). Kaip buvo nustatyta tyrimo metu, dažniausiai heparinų preparatai buvo panaudoti VT profilaktikai chirurginių intervencijų metu, 39,8 proc. (n = 135) ir nestabilios krūtinės anginos arba miokardo infarkto gydymui, 49,0 proc. (n = 166). Kitų indikacijų pacientų skaičiai buvo reikšmingai mažesni: giliųjų venų trombozė – 4,1 proc. (n = 14) ir profilaktika mažai judantiems pacientams 6,5 proc. (n = 22).

Santykinių kontraindikacijų dažnis buvo 69,0 proc. (n = 234). Dažniausia santykinė kontraindikacija buvo senyvas amžiaus, t.y. heparinų preparatai buvo skiriami vyresniems nei 65 metų amžiaus pacientams.

90,27 proc. visų gydymo rezultatų buvo vertinami teigiamai (n = 306), t.y. šie pacientai pasveiko. Iš viso 9,14 proc. gydymo rezultatų buvo neigiami, t.y. mirtis (6,49 proc., n = 22), pacientai dėl įvairių priežasčių nepasveiko (1,77 proc., n = 6), pasveiko su pasekmėmis (1,47 proc., n = 5). Dažniausios mirties priežastys buvo giliųjų venų trombozė ar plaučių embolija ir įvairūs širdies ir kraujagyslių sistemos sutrikimai.

Statistinė analizė neparodė jokio ryšio tarp heparinų preparato pavadinimo ir gydymo rezultatų (r_s = -0,043, $\chi 2$ = 0,158, p <0,663). Galima daryti išvadą, kad heparinų preparato pavadinimas nebuvo vienas iš kintamųjų, kuris galimai turėjo tiesioginės įtakos gydymo rezultatams.

Bendras nepageidaujamų reakcijų, nurodytų pacientų ligos istorijose, dažnis buvo 13,57 proc. (n = 46). Dažniausios nepageidaujamos reakcijos buvo trombocitopenija ir kraujavimas. Šie skaičiai nesiskyrė nuo nepageidaujamų reakcijos dažnio, nurodyto gamintojų preparatų charakteristikų santraukose.

Farmakoepidemiologinio tyrimo metu buvo vertinamas heparinų preparatų skyrimo atitikimas *NHS Devon'o* klinikinėms rekomendacijos ir gairėms (Mažos molekulinės masės heparinų preparatai – naudojimas ir prie-

žiūra bendruomenės ligoninėse). Tyrimo duomenys buvo dar kartą įvertinti, siekiant nustatyti, kaip heparinų preparatų skyrimas antrinio lygio klinikinėje ligoninėje atitiko tarptautinių gairių nuostatas.

Atliekant farmakoepidemiologinį tyrimą, pacientų ligos istorijose nebuvo rasta jokios informacijos, susijusios su venų tromboembolijos rizikos vertinimu, kartu vartojamų vaistinių preparatų, didinančių kraujavimo riziką vertinimu ir kontraindikacijų rizikos vertinimu.

Svarbu pabrėžti, kad laboratorinių tyrimų rezultatų stebėjimas turėtų būti atliekamas prieš skiriant heparinų preparatus pacientams, tačiau atitinkami laboratoriniai tyrimai nebuvo atlikti antrinio lygio klinikinėje ligoninėje 60,77 proc. visų atvejų (n = 206). Remiantis tyrimo duomenimis, laboratorinių tyrimų rezultatai buvo stebimi 39,23 proc. visų atveju (n = 133). Taip pat labai skyrėsi atliktų laboratorinių tyrimų apimtis, todėl visi reikiami laboratoriniai tyrimai buvo atlikti gerokai mažesniam pacientų skaičiui.

Pagal tarptautines rekomendacijas, laboratorinių tyrimų rezultatai turėtų būti stebimi naudojant heparinų preparatus hospitalizacijos metu. Remiantis tyrimo duomenimis, laboratorinių tyrimų rezultatai buvo stebimi 53,98 procentų visų atveju (n = 183).

Atsižvelgiant į šiuos rezultatus, rekomenduojama dažniau atlikti ir stebėti atitinkamus laboratorinius tyrimus pacientams, vartojantiems heparinų preparatus profilaktikos ar gydymo tikslais.

Atsižvelgiant į farmakoepidemiologinio tyrimo rezultatus, buvo suformuluotas farmakoekonominių sprendimų modelis antrinio lygio klinikinės ligoninės heparinų kaštų mažinimo galimybėms įvertinti. Remiantis išlaidų mažinimo modeliu, šios metodikos taikymas leistų sumažinti išlaidas heparinų preparatams 29,20 proc.

IŠVADOS

1. Meta-analizės tyrimas, kurio metu buvo tiesiogiai tarpusavyje palyginti mažos molekulinės masės heparinų preparatai pagal jų saugumo ir efektyvumo parametrus bei gydymo rezultatus, yra originalus. Nei vienas mažos molekulinės masės heparinų preparatas nebuvo statistiškai reikšmingai pranašesnis pagal saugumo ir efektyvumo parametrus bei gydymo rezultatus, atlikus tiesioginį šios grupės preparatų palyginimą. Meta-analizės rezultatai parodė MMMH pranašumą prieš NFH. MMMH gali būti tarpusavyje pakeičiami dėl analogiškų terapinių savybių tam tikrose indikacijose.
2. Atlikus heparinų preparatų suvartojimo tyrimą, buvo nustatyta, jos šių preparatų panaudojimas ir atitinkamos išlaidos tiriamuoju laiko-

tarpiu Lietuvoje nuolat didėjo, todėl būtų aktualu taikyti šiuolaikines farmakoekonomines išlaidų kontroliavimo / reguliavimo metodikas. Siekiant ateityje kontroliuoti išlaidas heparinų preparatams, galėtų būti rekomenduojama šiai vaistinių preparatų grupei taikyti referentinių kainų metodiką.

3. Meta-analizė patvirtino hipotezę, jog mažos molekulinės masės heparinų preparatai gali būti tarpusavyje pakeičiami tam tikrose gydymo schemose, todėl buvo pasirinkta kaštų mažinimo metodika farmakoekonominiam modeliui sukurti. Kaštų mažinimo modelio taikymas leistų sumažinti išlaidas šios grupės preparatams beveik 70 procentų. Šis modelis galėtų būti universalus ir pritaikomas praktikoje vertinant kitų vaistinių preparatų grupių panaudojimo kaštų racionalumą, pasirenkant analogiškus vertinimo kriterijus.
4. Farmakoepidemiologinio tyrimo rezultatai atskleidė, jog heparinų preparatų skyrimo praktika klinikinėje ligoninėje buvo nenuosekli ir nepakankamai reglamentuota. Heparinų preparatų vartojimo trukmė buvo svarbus veiksnys, turėjęs tiesioginį poveikį nepageidaujamų reakcijų dažniui, todėl gydymo trukmė turėtų būti vertinama atidžiau. Statistinė analizė parodė reikšmingą ryšį tarp gydymo rezultatų ir nepageidaujamų reakcijų dažnio, todėl rekomenduojama nuosekliau vykdyti saugumo parametrų stebėjimą. Šis tyrimas atskleidė esamą probleminę situaciją klinikinėje ligoninėje ir nurodė tolesnės mokslinės veiklos perspektyvas šia kryptimi. Tęstinių tyrimų metu būtų galima įvertinti, kaip keičiasi heparinų preparatų skyrimo praktika klinikinėje ligoninėje.
5. Farmakoepidemiologinio tyrimo rezultatai parodė, kad heparinų preparatų saugumo parametrų stebėjimo praktika ligoninėje neatitiko tarptautinių heparinų preparatų skyrimo rekomendacijų. Atliekant tyrimą, pacientų ligos istorijose nebuvo raportuota, jog buvo atliekamas venų tromboembolijos rizikos vertinimas, gretutinių vaistinių preparatų, didinančių kraujavimo riziką, vertinimas, galimos kontraindikacijos. Pacientų laboratorinių saugumo parametrų stebėjimas buvo atliekamas nepakankama apimtimi. Heparinų preparatų skyrimo gairių nebuvimas yra ribojantis veiksnys, kuris daro neigiamą poveikį pacientų saugumo stebėjimui ir gydymo rezultatams.

SUPPLEMENTS

Supplement 1

Example of Subject Identification Form

Subject Initials ___ ___ ___ Age ___ ___ Gender □ Female □ Male	Medical record No. _____

Currect diagnosis	_____
Treatment indication(s)	□ DVT (with or without Pulmonary Embolism) □ Prophylaxis of VT in orthopedic or general surgery □ Prophylaxis of VT for bedridden patients □ Prophylaxis of extracorporeal thrombosis at the time of the dialysis □ Treatment of UCAD or non Q-wave MI (together with aspirin) □ To decrease coagulation after the fibrinolytical treatment with streptokinase □ Other _____

Duration of hospitalization	___ ___ (days)
Duration of anticoagulation therapy	___ ___ (days)

Type of anticoagulation therapy	Drug name _____ Posology_____ Route _____ Frequency _____

Treatment outcomes	□ Recovered □ Recovered with sequel (*Indicate reason* _____) □ Not recovered (*Indicate reason* _____) □ Death (*Indicate reason* _____)

Efficacy Assessment	Safety Assessment
Was the treatment effective? □ Yes □ No If *No*, please, describe _____ _____	Adverse drug reactions reported: □ None □ Allergic reactions □ Thrombocytopenia □ Haemorrhages □ Major bleeding □ Local reactions □ Other_____
Monitoring of safety and efficacy criteria: □ Yes □ No If *Yes*, please, describe _____ _____	Follow-up of adverse drug reactions _____ _____ _____

Was LMWH used in patients with relative contraindications or other situations cautioned? □ Yes □ No *If Yes, identify the contraindication below* □ Curative treatment in patients with mild-to-moderate renal insufficiency (30–60 mL/min). □ Thromboprophylaxis in elderly patients (aged >65 years). □ Patients with cachexia (weight <40 kg) and having a duration of treatment of over 10 days. □ Co-prescription with drugs that increase the risk of bleeding.

Additional information		
Weight __ __ __ kg	BMI __ __ , __	Vital signs BP _____/___mm Hg Pulse___

Relevant medical history	Concomitant medications
1. 2. 3. 4.	1. 2. 3. 4.

Supplement 2

Kaunas Regional Biomedical Research Ethics Committee approval to conduct a pharmacoepidemiological study (document in Lithuanian language, dated 08 June 2009, No. BE-2-9).

KAUNO REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
KMUK Eivenių 2, Centrinis korpusas 71 kab., 50009 Kaunas, tel. +370 37 326168; faks. +370 37 326901, e-mail: **cmeinfo@kmu.lt**

LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2009-06-08 Nr. BE-2- 9

Biomedicininio tyrimo pavadinimas: **„Numatomas stebėjimo tyrimas Kauno 2-ojoje klinikinėje ligoninėje hospitalizuotiems pacientams paskiriamų heparinų vartojimui ir saugumui įvertinti“**	
Pagrindinis tyrėjas:	**Doc. med.m.dr. Edmundas Kaduševičius**
Biomedicininio tyrimo vieta: Įstaigos pavadinimas: Adresas:	**Kauno 2-oji klinikinė ligoninė** **Josvainių g. 2, LT-47144** **Kaunas**

Išvada:
Kauno regioninio biomedicininių tyrimų etikos komiteto posėdžio, įvykusio **2009m. birželio 2 d.** (protokolo Nr. 46/2009) sprendimu pritarta biomedicininio tyrimo vykdymui.

Mokslinio eksperimento vykdytojai įsipareigoja: (1) nedelsiant informuoti Kauno Regioninį biomedicininių Tyrimų Etikos komitetą apie visus nenumatytus atvejus, susijusius su studijos vykdymu, (2) iki sausio 15 dienos – pateikti metinį studijos vykdymo apibendrinimą bei, (3) per mėnesį po studijos užbaigimo, pateikti galutinį pranešimą apie eksperimentą.

Kauno regioninio biomedicininių tyrimų etikos komiteto nariai			
1.	Doc. Irena Marchertienė	anesteziologija	taip
2.	Doc. Romaldas Mačiulaitis	klinikinė farmakologija	ne
3.	Prof. Nijolė Dalia Bakšienė	pediatrija	taip
4.	Prof. Irayda Jakušovaitė	filosofija	taip
5.	Dr.Eimantas Peičius	filosofija	taip
6.	Laima Vasiliauskaitė	psichoterapija	taip
7.	Gintaras Česnauskas	chirurgija	ne
8.	Zelmanas Šapiro	terapija	ne
9.	Jurgita Laurinaitytė	bioteisė	taip

Kauno regioninis biomedicininių tyrimų etikos komitetas dirba vadovaudamasis etikos principais nustatytais biomedicininių tyrimų Etikos įstatyme, Helsinkio deklaracijoje, vaistų tyrinėjimo Geros klinikinės praktikos taisyklėmis.

Pirmininkė Irena Marchertienė

Supplement 3

State Data Protection Inspectorate permission to collect personal date for pharmacoepidemiological study purpose (document in Lithuanian language, dated 19 June 2009, No. 2R-1570 (2.6)).

VALSTYBINĖ DUOMENŲ APSAUGOS INSPEKCIJA

Všį Kauno 2-ajai klinikinei ligoninei
Josvainių g. 2 , LT-47144 kaunas
(registruotu laišku)

SPRENDIMAS
DĖL LEIDIMO VŠĮ KAUNO 2-AJAI KLINIKINEI LIGONINEI ATLIKTI ASMENS DUOMENŲ TVARKYMO VEIKSMUS

2009 m. birželio 19 d. Nr. 2R-1570 (2.6)
Vilnius

Valstybinė duomenų apsaugos inspekcija, išnagrinėjusi Všį Kauno 2-osios klinikinės ligoninės 2009 m. birželio 3 d. Pranešimą dėl išankstinės patikros (toliau – Pranešimas) (Inspekcijoje gauta 2009-06-15, reg. Nr. 1R-1532)

n u s t a t ė,

kad Všį Kauno 2-oji klinikinė ligoninė Pranešime nurodytus asmens duomenis tvarkys teisėtai ir nepažeidžiant Lietuvos Respublikos asmens duomenų teisinės apsaugos įstatyme (Žin., 1996, Nr. 63-1497; 2008, Nr. 22-804) nustatytų asmens duomenų tvarkymo reikalavimų ir duomenų subjektų teisių, bei įgyvendins tinkamas organizacines ir technines duomenų saugumo priemones.

Valstybinė duomenų apsaugos inspekcija, vadovaudamasi Lietuvos Respublikos asmens duomenų teisinės apsaugos įstatymo 33 straipsniu, Valstybinės duomenų apsaugos inspekcijos direktoriaus 2006 m. vasario 2 d. įsakymu Nr. 1T-6 (Žin., 2006, Nr. 18-653; 2009, Nr. 11-447) patvirtintų Išankstinės patikros atlikimo taisyklių 11 ir 18.1 punktais,

n u s p r e n d ž i a

Všį Kauno 2-ajai klinikinei ligoninei išduoti leidimą atlikti Pranešime dėl išankstinės patikros nurodytų nuasmenintų asmens duomenų mokslinio biomedicininio tyrimo tikslais be duomenų subjekto sutikimo, tvarkymo veiksmus.

Direktorius dr. Algirdas Kunčinas

V. Perednienė, tel. (8 5) 219 7279, el.p. v.perednienе@ada.lt

Z. Medutis, tel. 2713028, el. p. z.medutis@ada.lt

Valstybės biudžetinė įstaiga
A. Juozapavičiaus g. 6 / Slucko g. 2,
LT-09310 Vilnius

Tel. (8 5) 279 1445
Faks. (8 5) 261 9494
El. p. ada@ada.lt

Duomenys kaupiami ir saugomi
Juridinių asmenų registre
Kodas 188607912

Table 1. *Results of studies comparing low-molecular-weight heparins: Enoxaparin, Dalteparin, Nadroparin and Tinzaparin (data used for meta-analysis)*

Authors	No. of patients	Evaluated endpoints	Number of endpoints occurred	Number of endpoints occurred
Chiou-Tan FY, et al. 2003	n=95	DVT, Bleeding	Enoxaparin group=4	Dalteparin group=4
Montalescot G, et al. 2003	n=94	Incidence of the composite clinical efficacy	Enoxaparin group=6	Dalteparin group=9
Ozdemir M, et al. 2002	n=142	MI, Angina recurrence, Overall endpoint, Major bleeding	Enoxaparin group=39	Dalteparin group=48
Shafiq N, et al. 2006	n=100	Cardiovascular death, Myocardial Infarction, Recurrent angina, need for intervention, Silent ischemia	Enoxaparin group=12	Dalteparin group=14
Simonneau G, et al. 2006	n=950	DVT, PE, Major bleeding	Nadroparin group=124	Enoxaparin group=168
Okmen E, et al. 2004	n=68	MI, Recurrent angina, Death, Urgent revascularization, MACE	Nadroparin group=5	Enoxaparin group=5
Shafiq N, et al. 2006	n=100	Cardiovascular death, Myocardial Infarction, Recurrent angina, need for intervention, Silent ischemia	Nadroparin group=15	Enoxaparin group=12
Bounameaux H, et al. 1993	n=194	DVT	Dalteparin group=30	Nadroparin group=15
Shafiq N, et al. 2006	n=100	Cardiovascular death, Myocardial Infarction, Recurrent angina, need for intervention, Silent ischemia	Dalteparin group=14	Nadroparin group=15
Kuczka K, et al. 2009 Mahé I, et al. 2007 Katsouras C, et al. 2005	n=64 n=45 n=438	Bleeding events Accumulation factor Death, MI, or recurrent angina	Tinzaparin group=2 Tinzaparin group=1.22 Tinzaparin group=56	Enoxaparin group=4 Enoxaparin group=1.05 Enoxaparin group=97

Table 2. *Results of studies comparing UFH and low-molecular-weight heparins Nadroparin and Dalteparin (data used for meta-analysis)*

Authors	No. of patients	Evaluated endpoints	No of endpoints	No of endpoints
Gurfinkel EP, et al. 1995	n=219	Recurrent angina, Nonfatal MI, Urgent revalscularization	UFH group=59	Nadroparin group=24
Sirenko IuN, et al. 1994	n=30	Hemorrhagic complications	UFH group=7	Nadroparin group=1
Burotto M, et al. 2004	n=720	Recurrent thromboembolic event, Major bleeding, overall mortality	UFH group=29	Nadroparin group=27
Egger B, et al. 2000	n=1190	DVT, PE	UFH group=1	Nadroparin group=8
Belcaro, et al. 1999	n=294	DVT	UFH group=9	Nadroparin group=9
FRAX.I.S. Study Group, 1999	n=3468	Cardiac death, MI, Recurrent angina, Major hemorrhages	UFH group=60	Nadroparin group=28
Goday I, et al. 1998	n=70	Recorrent angina, Urgent revascularization	UFH group=23	Nadroparin group=9
Koopman MM, et al. 1996	n=400	Recurrent thromboembolism, Major bleeding	UFH group=21	Nadroparin group=15
The European Fraxiparin Study (EFS) Group, 1998	n=1896	Venous thromboembolism (VT), priximal VT, PE	UFH group=60	Nadroparin group=33
Stephenson MD, et al. 2004	n=26	Successful pregnancy	UFH group=4	Dalteparin group=9
Hong YJ, et al. 2003	n=180	Accute MI, Incidence of re-stenosis, Vessel revascularization	UFH group=59	Dalteparin group=47
Wallentin L, et al. 2003	n=439	Thrombolysis in MI	UFH group=262	Dalteparin group=291
Montalescot G, et al. 2003	n=95	Incidence of the composite clinical efficacy	UFH group=13	Dalteparin group=9
Moreno-Palomares JJ, et al. 2001	n=32	Clinical effectiveness, side effects	UFH group = Not statistically significant	Dalteparingroup = Not statistically significant

Table 2. *Continued*

Authors	No. of patients	Evaluated endpoints	No of endpoints	No of endpoints
Hafeli R, et al. 2001	n=138	Complication rate	UFH group=5	Dalteparin group=4
Holmstrom M, et al. 1999	n=265	Recurrent VT	UFH group=20	Dalteparin group=53
Ward B, et al. 1998	n=552	Thromboembolic events	UFH group=2	Dalteparin group=5
Klein W, et al. 1997	n=1482	Death, MI, recurrence of angina	UFH group=53	Dalteparin group=69
Luomanmaki K, et al. 1996	n=330	PE, Bleeding	UFH group=6	Dalteparin group=7
Lindmarker P, et al. 1994	n=204	VT	UFH group=3	Dalteparin group=5
Hartl P, et al. 1990	n=250	Thromboembolism, Blood transfusion	UFH group=22	Dalteparin group=12

Table 3. *Results of studies comparing UFH and low-molecular-weight heparins Enoxaparin and Tinzaparin (data used for meta-analysis)*

Authors	No. of patients	Evaluated endpoints	Number of end-points occurred	Number of endpoints occurred
Antman EM, et al. 2006	n=20506	Death, recurrent MI, Non-fatal reinfarction	UFH group=2461	Enoxaparin group=2030
Montalescot G, et al. 2003	n=93	Incidence of the composite clinical efficacy	UFH group=13	Enoxaparin group=6
Fitchett DH, et al. 2006	n=669	Death, MI	UFH group=49	Enoxaparin group=30
Chong BH, et al. 2005	n=298	DVT, PE	UFH group=14	Enoxaparin group=4
Madan M, et al. 2005	n=200	MI, Bleeding	UFH group=24	Enoxaparin group=13
de Lemos JA, et al. 2004	n=1778	Death, MI, refractory ischemia, Bleeding	UFH group=108	Enoxaparin group=82
Cohen M, et al. 2003	n=1224	Efficacy, Major hemorrhages	UFH group=114	Enoxaparin group=115

Table 3. *Continued*

Authors	No. of patients	Evaluated endpoints	Number of end-points occurred	Number of endpoints occurred
Spinal Cord Injury Thromboprophy-laxis Investigators, 2003	n=107	VT, PE, Major bleeding	UFH group=39	Enoxaparin group=46
Spinal Cord Injury Thromboprophy-laxis Investigators, 2003	n=119	VTE	UFH group=13	Enoxaparin group=5
Goodman SG, et al. 2003	n=746	Death, MI, Major bleeding, Ischemia	UFH group=145	Enoxaparin group=78
Findik S, et al. 2002	n=59	VTE, Major bleeding	UFH group=3	Enoxaparin group=1
Cohen M, et al. 2002	n=525	Bleeding, Death, MI, Refractory ichemia	UFH group=38	Enoxaparin group=42
Ross AM, et al. 2001	n=400	Thrombolysis in MI	UFH group=150	Enoxaparin group=160
Bozovich GE, et al. 2000	n=3831	Cardiac events, Major bleeding	UFH group=141	Enoxaparin group=120
Goodman SG, et al. 2000	n=3171	Death, MI, Coronary revascularization	UFH group=1428	Enoxaparin group=1315
ENOXACAN study group, 1997	n=631	Thromboembolic complications	UFH group=57	Enoxaparin group=46
Colwell CW, et al. 1995	n=453	DVT, Major hemorrhages	UFH group=80	Enoxaparin group=59
Malo J, et al. 2010	n=1544	Need for thrombolytic catheter lock use	UFH group=49	Tinzaparin group=23
Sabry A, et al. 2009	n=23	Clinical clotting grade	UFH group=2	Tinzaparin group=1
Bramham K, et al. 2008	n=108	Haemorrhages	UFH group=4	Tinzaparin group=0
Daskalopoulos ME, et al. 2005	n=108	Mortality, DVT, PE, HIT, major bleedin	UFH group=17	Tinzaparin group=7

International Journal of Technology Assessment in Health Care, **26:3** (2010), 272–279.

doi:10.1017/S0266462310000310

Low-molecular-weight heparins: Pharmacoeconomic decision modeling based on meta-analysis data

Edmundas Kadusevicius
Kaunas Medical University and Kaunas Medical University Hospital

Gabriele Kildonaviciute
Kaunas Medical University and Quintiles, *JSC*

Birute Varanaviciene
Kaunas Medical University Hospital

Danguole Jankauskiene
Mykolas Romeris University

Objectives: The aim of this study was to compare efficacy, safety, and consumption of low-molecular-weight heparins with unfractionated heparin, and to develop a pharmacoeconomic decision model based on meta-analysis data.
Methods: Review and meta-analysis were performed of published randomized control trials directly comparing the safety and efficacy of low-molecular-weight heparins (LMWHs)—that is, nadroparin, enoxaparin, and dalteparin—and unfractionated heparin (UFH) was performed by two reviewers using inclusion/exclusion criteria based on the research objectives. The value of fixed effects and random effects odds ratio (95 percent confidence interval) was calculated for each trial for the composite end point. Subsequently, a pharmacoeconomic decision modeling based on reference pricing methodology was implemented.
Results: In comparison to UFH, all LMWHs have independently demonstrated greater safety and effectiveness. None of the LMWHs demonstrated a significant superiority over each other; therefore, the group of LMWHs was interchangeable and suitable for cost minimization analysis and reference price implementation. Being the least expensive option, dalteparin single DDD price was set as the reference. Introduction of reference pricing for LMWHs would decrease the total expenditure on LMWHs of approximately 30 percent and would result in total savings of 1.830–2.070 thousand LTL in the country of Lithuania (approximately 0.8 million USD) per year.
Conclusions: The meta-analysis results of LMWHs could be used to support a policy on reference-based pricing and pharmacoeconomic decision modeling in healthcare institutions, which would allow a decrease in healthcare expenditures.

Keywords: Meta-analysis, Low-molecular-weight heparins (LMWHs), Unfractionated heparin (UFH), Reference pricing, Cost-minimization

Unfractionated heparin and low-molecular-weight heparins belong to B01AB ATC class of antithrombotic compounds used as anticoagulants in various indications, such as thrombosis and thrombosis prophylaxis (24).

As the single most expensive aspect of medical care, drugs have become the fastest growing component of healthcare costs: expenditures on medications set to outstrip hospital costs in many healthcare systems. Drug expenditure growth should continue outpacing the growth in overall healthcare expenditures and the growth in economy (2,27,35).

As per statistics, the annual global LMWHs market amounts to approximately 3.5 billion USD. Apparently, the antithrombotic market is expected to peak at just over 20 billion USD in 2012 across the seven major markets, including United States, France, Germany, Italy, Spain, United Kingdom, and Japan. In the meantime, the increase in expenditures for low-molecular-weight heparins is continuing. As yet, there are no breakthrough antithrombotic drugs in the pipeline that will threaten the main indications for LMWHs (16,27).

In Lithuania, utilization of LMWHs increased by 29.9 percent from approximately 789 thousand DDDs in 2007 to more than 1,025 thousand DDDs in 2008. The growth of utilization was consequently followed by the increase in expenditures; therefore, the total revenue from LMWHs in Lithuania increased by 23.6 percent, that is, from 5,723 thousand Lithuanian litas (LTL) in 2007 to 7,072 thousand LTL in 2008.

At Kaunas Medical University Hospital (KMUH)—the largest healthcare provider in Lithuania (40)—almost 8 percent of total medication expenditures are allocated to heparins annually. These costs represent approximately 15 percent of the total revenue from LMWHs in Lithuania. Utilization of LMWHs in KMUH increased more than fivefold during the 7-year period 2001–07 from 46.6 DDDs/1,000 hospitalization days in 2001 to 2,46.0 DDDs/1,000 hospitalization days in 2007. Hence, the expenditures also grew by 220.8 percent from more than 300 thousand LTL in 2001 to almost 1,000 thousand LTL in 2007.

The majority of low-molecular-weight heparins are being administered in inpatient settings. These institutions are particularly sensitive to the increase of expenditures and utilization; therefore, implementation and use of pharmacoeconomic analyses would enable hospitals to balance their budgets.

The key objective of our work was to perform pharmacoeconomic analysis for low-molecular-weight heparins based on their efficacy, safety, and treatment outcomes data to control the expenditures on LMWHs drug therapies.

In Lithuania, this type of study was original and the results would have direct implications for drug related decision making in healthcare institutions. It would enable all healthcare providers to rationalize the use of financial resources for heparins in considering choices among alternative use of economic resources. That could yield cost savings without compromising clinical outcomes or patient safety.

METHODS

Meta-analysis

Literature Search Strategy. The PubMed.gov database was used to conduct a comprehensive literature search for randomized controlled trials comparing safety and efficacy values of four different low-molecular-weight heparins with unfractionated heparin. The research was conducted by two independent reviewers who used inclusion/exclusion criteria based on objectives of the research. Keywords for the search were *Enoxaparin, Dalteparin, Nadroparin, LMWHs, unfractionated heparin (UFH)*, and different combinations of those words (e.g. *Dalteparin and Nadroparin, etc.*). They were defined as keywords and text words.

The goal was to evaluate the overall superiority of heparins in comparison with each other.

Inclusion and Exclusion Criteria. Articles published in English between January 1990 and January 2008 were included in the meta-analysis. Each article had to contain information about randomized control trial methodology and results with direct comparison of two heparins in the treatment of the following conditions or diseases like: deep venous thrombosis (DVT), pulmonary embolism (PE), recurrent angina (RA), myocardial infarction (nonfatal MI, acute MI, and re-infarction), revascularization, hemorrhagic complications (e.g. major bleeding), and death. Meta-analysis was performed to assess the overall effect and safety of different low molecular weight heparins in comparison with unfractionated heparin.

Statistical Analysis

All meta-analyses were performed on studies that compared two low-molecular weight heparins or LMWH with unfractionated heparin. Under the fixed effects model, it was assumed that all studies come from a common population and that the effect size (odds ratio) was not significantly different among the different trials. This assumption was tested by the "Heterogeneity test." If this test yielded a low p value ($p < .05$), then the fixed effects model might have been invalid. In this case, the random effects model might have been more appropriate, in which both the random variation within the studies and the variation between the different studies were incorporated.

A statistical software *MedCalc* was used for all calculations. MedCalc used the Mantel-Haenszel method for calculating the weighted summary odds ratio under the fixed effects model. Next, the heterogeneity statistic was incorporated to calculate the summary odds ratio under the random effects model. The program listed the results of the individual studies: several positive cases, the total number of cases,

Table 1. Data from the Accomplished Meta-analysis Comparing LMWHs with Each Other, and UFH

Compared compounds	No. of studies	No. of subjects involved	End points occurred to the no. of subjects involved	Odds (fixed effects)	95% CI	Odds (random effect)	95% CI
UFH *vs.* dalteparin	12	3993	547/1846 (29.63%) *vs.* 603/2147 (28.09%)	1.024	0.750–1.397	1.141	0.952–1.368
UFH *vs.* nadroparin	9	8273	269/4123 (6.52%) *vs.* 154/4150 (3.71%)	0.481	0.285–0.812	0.487	0.393–0.604
UFH *vs.* enoxaparin	17	34801	4867/17454 (27.88%) *vs.* 3238/17347 (18.67%)	0.696	0.591–0.821	0.753	0.713–0.796
Enoxaparin *vs.* dalteparin	4	471	130/228 (52.02%) *vs.* 119/243 (48.97%)	1.447	0.957–2.281	1.470	0.949–2.277
Nadroparin *vs.* enoxaparin	3	1118	402/546 (73.63%) *vs.* 385/572 (67.31%)	1.36	1.050–1.762	1.352	1.028–1.779
Dalteparin *vs.* nadroparin	2	294	103/147 (70.07%) *vs.* 118/147 (80.27%)	0.577	0.337–0.988	0.626	0.219–1.789

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; CI, confidence interval.

and the odds ratio with 95 percent confidence interval (CI). The total odds ratio with 95 percent CI was given both for the fixed effects model and the random effects model. If the value 1 was not within the 95 percent CI, then the odds ratio was statistically significant at the 5 percent level ($p < .05$). The random effects model would tend to give a more conservative estimate (i.e., with a wider confidence interval), but the results from the two models usually agreed where there was no heterogeneity. If the test of heterogeneity was statistically significant ($p < .05$) then more emphasis should have been placed on the random effects model.

Pharmacoeconomic Analysis

A cost minimization pharmacoeconomic analysis method was implemented and based on meta-analysis data, considering LMWHs as having a similar therapeutic effectiveness and safety parameters.

Cost Minimization Analysis

Cost minimization is one of the pharmacoeconomic tools and is applied when comparing several drugs of equal efficacy and safety results. This type of analysis is used when searching for the lowest cost alternative between competing therapies (4,39,51). The cost minimization analysis involved the expenditures on LMWHs in KMUH from 2005 to 2007 as well as the costs of LMWHs in Lithuania in 2007 and 2008. The pharmacoeconomic analysis included all LMWHs used at KMUH and in Lithuania (DU100 percent) during the aforementioned periods.

Reference Price

As per definition, the reference price allows paying a similar price for medications ensuring a similar benefit. Consequently, it creates an opportunity for reduction of costs of higher-priced products, that is, paying only the price of the lowest common denominator (36,43,52).

As a result of the pharmacoeconomic analysis, it was reasonable to set the lowest price (i.e., single DDD price of one LMWH) as the reference. Further calculations demonstrated the economic advantages of the pharmacoeconomic analysis for the state government and healthcare provider budgets.

RESULTS

Meta-analysis of Heparins: Studies and Outcomes

The following results were obtained from meta-analysis:

UFH vs. Dalteparin. Twelve studies involving 3,993 patients were included. The evaluated end points occurred in 547/1,846 (29.63 percent) patients treated with UFH versus 603/2147 (28.09 percent) patients treated with dalteparin. There were no statistically significant differences in the efficacy values of those two medicines, fixed effects odds ratio 1.141 [95 percent CI, 0.952 – 1.368]. Test for heterogeneity ($Q = 23.2064$; $DF = 11$; $p = .0165$) (Tables 1 and 2; Figure 1).

UFH vs. Nadroparin. Nine studies involving the total of 8,283 patients were included. The end points occurred in 269/4,123 (6.52 percent) participants treated with UFH versus 154/4150 (3.71 percent) participants treated with nadroparin. There was a statistically significant difference in the efficacy values of those two medicines, fixed effects odds ratio 0.487 [95 percent CI, 0.393 – 0.604]. Test for heterogeneity ($Q = 34.6006$; $DF = 8$; $p < .0001$) (Tables 1 and 2; Figure 1).

UFH vs. Enoxaparin. Seventeen studies, involving the total of 34,801 patients were included. Aforementioned end points occurred in 4,867/17,454 (27.88 percent) participants treated with UFH versus 3238/17347 (18.67 percent) participants treated with enoxaparin. There was a statistically

Table 2. Pharmacoeconomic Calculations Based on the Utilization of LMWHs in Lithuania in 2007 and 2008 Suggesting Dalteparin Single DDD Price as the Reference

	Reference price in 2007 (LTL)	Reference price in 2008 (LTL)	Costs using reference price in 2007 (LTL)	Costs using reference price in 2008 (LTL)	Total savings in 2007 (LTL)	Total savings in 2007 (%)	Total savings in 2008 (LTL)	Total savings in 2008 (%)
Dalteparin (Fragmin)	4.93	4.88	486,041.05	769,864.83	—	—	—	—
Enoxaparin (Clexane)	4.93	4.88	1,630,568.67	2,321,479.82	468,894.69	22.33%	689,222.28	22.89%
Nadroparin (Fraxiparin)	4.93	4.88	468,894.69	1,910,201.12	1,361,551.25	43.40%	1,381,347.57	41.97%
Grand total	—	—	**3,892,609.84**	**5,001,545.77**	**1,830,445.94**	**31.98%**	**2,070,569.85**	**29.28%**

LMWH, low-molecular-weight heparin; LTL, Lithuanian litas.

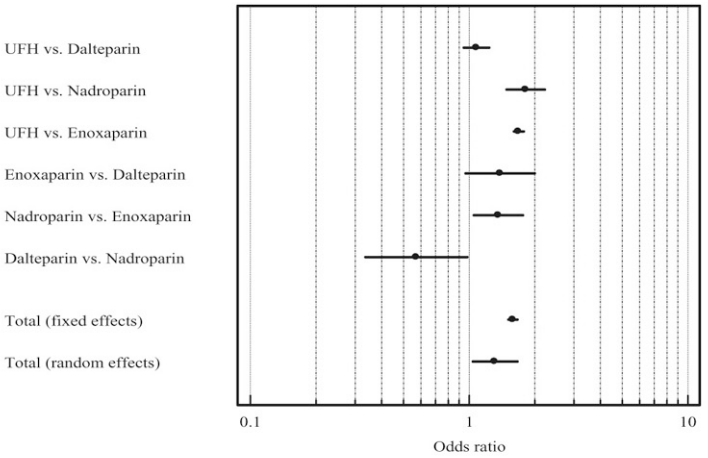

Figure 1. Forest plot of odds ratio (95 percent CI) for meta-analysis of heparins.

significant difference in the efficacy values that were estimated, fixed effects odds ratio 0.753 [95 percent CI, 0.713 – 0.796]. Test for heterogeneity (Q = 53.7578; DF = 16; $p <$ .0001) (Tables 1 and 2; Figure 1).

Enoxaparin vs. Dalteparin. Four studies involving 471 patients were include. The end points occurred in 130/228 (52.02 percent) patients treated with enoxaparin and in 119/243 (48.97 percent) patients treated with dalteparin. There were no statistically significant differences in the efficacy values that were estimated, fixed effects odds ratio 1.447 [95 percent CI, 0.957 – 2.281]. Test for heterogeneity (Q = 1.4669; DF = 3; $p = .6899$) (Tables 1 and 3; Figure 1).

Nadroparin vs. Enoxaparin. Three studies involving 1118 patients were included. The end points occurred in 402/546 (73.63 percent) patients treated with nadroparin and in 385/572 (67.31 percent) patients treated with enoxaparin. There were no statistically significant differences in the efficacy values that were estimated, fixed effects odds ratio 1.360 [95 percent CI, 1.050 – 1.762]. Test for heterogeneity (Q = 2.0356; DF = 2; $p = .3614$) (Tables 1 and 3; Figure 1).

Dalteparin vs. Nadroparin. Two studies involving 294 patients were included. The aforementioned end points occurred in 103/147 (70.07 percent) participants treated with dalteparin versus 118/147 (80.27 percent) participants treated with nadroparin. There were significant differences in the efficacy values, fixed effects odds ratio 0.577 [95 percent CI, 0.337 – 0.988], although the results were not statistically reliable. Test for heterogeneity Q = 3.5333; DF = 1; $p =$ .0601 (Tables 1 and 3; Figure 1).

Cost-Minimization Analysis and Reference Pricing

At KMUH, heparins amount to approximately 8 percent of the total medication costs annually; furthermore, the consumption rates are increasing gradually. The analysis also demonstrated that DDD/1,000HD (hospitalization days) values fluctuate significantly within the group of heparins;

Table 3. Results of Studies Comparing LMWHs (Enoxaparin, Dalteparin, and Nadroparin)

Authors	No. of patients	Evaluated end points	No. of end points occurred	No. of end points occurred
Chiou-Tan FY, et al. 2003 (9)	$n = 95$	DVT, bleeding	Enoxaparin group = 4	Dalteparin group = 4
Montalescot G, et al. 2003 (36)	$n = 94$	Incidence of the composite clinical efficacy	Enoxaparin group = 6	Dalteparin group = 9
Ozdemir M, et al. 2002 (42)	$n = 142$	MI, angina recurrence, overall end point, major bleeding	Enoxaparin group = 39	Dalteparin group = 48
Shafiq N, et al. 2006 (45)	$n = 100$	Cardiovascular death, myocardial Infarction, recurrent angina, need for intervention, silent ischemia	Enoxaparin group = 12	Dalteparin group = 14
Simonneau G, et al. 2006 (45)	$n = 950$	DVT, PE, major bleeding	Nadroparin group = 124	Enoxaparin group = 168
Okmen E, et al. 2004 (41)	$n = 68$	MI, recurrent angina, death, urgent revascularization, MACE	Nadroparin group = 5	Enoxaparin group = 5
Shafiq N, et al. 2006 (45)	$n = 100$	Cardiovascular death, myocardial infarction, recurrent angina, need for intervention, silent ischemia	Nadroparin group = 15	Enoxaparin group = 12
Bounameaux H, et al. 1993 (6)	$n = 194$	DVT	Dalteparin group = 30	Nadroparin group = 15
Shafiq N, et al. 2006 (45)	$n = 100$	Cardiovascular death, myocardial infarction, recurrent angina, need for intervention, silent ischemia	Dalteparin group = 14	Nadroparin group = 15

LMWH, low-molecular-weight heparin; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; MACE, major adverse cardiac event.

for example, in 2005, the consumption of dalteparin reached the value of 74.11DDD/1,000HD, and the utilization of enoxaparin grew from 1.38DDD/1,000HD in 2001 up to 29.55DDD/1,000HD in 2005, which is over 21.4 times more during a 5-year period (Supplementary Table 1 which can be viewed online at www.journals.cambridge.org/thc2010019).

The cost minimization analysis was performed based on results of heparins' meta-analysis, considering LMWHs as having a similar therapeutic effectiveness and safety. The lowest price (i.e., single DDD price of dalteparin) was set as the reference. It is important to emphasize that in Lithuania, a portion of all expenditures amounting to 8.49 percent in 2007 and 10.89 percent in 2008 were allocated to dalteparin, although the distribution of utilization totaled 12.49 percent in 2007 and 15.39 percent in 2008. Moreover, a total of 54.82 percent in 2007 and 46.54 percent in 2008 of all expenditures were allocated to nadroparin but that only reflected the distribution of utilization of only 45.62 percent in 2007 and 38.19 percent in 2008 (Supplementary Table 1).

Pharmacoeconomic estimations were performed using the cost-minimization analysis for obtained data of heparin sales in Lithuania in 2007 and 2008. Heparin costs in KMUH in 2005, 2006, and 2007 were also taken into consideration. The estimations included all LMWHs used at KMUH (DU100 percent) during the aforementioned period. As new LMWH bemiparin was introduced in Lithuanian market in spring of 2008, it was excluded from estimations.

Setting the reference price for low LMWHs would result in total savings of 1.830–2.070 thousand LTL in Lithuania annually. This provides that implementation of reference pricing would enable to decrease the total expenditures by 31.98–29.28 percent (Supplementary Table 2, which can be viewed online at www.journals.cambridge.org/thc2010019).

In the KMUH, the total savings varied from 171 thousand LTL in 2007 to 120 thousand LTL in 2006 and 144 thousand LTL in 2005; therefore, the findings from this study would enable the institution to decrease the expenditures on the group of LMWHs by 17–24 percent per annum.

DISCUSSION

In comparison to UFH, all LMWHs have independently proved to be safer and more effective than UFH, but within the group of LMWH, according to the meta-analysis results, none of the LMWHs demonstrated a significant superiority over each other; therefore, the group of LMWHs was interchangeable in terms of efficacy, safety, and treatment outcomes results and due to that suitable for cost minimization analysis and reference price implementation.

POLICY IMPLICATIONS

Several reviews published by other authors (1) established that reference pricing resulted in less use of the more expensive drugs and more use of reference drugs. This generally decreased the amount spent on drugs by third party payers. Reference pricing was not found to have adverse effects on health, nor did it increase the use of health services (27).

LMWHs are most frequently used in the inpatient settings; therefore, as the utilization of heparins in the outpatient environment is very limited, hospital budgets would significantly benefit from implementation of reference pricing. LMWHs could be interchangeable in terms of their health benefits; that is the idea behind reference pricing, in which reimbursement of a drug is based on the least expensive option.

Subsequent to several estimations, dalteparin was selected as the reference drug, and reference pricing calculations were performed using dalteparin single DDD price as the reference. In KMUH, the estimated possible savings varied in the range of 120–171 thousand LTL from 2005 to 2007, therefore, the aforementioned methodology would enable the institution to decrease the expenditures for LMWHs by 16.54 percent to 23.63 percent annually (Supplementary Tables 1 and 2).

Understandably, it would be extremely important to start implementing the reference pricing in the largest healthcare institutions as that would results in significant decrease of expenditures. KMUH has recently launched the abovementioned methodology and implemented the pharmacoeconomic decision modeling within the group of LMWHs. As these developments commenced in January 2009, the results concerning the expenditures for LMWHs should be available in the nearest future.

LMWHs were considered to be interchangeable after the meta-analysis results were obtained, where efficacy, safety, and treatment outcomes parameters of heparins were analyzed. The direct costs of LMWHs were shown to be very different at KMUH and other Lithuanian hospitals as well. Therefore, voluntary introduction of cost-minimization policies could become a useful tool enabling healthcare providers and inpatient settings balance their budgets and rationalize expenditures on anticoagulation therapies.

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Supplementary Table 2
www.journals.cambridge.org/thc2010019

CONTACT INFORMATION

Edmundas Kadusevicius, PharmD, MD, PhD (e610614@yahoo.com), Associate Professor, Basic & Clinical Pharmacology, Kaunas Medical University, 9 Mickeviciaus, Kaunas LT-44307, Lithuania; Clinical Pharmacist, Department of Hospital Pharmacy, Kaunas Medical University Hospital, 2 Eiveniu, Kaunas LT-50009, Lithuania
Gabriele Kildonaviciute, PharmD (gabrielekil@yahoo.com), Assistant, Basic & Clinical Pharmacology, Kaunas Medical University, 9 Mickeviciaus, Kaunas LT-44303, Lithuania; Assistant Site Start-up Team Lead, Quintiles, JSC, 349 Savanoriu av., LT-49425, Lithuania
Birute Varanaviciene, PharmD (birute.varanaviciene@kmuk.lt), Head, Department of Hospital Pharmacy, Kaunas Medical University Hospital, 2 Eiveniu, Kaunas Lt-50009, Lithuania
Danguole Jankauskiene, MD, PhD (djank@mruni.lt), Professor, Department of Policy and Management, Mykolas Romeris University, 20 Ateities Street, Vilnius LT08303, Lithuania

CONFLICT OF INTEREST

All authors report having no potential conflicts of interest.

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Mažos molekulinės masės heparinai: panašumų ir skirtumų apžvalga

Racionalus heparinų skyrimas klinikinėje praktikoje

Edmundas Kadušević ius, Gabrielė Kildonavičiūtė
LSMU MA Teorinės ir klinikinės farmakologijos katedra

Santrauka

Uždaviniai. Įvertinti mažos molekulinės masės heparinų (MMMH) skirtumus bei palyginti juos su nefrakcionuotu heparinu ir fondaparinuksu. **Metodikos.** Mažos molekulinės masės heparinai (MMMH) – tai antikoaguliantai, kurių veikimo mechanizmas pagrįstas antitrombino III aktyvavimu ir tiesioginiu IIa (trombino) ir Xa krešėjimo faktorių slopinimu (ATC klasifikacijos kodas B01AB). Fondaparinukso natris yra naujos kartos antikoaguliantas, kuris selektyviai slopina vienintelį iš kraujo krešėjimo procese dalyvaujančių faktorių Xa. Atliekant metaanalizę, mažos molekulinės masės heparinai buvo lyginami tarpusavyje ir su nefrakcionuotu heparinu pagal saugumo ir veiksmingumo parametrus bei gydymo rezultatus. **Rezultatai.** Pagrindinės mažos molekulinės masės heparinų indikacijos: giliųjų venų trombozės ir plaučių embolijos gydymas bei profilaktika; nestabiliosios krūtinės anginos ir miokardo infarkto gydymas. Vartojant MMMH, nėra būtinybės nuolat stebėti laboratorinių parametrų, todėl jų skiriama pacientams dažniau nei nefrakcionuotas heparinas. MMMH vartojimas patogesnis pacientams ir medicinos personalui – per parą pakanka vienos ar dviejų injekcijų po oda. Vartojant MMMH, rečiau randasi nepageidaujamų reakcijų, juos galima ilgiau vartoti. Fondaparinuksas kaip ir MMMH yra patogus vartoti, nereikia nuolatinio laboratorinių parametrų stebėjimo, o saugumo rodikliai yra geresni nei MMMH ir nefrakcionuoto heparino. **Išvados.** Svarbiausi mažos molekulinės masės heparinų privalumai lyginant su nefrakcionuotu heparinu: patogesnis vartojimo būdas, geresni veiksmingumo ir saugumo parametrai.
Reikšminiai žodžiai: mažos molekulinės masės heparinai, bemiparinas, dalteparinas, enoksaparinas, fondaparinuksas, nadroparinas.

Summary

Objectives. to assess diferences of low-molecular-weight heparino and to compare them with the unfractionated heparin and Fondaparinux. **Methods.** Low-molecular-weight heparins (LMWHs) are anticoagulants which accelerate the activity of antithrombin III and preferentially potentiate the inhibition of coagulation factors IIa (thrombin) and Xa (ATC code B01 AB). Fondaparinus is a new generation anticoagulant, selective Factor Xa inhibitor. Meta-analysis was conducted comparing low-lomecular-weight heparins with each other and with unfractionated heparin by the means of their safety and efficacy parameters, and treatment outcomes. **Results.** Prime low-molecular weight heparins indications – treatment and prophylaxis of deep venous thrombosis (DVT) and pulmonary embolism (PE), treatment of unstable coronary artery disease (UCAD) and myocardial infarction (MI). LMWHs are prescribed more frequently to patients, as laboratory parameters monitoring is not required. Administration of LMWHs is more convenient for patients and medical personnel, as sub-cutaneous injections once or twice daily are sufficient. Prescription of LMWHs is related with rare adverse reactions, therefore longer treatment periods are allowed. Fondaparinux similarly to LMWHs is convenient for administration and does not require lab monitoring. Yet Fondaparinux has superior safety parameters over LMWHs and unfractionated heparin. **Conclusions.** Primary advantages of low-molecular-weight heparins compared to unfractionated heparin - convenient type of administration and superior safety and efficacy parametres.
Key words: Low-molecular-weight heparins, Bemiparin, Dalteparin, Enoxaparin, Fondaparinux, Nadroparin.

MAŽOS MOLEKULINĖS MASĖS HEPARINŲ VEIKIMO MECHANIZMAS

Mažos molekulinės masės heparinai (MMMH) – tai antikoaguliantai (antitromboziniai preparatai), kurių veikimo mechanizmas pagrįstas antitrombino III aktyvavimu ir tiesioginiu IIa (trombino) ir Xa krešėjimo faktorių slopinimu (ATC klasifikacijos kodas B01AB). Šių vaistinių preparatų antitrombinį aktyvumą didina

audinių faktoriaus kelio inhibitoriaus (AKFI) stimuliacija, fibrinolizės suaktyvinimas tiesiogiai atpalaiduojant iš endotelio ląstelių audinių plazminogeno aktyvatorių ir kraujo parametrų pokytis. MMMH molekulės dydis taip pat turi įtakos antitrombiniam aktyvumui. Kiekvieną MMMH sudaro įvairios molekulinės masės pentasacharidai. MMMH gaminami depolimerizuojant heparino natrio druską, išgaunant glikozaminoglikanus, kurių vidutinė molekulinį masė yra apie 5000 Daltonų (nuo <2000 iki >8000 Daltonų) [1–3].

Fondaparinukso natris yra naujos kartos antikoaguliantas, sintetinis pentasacharidas, kuris selektyviai slopina vienintelį iš kraujo krešėjimo procese dalyvaujančių faktorių Xa. Neutralizavus šį krešėjimo faktorių, nesusidaro trombinas ir nesiformuoja krešuliai [1, 2, 6].

Mažos molekulinės masės heparinų, kaip ir nefrakcionuotas heparinas, skiriama giliųjų venų trombozei ir plaučių embolijai gydyti, miokardo infarktokto ir nestabilios krūtinės anginos gydymui, taip pat norint apsaugoti ekstrakorporalinę sistemą nuo krešėjimo. Kunderer ir kt., Lazo-Langner ir kt., De Luca ir kt., Kaduševičius ir kt. metaanalizių duomenimis, įrodytas mažos molekulinės masės heparinų pranašumas prieš nefrakcionuotą hepariną: jie veiksmingesni, mažesnė trombocitopenijos rizika. Mažos molekulinės masės heparinų ir nefrakcionuoto heparino metaanalizės atliktos, remiantis randomizuotais, kontroliuojamaisiais klinikiniais tyrimais, kurių metu tiesiogiai buvo lyginami šių vaistinių preparatų veiksmingumo ir saugumo parametrai bei gydymo rezultatai. Atliekant tiesioginį palyginimą, nenustatyta nė vieno mažos molekulinės masės heparino reikšmingo pranašumo, tačiau visi MMMH buvo pranašesni už nefrakcionuotą hepariną pagal saugumo ir veiksmingumo parametrus bei gydymo rezultatus [10–12].

Vartojant MMMH, nereikia papildomos kraujo krešėjimo parametrų stebėsenos, o dėl pakankamai ilgos veikimo trukmės MMMH galima vartoti vieną kartą per dieną, po oda, todėl šis skyrimo būdas labai patogus medicinos personalui. Mažos molekulinės masės heparinų indikacijos pateikiamos 1 lentelėje.

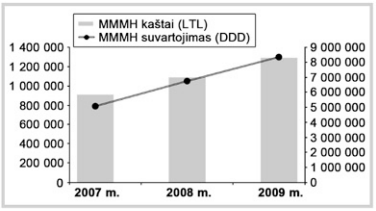
Dėl pakankamai ilgo indikacijų sąrašo ir pranašumo prieš nefrakcionuotą hepariną MMMH suvartojimas pasaulyje ir Lietuvoje nuolat didėja. Pasaulinė mažos molekulinės masės heparinų rinka kasmet siekia apie 3,5 mlrd. JAV dolerių ir nuolat auga. Manoma, kad 2012 m. išlaidos antikoaguliantams septyniose didžiausiose pasaulio rinkose (JAV, Prancūzija, Vokietija, Italija, Ispanija, Jungtinė Karalystė ir Japonija) gali 20 mlrd. JAV dolerių.

Lietuvoje mažos molekulinės masės heparinų suvartojimas nuo 2007 iki 2009 m. padidėjo beveik 68 proc., nuo 789 tūkst. DDD (apibrėžta dienos dozė, angl. *DDD – Defined Daily Dose*) 2007 m. (t. y. 0,65 DDD/1000 gyventojų/per dieną) iki 1,285 tūkst. DDD 2009 m. (t. y. 1,05 DDD/1000 gyventojų/per dieną). Didėjant suvartojimui, reikšmingai išaugo ir išlaidos šiems vaistiniams preparatams – nuo 5,7 mln. LTL 2007 m. iki 8,2 mln. LTL 2009 m., t. y. beveik 44 proc. Šie duomenys pateikiami pav.

Deja, skiriant MMMH, dar neretai pasitaiko neracionalių sprendimų ir klaidingų skyrimų, todėl šiuo straipsniu siekiama sveikatos priežiūros specialistams dar kartą priminti apie šių vaistinių preparatų panašumus ir skirtumas bei atkreipti dėmesį į dažniausiai pasitaikančias klaidas.

1 lentelė. Mažos molekulinės masės heparinų indikacijos [1–5]

Indikacijos	Bemiparinas	Dalteparinas	Enoksaparinas	Nadroparinas	Fondaparinuksas
Giliųjų venų trombozės ir plaučių embolijos gydymas	+	+	+	+	+
Nestabilioji krūtinės angina ir ne Q bangos miokardo infarktas		+	+	+	
Venų tromboembolijos, susijusios su operacijomis, profilaktika	+	+	+	+	+
Ilgalaikis giliųjų venų trombozės ir (arba) plaučių embolijos gydymas bei antrinė profilaktika ligoniams, sergantiems onkologinėmis ligomis		+			
Trombozės profilaktika ligoniams, kurie dėl ūminių sveikatos sutrikimų negali daug judėti		+	+		
Ekstrakorporalinės sistemos apsauga nuo krešėjimo hemodializės ir hemofiltracijos metu, kai yra ūminis arba lėtinis inkstų funkcijos nepakankamumas	+	+	+	+	



Pav. Mažos molekulinės masės heparinų suvartojimas ir kaštai Lietuvoje 2007–2009 m.

2 lentelė. Mažos molekulinės masės heparinų farmakokinetinės savybės

Absorbcija (suleidus preparato po oda)	• Didžiausia anti-Xa koncentracija kraujo plazmoje (C_{max})– susidaro maždaug per 3–5 val. • Biologinis prieinamumas daugiau kaip 90 proc.
Eliminacija (suleidus preparato po oda)	• Pusinės eliminacijos periodas yra maždaug 3–6 val. • Aktyvumas išlieka ne mažiau kaip 18 val., todėl šių preparatų skiriama kartą per parą. • Daugiausia metabolizuojama kepenyse • Daugiausia išsiskiria per inkstus

FARMAKOLOGINĖS MMMH SAVYBĖS

Farmakodinaminės savybės –antitrombinis poveikis yra greitas ir ilgas, o anti-Xa aktyvumo santykis su anti-IIa aktyvumu yra didelis. Lyginant su nefrakcionuotu heparinu, silpniau veikiama trombocitų funkcija ir jų agregacija.

Farmakokinetinės savybės – linijinio pobūdžio, nustatytos remiantis biologiniu aktyvumu (matuojant anti-Xa aktyvumą kraujo plazmoje) [1–3].

ATSARGUMO PRIEMONĖS IR KONTRAINDIKACIJOS SKIRIANT MMMH

Skiriant mažos molekulinės masės heparinus, būtina atsižvelgti į šias būkles, susijusias su padidėjusia kraujavimo rizika:

- Kepenų funkcijos nepakankamumas.
- Inkstų funkcijos sutrikimas.
- Senyvas paciento amžius (> 65 metų).
- Kūno svorio kritimas.
- Sunki arterinė hipertenzija.
- Akių kraujotakos sutrikimai.
- Anksčiau buvęs organų pažeidimas, didinantis kraujavimo riziką.
- Pooperacinis laikotarpis po galvos, nugaros smegenų arba akies operacijų.

Šių būklių metu būtina koreguoti skiriamo MMMH dozę, atsižvelgiant į gamintojo rekomendacijas [1–5].

SĄVEIKA SU KITAIS VAISTINIAIS PREPARATAIS

Mažos molekulinės masės heparinų antikoaguliacinis poveikis gali sustiprėti, jeigu jie bus vartojamai kartu su preparatais, veikiančiais hemostazę (trombolizinia vaistai, sisteminiai salicilatai (pvz., acetilsalicilo rūgštis), nesteroidiniai priešuždegiminiai vaistai, vitamino K antagonistai ir dekstranu, tiklopidinu, klopidogreliu ir kitais trombocitų inhibitoriais, sisteminiais gliukokortikoidais). Visi šie vaistai didina farmakologinį poveikį krešumui ir (arba) trombocitų funkcijai bei didina kraujavimo riziką. Jeigu nėra specifinių kontraindikacijų, pacientams, kurie serga nestabiliąja krūtinės angina arba ne Q bangos miokardo infarktu, reikia vartoti geriamąją acetilsalicilo rūgštį mažomis dozėmis.

Vaistinius preparatus, didinančius kalio koncentraciją kraujo plazmoje, pacientai gali vartoti kartu tik atidžiai prižiūrimi medikų.

Tais atvejais, kai vaistinių preparatų derinio neįmanoma išvengti, būtina stebėti pacientą, jo klinikinius ir laboratorinius rodiklius [1–5].

MMMH nepageidaujamos reakcijos

Skiriant mažos molekulinės masės heparinus, tikėtinos šios nepageidaujamos reakcijos:

- Kraujavimas.
- Trombocitopenija, kuri gali būti dviejų rūšių. Dažnesnė yra I tipo trumpalaikė neimunologinė trombocitopenija. Paprastai ji būna vidutinio sunkumo (trombocitų daugiau kaip 100 000/mm^3), dėl jos gydymo nutraukti nereikia. Retai pasireiškia sunki II tipo imunoalerginė trombocitopenija.
- Laikinas kepenų fermentų transaminazių (ASAT, ALAT) ir gama GT kiekio padidėjimas.
- Bendrieji sutrikimai ir injekcijos vietos pažeidimai (skausmas, kraujavimas, hematoma injekcijos vietoje, lokalus suerzinimas, alerginės reakcijos).
- Imuninės sistemos sutrikimai (anafilaksinės reakcijos).
- Ilgai vartojant, gali pasireikšti osteoporozė [1–3].

SAUGUMO IR VEIKSMINGUMO PARAMETRŲ STEBĖSENA

Trombocitopenija

Heparinai gali sukelti trombocitopeniją, todėl viso gydymo kurso metu būtina reguliariai stebėti trombocitų kiekį. Jeigu, vartojant MMMH, pacientui nustatoma trombocitopenija (mažiau kaip 100 000/ml arba mm^3), būtina elgtis atsargiai. Visais atvejais rekomenduojama atlikti antitrombocitinių antikūnų mėginius su mažo molekulinės masės heparinais *in vitro*. Gavus teigiamus rezultatus, gydymą heparinais

3 lentelė. Mažos molekulinės masės heparinų kontraindikacijos

Kontraindikacijos	Bemiparinas	Daltepa-rinas	Enoksa-parinas	Nadropa-rinas	Fondapa-rinuksas
Anksčiau patvirtinta ar įtarta heparino sukelta sunki trombocitopenija	+	+		+	+
Aktyvus kliniškai reikšmingas kraujavimas	+	+	+	+	+
Sunkūs kraujo krešėjimo sutrikimai	+	+	+	+	
Sepsinis endokarditas	+	+			+
Neseniai patirtas centrinės nervų sistemos, akių ir (arba) ausų sužalojimas arba atlikta operacija	+	+			
Padidėjęs jautrumas veikliajai medžiagai, kitiems MMMH arba heparinui	+	+	+	+	
Neseniai įvykęs insultas (išskyrus dėl sisteminės embolizacijos įvykusį insultą), nes yra kraujo išsiliejimo į smegenis grėsmė		+	+		
Sunkus kepenų ar kasos veiklos sutrikimas	+			+	

4 lentelė. Tikėtinai MMMH sukeltų nepageidaujamų reakcijų dažnis (proc.)

Nepageidajamos reakcijos	Bemi-parinas	Daltepa-rinas	Enoksa-parinas	Nadropa-rinas	Fondapa-rinuksas
Kraujavimas	1–10	>1	>2	10	>2
Trombocitopenija	0,1–0,01	>1	>2	0,1–0,01	>2
Imuninės sistemos sutrikimai	0,1–0,01	>1	–	0,01	–
Bendrieji sutrikimai	15	>1	>2	10	>2
Kepenų funkcijos sutrikimai	1–10	>1	6	1–10	–
Metabolizmo sutrikimai (laikina hiperkalemija)	–	–	–	0,01	>4
Epidurinė ir spinalinė hematoma po epidurinės arba spinalinės anestezijos bei lumbalinės punkcijos	0,01	–	–	–	–
Odos nekrozė injekcijos vietoje	0,1–0,01	–	–	–	–

5 lentelė. Veiksmingumo ir saugumo parametrų palyginimas

	Nefrakcionuotas heparinas	MMMH	Fondaparinuksas
Veiksmingumo parametrai			
Biologinis prieinamumas	20–30 proc.	90–100 proc.	100 proc.
Skyrimo galimybės	IV	Po oda	Po oda
Vartojimo būdas	Kelis kartus per parą	1–2 kartus per parą	Kartą per parą
Galima gydymo kurso trukmė	Trumpa	Vidutinė-Ilga	Ilga
Saugumo parametrai			
Nepageidaujamų reakcijų dažnis	Dažnos	Retos	Retos
Laboratorinių parametrų stebėsena	Būtinas	Nereikalingas	Nereikalingas

reikia nutraukti. Šie reiškiniai paprastai pasireiškia 5–21 gydymo dieną, bet gali atsirasti ir anksčiau, jei kada nors anksčiau buvo trombocitopenija, atsiradusi vartojant heparinų [1, 3].

Anti-Xa koncentracijos stebėsena

Dažniausiai MMMH poveikio krešėjimui stebėti nebūtina, bet rekomenduojama tą daryti rizikos grupių pacientams (pvz., sergantiesiems inkstų funkcijos

MMMH PREPARATŲ DOZAVIMAS

Dalteparinas

Indikacijos	Rekomenduojamas dozavimas	Vartojimo trukmė
Venų tromboembolijos profilaktikai atliekant chirurginę operaciją	2500 TV kartą per parą (švirkščiama po oda)	Pirmoji injekcija atliekama likus 1–2 val. iki operacijos, vartojimas tęsiamas 5–7 paras ar ilgiau
Operacijos, susijusios su papildomais rizikos veiksniais ir ortopedinės operacijos	5000 TV skiriama vakare prieš operaciją, vėliau – 5000 TV kartą per parą (švirkščiama po oda)	Gydymas tęsiamas 5–7 dienas, arba ilgiau
Ilgalaikė tromboembolijų profilaktika atliekant ortopedinę operaciją	5000 TV skiriama vakare prieš operaciją, vėliau – 5000 TV kartą per parą (švirkščiama po oda)	Gydymas tęsiamas penkias savaites
Ūminės giliųjų venų trombozės ir plaučių embolijos gydymas	200 TV/kg skiriamos dvi injekcijos per parą (švirkščiama po oda)	Gydymas tęsiamas mažiausiai 5 dienas
Nestabiliosios krūtinės anginos ir ne Q bangos miokardo infarkto gydymas	120 TV/kg skiriamos dvi injekcijos per parą (švirkščiama po oda)	Gydymas paprastai tęsiamas 6 paras arba ilgiau
Krešėjimo stabdymas hemodializės ir hemofiltracijos metu	5000 TV (švirkščiama į veną)	Tinka dializei, trunkančiai ne ilgiau kaip 4 val.
Ilgalaikis giliųjų venų trombozės ir (arba) plaučių embolijos gydymas bei antrinė profilaktika ligoniams, sergantiems onkologinėmis ligomis	200 TV/kg kartą per parą (pirmąsias 30 dienų) ir 150 TV/kg kartą per parą (2–6 gydymo mėnesį)	Ilgalaikis vartojimas (iki 6 mėnesių)
Trombozės profilaktika ligoniams, kurie negali judėti	5000 TV kartą per parą (švirkščiama po oda)	Gydymas tęsiamas 12–14 dienų arba ilgiau

Bepimarin

Indikacijos	Rekomeduojamas dozavimas	Vartojimo trukmė
Bendrosios chirurginės operacijos su didele venų tromboembolijos rizika	2500 TV (2 val. prieš operaciją arba 6 val. po operacijos). Vėliau – po 2500 TV kas 24 val. (švirkščiama po oda)	Profilaktinis gydymas tęsiamas bent 7–10 dienų po chirurginės procedūros
Krešumo profilaktika ekstrakorporinėje sistemoje hemodializės metu	2500–3500 TV (švirkščiama viena dozė boliusu į arteriją dializės procedūros pradžioje)	Hemodializei, trunkančiai ne ilgiau kaip 4 val.

nepakankamumu, mažo kūno svorio pacientams, taip pat tais atvejais, kai yra kraujavimo ar trombozės pasikartojimo pavojus). Rekomenduojama anti-Xa koncentracijai nustatyti naudoti chromogenines medžiagas. Dalinio aktyvinto tromboplastino laiko (DATL) arba trombino laiko matuoti negalima, nes minėti tyrimai MMMH poveikiui gali būti santykinai nejautrūs [1, 3].

Inkstų funkcijos sutrikimas

Žinoma, kad MMMH išskiriamas daugiausia per inkstus, todėl jų poveikis sustiprėja tiems pacientams, kurių inkstų funkcija sutrikusi. Pacientams, kurių inkstų funkcija sutrikusi, padidėja kraujavimo pavojus, todėl juos reikia gydyti atsargiai. Sumažinti vaisto dozę, kai kreatinino klirensas yra 30–50 ml/min., gydytojas gali nuspręsti įvertinęs individualų kraujavimo ir tromboembolijos pavojų pacientui.

Senyvo amžiaus pacientams paprastai susilpnėja inkstų funkcija, todėl vaisto pasišalinimas šiems pacientams yra lėtesnis. Reikia įvertinti inkstų funkcijos sutrikimus šio amžiaus grupės pacientams ir atitinkamai koreguoti MMMH dozę [1, 3].

APIBENDRINIMAS

Mažos molekulinės masės heparinų nuolat skiriama giliųjų venų trombozės ir plaučių embolijos gydymui ir profilaktikai, taip pat nestabiliosios krūtinės anginos ir miokardo infarkto gydymui. Svarbiausi šių antikoaguliantų privalumai, lyginant su nefrakcionuotu heparinu, yra patogesnis vartojimo būdas, taip pat geresni veiksmingumo ir saugumo

MMMH PREPARATŲ DOZAVIMAS

Nadroparinas

Indikacijos	Rekomenduojamas dozavimas	Vartojimo trukmė
Venų tromboembolijos profilaktikai atliekant chirurginę operaciją	2850 TV (0,3 ml) kartą per parą (švirkščiama po oda)	Pirmoji injekcija atliekama likus 2 val. iki operacijos, vartojimas tęsiamas 3 paras
Giliųjų venų trombozės gydymas	85 TV/kg skiriamos dvi injekcijos per parą, kas 12 val. (švirkščiama po oda)	Ne ilgiau kaip 10 parų
Nestabiliosios krūtinės anginos ir ne Q bangos miokardo infarkto gydymas	86 TV/kg skiriamos dvi injekcijos per parą, kas 12 val. (švirkščiama po oda)	Gydymas paprastai tęsiamas 6 paras
Krešėjimo profilaktika ekstrakorporalinėje kraujotakos kilpoje inkstų dializės metu	65 TV/kg (injekuojama procedūros pradžioje į arterinę kilpos šaką)	Tinka dializei, trunkančiai ne ilgiau kaip 4 val.

Enoksaparinas

Indikacijos	Rekomenduojamas dozavimas	Vartojimo trukmė
Venų tromboembolijos profilaktikai vidaus organų terapinėmis ligomis sergantiems pacientams	4000 TV 1 kartą per parą (švirkščiama po oda)	Vartoti bent 6 dienas, bet ne ilgiau 14 dienų
Giliųjų venų trombozės gydymas	150 TV/kg 1 kartą per parą arba 100 TV/kg 2 kartus per parą (švirkščiama po oda)	Vidutiniškai skiriama 10 dienų
Nestabiliosios krūtinės anginos ir ne Q bangos miokardo infarkto gydymas	100 TV/kg kas 12 val. (švirkščiama po oda)	Vartoti bent 2 dienas (dažniausiai 2–8 dienas)
Ekstrakorporalinės trombozės profilaktika hemodializės metu	100 TV/kg (švirkščiama į kontūro arterinę liniją hemodializės pradžioje)	Nurodytos dozės pakanka 4 val. trukmės hemodializei

Fondaparinukso natris

Indikacijos	Rekomenduojamas dozavimas	Vartojimo trukmė
Venų tromboembolijos profilaktikai atliekant chirurginę operaciją	2,5 mg kartą per parą (švirkščiama po oda)	Gydymas pradedamas praėjus 6–8 val. po operacijos, tęsiamas 5–9 dienas
Giliųjų venų trombozės ir plaučių embolijos gydymas	5–10 mg (atsižvelgiant į kūno svorį) injekcijos skiriamos kartą per parą (švirkščiama po oda)	Gydymas tęsiamas 5–9 dienas

parametrai. Dėl MMMH farmakologinių savybių nebūtina nuolat stebėti laboratorinius parametrus, todėl jų skiriama pacientams gerokai dažniau nei nefrakcionuotas heparinas stacionarinio gydymo metu. MMMH vartojimas patogesnis ir priimtinesnis pacientams ir medicinos personalui, nes per parą pakanka vienos ar dviejų injekcijų po oda, rečiau randasi nepageidaujamų reakcijų arba komplikacijų. MMMH galima ilgiau vartoti. Atsižvelgiant į gamintojo rekomendacijas ir gydymo indikaciją, MMMH skyrimą galima tęsti nuo kelių dienų iki kelių mėnesių [7–9].

Fondaparinux (fondaparinuksas) kaip ir MMMH pasižymi aukštu biologinio prieinamumo rodikliu (iki 100 proc.), patogus vartojimui (injekcijos po oda skiriamos vieną kartą per parą), išskiriamas pro inkstus, nereikalinga nuolatinė laboratorinių parametrų stebėsena. *Fondaparinux* pasižymi gerais saugumo rodikliais, t. y. nesukelia trombocitopenijos ir kitų komplikacijų. Kaip ir MMMH reikia skirti atsargiai esant inkstų funkcijos nepakankamumui (kreatinino klirensas <30 ml/min.). Šio vaistinio preparato saugumo rodikliai yra geresni nei MMMH ir nefrakcionuoto heparino. Prireikus *Fondaparinux* galima skirti ilgalaikei antikoaguliacijai (iki penkių savaičių). Tikėtini nepageidaujami reiškiniai kaip ir MMMH, t. y. kraujavimas, trombocitopenija, reakcija injekcijos vietoje, alergija ir kt. [1, 2, 6].

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Gauta: 2010 11 04
Priimta spausdinti: 2010 11 04

FARMAKOEPIDEMIOLOGINIŲ IR FARMAKOEKONOMINIŲ TYRIMŲ SVARBA, SKATINANT RACIONALIĄ MAŽOS MOLEKULINĖS MASĖS HEPARINŲ VARTOJIMO POLITIKĄ LIETUVOJE

Gabrielė Kildonavičiūtė
UAB Quintiles, Vadovė klinikinėms operacijoms
Savanorių pr. 349, LT-49425 Kaunas, Lietuva
Telefonas +370-611-24373
Elektroninis paštas: gabrielekil@yahoo.com

Vilma Morkūnienė
Kauno Kolegijos, Bendratechninių mokslų katedra
Pramonės pr. 20, LT-50468 Kaunas, Lietuva
Elektroninis paštas: evamorkunas@gmail.com
Telefonas +370 687 34304

Edmundas Kaduševičius
Lietuvos sveikatos mokslų universiteto Fiziologijos ir farmakologijos institutas
Mickevičiaus g. 9, LT-44303 Kaunas, Lietuva
Elektroninis paštas: e610614@yahoo.com

Santrauka

Tyrimo tikslas *– skatinti racionalią mažos molekulinės masės heparinų vartojimo politiką, remiantis farmakoekonominių ir farmakoepidemiologinių tyrimų duomenimis.* ***Metodai*** *– darbas atliktas panaudojant vaistų suvartojimo tarptautinę PSO ATC/DDD metodiką, farmakoekonominį kaštų mažinimo metodą bei perspektyvinį biomedicininį stebėjimo tyrimą.* ***Rezultatai*** *– Heparinų suvartojimas Lietuvoje didėjo nuo 40,12 ADD / 1000 lovadienių 2003 m. iki 309,60 ADD / 1000 lovadienių 2011 m. Bendri heparinų kaštai Lietuvoje didėjo nuo 1088 tūkst. LTL 2003 m. iki 10284 tūkst. LTL 2011 m. Pasirenkant referentine kaina žemiausią vienos Dalteparino apibrėžtos dienos dozės (ADD) kainą (2,75 LTL), kasmet būtų galima racionaliau panaudoti 3218–4679 tūkst. LTL (2008 – 2011 m. duomenys), t. y. heparinų kaštai sumažėtų apie 60%. Tik nedidelei dalei ligonių heparinų efektyvumo ir saugumo monitoringas atitiko tarptautines rekomendacijas. Saugumo laboratorinių tyrimų rezultatai buvo stebimi tik 39,23% visų atveju (n = 133) prieš skiriant heparinus ir 53,98% visų atveju (n = 183) gydymo metu.* ***Išvados*** *– Heparinų suvartojimas ir kaštai Lietuvoje reikšmingai didėjo, tai rodo, jog būtina taikyti farmakoekonominį modelį išlaidoms reguliuoti. Heparinų efektyvumo ir saugumo monitoravimas tik maža apimtimi atitinka tarptautines rekomendacijas, todėl nacionalinės gydymo rekomendacijos ir gydymo auditas turėtų būti prioritetiniai siekiniai skatinant racionalų heparinų vartojimą.*

Reikšminiai žodžiai: *Mažos molekulinės masės heparinai, farmakoekonomika, referentinė kaina, kaštų mažinimas.*

Įvadas

Pastaraisiais metais daugelyje šalių sveikatos priežiūros išlaidos augo daug greičiau nei bendras gerovės lygis, todėl yra nuolat diskutuojama, kaip šį išlaidų augimą reikėtų kontroliuoti. Pateikiamos kelios pagrindinės priežastys, lemiančios nuolatinį išlaidų augimą: bendras gyventojų senėjimas, brangių sveikatos priežiūros technologijų naudojimas, didėjantys gyventojų lūkesčiai dėl geresnės sveikatos priežiūros ir kt. Tačiau išlaidų augimas nėra vienintelis susirūpinimą keliantis klausimas. Kitos problemos yra sveikatos priežiūros nehomogeniškumas, nelygios galimybės naudotis sveikatos priežiūros paslaugomis, optimaliausių sprendimų priėmimas koordinuojant vaistinių preparatų skyrimą pacientams ir t.t. Sprendžiant šiuos uždavinius, sveikatos priežiūros sprendimus priimantiems asmenims labai svarbu sumažinti sveikatos priežiūros išlaidas bei išlaikyti biudžeto kontrolę[1,2].

Sveikatos priežiūros programų ekonominis įvertinimas yra nauja disciplina, ja susidomėjimas pastaraisiais metais gerokai išaugo. Sveikatos priežiūros ekonominis vertinimas (*farmakoekonomika*) yra viena iš plačios disciplinos, vadinamos sveikatos ekonomika, dalių. Sveikatos priežiūros ekonomikos vertinimas yra apibrėžiamas kaip lyginamosios analizės metodas, tiriantis išlaidas ir dviejų ar daugiau alternatyvių intervencijų poveikį sveikatai. Šiame apibrėžime yra svarbūs du elementai – gydymo alternatyvų palyginimas ir dviejų matmenų - išlaidų ir poveikio sveikatai palyginimas[3].

Farmakoekonominių sprendimų modeliavimas yra naujas ir efektyvus įrankis, plačiai naudojamas įvairių šalių sprendimus priimančių asmenų ir atitinkamų sveikatos priežiūros institucijų, priimant sprendimus dėl naujų ir esamų gydymo būdų[4].

Farmakoekonominių sprendimų modeliai gali būti naudingi įrankiai, atliekant išlaidų mažinimo, išlaidų efektyvumo ir kaštų naudingumo analizes bet kuriame vaistinio preparato tyrimo, vystymo ir prekybos etapuose. Sprendimų analizė pateikia struktūrizuotas schemas, kaip turėtų būti lyginamos gydymo vaistiniais preparatais sąnaudos ir pasekmės.

Sprendimų analizėms dažniausiai yra naudojami klinikinių tyrimų metu surinkti duomenys, kurie yra patikimas informacijos šaltinis apie galimą vaistinių preparatų poveikį. Klinikinių sprendimų modelių pranašumas yra tai, kad jie skatina apsvarstyti

1 Kikkert W.J., Piek J.J., de Winter R.J., et al. Guideline adherence for antithrombotic therapy in acute coronary syndrome: an overview in Dutch hospitals. *Netherland Heart Journal*, Vol 18., No. 6., June 2010.

2 Pan SY, Pan S, Yu ZL, et al. New perspectives on innovative drug discovery: an overview. *J Pharm Pharm Sci*. 2010; 13(3):450-71.

3 Kikkert W.J., Piek J.J., de Winter R.J., et al. Guideline adherence for antithrombotic therapy in acute coronary syndrome: an overview in Dutch hospitals. *Netherland Heart Journal*, Vol 18., No. 6., June 2010.

4 Ten pat, Bootman J.L, Townsend R.J, McGham W.F. Introduction to Pharmacoeconomics. Chapter 1. Available at URL://www.hwbooks.com/pharmacoeconomics3ed/chp1.pdf.; Introduction to drug utilization research / WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. World Health Organization 2003. ISBN 92 4 156234 X; Walley T. Chapter 9. Pharmacoeconomics and Economic Evaluation of Drug Therapies. Available at URL:// http://www.iuphar.org/pdf/hum_67.pdf.

ir aiškiai įvertinti visas įmanomas sąnaudas ir rezultatus. Modelis apibrėžia galimą klinikinio gydymo modeliavimą ir atitinkamų medicinos išteklių naudojimo vertinimą, gydant tam tikras ligas[5].

Pasinaudojus farmakoekonominių sprendimų metodikomis gali būti sukurti sprendimų modeliai, kurie potencialiai galėtų būti naudojami sveikatos priežiūros sprendimus priimančių asmenų nutarimams dėl išlaidų heparinų grupės preparatams pagrįsti[6].

Finansiniai sprendimai yra reikšmingi dabartinės medicinos ir farmacijos aplinkoje. Todėl šiuolaikinės farmakoekonominės metodikos, leidžiančios pasirinkti racionaliausią sprendimą medicininiu ir finansiniu aspektu, turėtų būti plačiai naudojamos, siekiant subalansuoti sveikatos priežiūros biudžetus šalyse[7].

Lietuvoje išlaidos heparinams pastarąjį dešimtmetį reikšmingai didėjo. Remiantis atliktu tyrimu, heparinų išlaidos išaugo daugiau nei devynis kartus per 8 metų laikotarpį, t. y. nuo 1,088 tūkst. Lt 2003 m. iki 10284 tūkst. LTL 2011 m. Tačiau heparinų suvartojimo rodiklis išaugo daugiau nei septynis kartus, nuo 322 tūkst. ADD (apibrėžta dienos dozė) 2003 m. iki 2,307 tūkst. ADD 2011 m. Toks reikšmingas išlaidų ir suvartojimo augimas buvo šio tyrimo objektas.

Vaistinių preparatų suvartojimo mokslinių tyrimų pagrindinis tikslas yra skatinti racionalų vaistų vartojimą visuomenėje. Pirmiausia reikia išsiaiškinti, kaip vaistiniai preparatai yra skiriami ir naudojami. Surikus ir apibendrinus šią informaciją, svarbu inicijuoti diskusiją apie racionalų vaistų vartojimą, o vėliau pasiūlyti priemonių, kurios galėtų pakeisti vaistinių preparatų skyrimo įpročius. Informacija apie praeityje fiksuotus paskyrimus yra labai svarbi atliekant tolesnius tyrimus ir taikant farkamoekonominių sprendimų metodikas[8].

Heparinai yra dažnai skiriami hospitalizuotiems pacientams, esant įvairioms indikacijoms, prevencijos ir gydymo tikslais, jiems taip pat yra numatytas svarbus vaidmuo daugelyje gydymo schemų. Dėl šių priežasčių racionalus heparinų skyrimas tapo svarbia daugelio sveikatos sutrikimų valdymo dalimi. Tinkamas ir racionalus heparinų skyrimas, turėtų teigiamos įtakos gydymo rezultatams, taip pat sumažintų nepageidaujamų reakcijų dažnį.

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5 Bootman J.L, Townsend R.J, McGham W.F. Introduction to Pharmacoeconomics. Chapter 1. Available at URL://www.hwbooks.com/pharmacoeconomics3ed/chp1.pdf; Introduction to drug utilization research / WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacological Services. World Health Organization 2003. ISBN 92 4 156234 X; Stahl J.E. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. *Pharmacoeconomics*. 2008; 26(2):131-48.

6 *Ibid.*

7 *Ibid.*; Kikkert W.J., Piek J.J., de Winter R.J., et al. Guideline adherence for antithrombotic therapy in acute coronary syndrome: an overview in Dutch hospitals. *Netherland Heart Journal*, Vol 18., No. 6., June 2010; Walley T. Chapter 9. Pharmacoeconomics and Economic Evaluation of Drug Therapies. Available at URL:// http://www.iuphar.org/pdf/hum_67.pdf.

8 Kikkert W.J., Piek J.J., de Winter R.J., et al. Guideline adherence for antithrombotic therapy... in *Netherland Heart Journal*, Vol 18., No. 6., June 2010; Pan SY, Pan S, Yu ZL, et al. New perspectives... 2010; 13(3): 450–71.

Todėl galimai sumažėtų tiesioginiai heparinų kaštai, ir atitinkamai mažėtų išlaidos susijusios su pacientų hospitalizavimu sveikatos priežiūros įstaigose.

Šiuo metu farmakoekonominių sprendimų modeliavimas nėra naudojamas sveikatos priežiūros įstaigose Lietuvoje. Šio darbo pasiūlyti modeliai galėtų būti taikomi praktikoje, norint geriau kontroliuoti sveikatos priežiūros įstaigų išlaidas mažos molekulinės masės heparinams.

Pasiūlyti farmakoekonominių sprendimų modeliai yra nauji ir dar nėra plačiai taikomi sveikatos priežiūros įstaigose ir institucijose sprendimams dėl išlaidų vaistiniams preparatams pagrįsti.

Pasinaudojus siūlomais metodais būtų galima racionaliau ir efektyviau panaudoti lėšas, skirtas vaistinių preparatų įsigijimui sveikatos priežiūros įstaigose.

Atlikto tyrimo tikslas - remiantis farmakoekonominių ir farmakoepidemiologinių tyrimų duomenimis, skatinti racionalią mažos molekulinės masės heparinų vartojimo politiką Lietuvoje.

1. Tyrimo metodai

1.1. Meta-analizės metodika. Atliekant meta-analizę buvo palyginti mažos molekulinės masės heparinai

(Dalteparinas, Enoksaparinas, Nadroparinas, Bemiparinas ir Tinzaparinas) su nefrakcionuotu heparinu (NFH) pagal jų veiksmingumo ir saugumo parametrus bei gydymo rezultatus.

1.2. Vaistinių preparatų suvartojimo tyrimo metodika. Tyrimo objektas – heparinų pardavimo

duomenys piniginiais vienetais (didmeninėmis kainomis) ir pakuotėmis nuo 2003 iki 2011 m. Pardavimų duomenys buvo gauti iš visų licencijuotų farmacinių didmeninės prekybos įmonių šalyje.

Visų farmacinių formų heparinai, suvartoti Lietuvos rinkoje nuo 2003 iki 2011 m. buvo įtraukti į vaistinių preparatų suvartojimo analizę. Iš viso buvo įvertinti šeši junginiai, t. y. penki MMMH ir nefrakcionuotas heparinas. Kiekvienas MMMH buvo parduodamas tik vienu prekybiniu pavadinimu, o NFH tiekė trys skirtingi gamintojai, todėl atitinkamai trys prekiniai pavadinimai buvo įvertinti atliekant skaičiavimus. Heparinų suvartojimo tyrime buvo panaudoti duomenys apie 24 farmacinių formų preparatus. Šie įvertinimai apima visus heparinus, suvartotus Lietuvoje per minėtą laikotarpį (*angl. DU100%*).

Anatominėje terapinėje cheminėje (ATC) klasifikacijos sistemoje veikliosios medžiagos yra skirstomos į grupes pagal organų sistemas, kuriose jie veikia ir jų terapines, farmakologines ir chemines savybes. Apibrėžta dienos/paros dozė (ADD) – tai vidutinė palaikomoji vaistinio preparato dozė per dieną suaugusiems. ATC/ADD sistema patogi priemonė pateikti statistiniams duomenims apie vaistinių preparatų suvartojimą šalyse. Pageidautina, kad vaistinių preparatų suvartojimo skaičiai būtų pateikiami kaip ADD skaičius / 1000 gyventojų / per dieną arba, kai preparatai vartojami ligoninėse, kaip ADD skaičius 100 arba 1000 lovadienių[9].

9 BNF. British National Formulary. Available from URL: http://bnf.org/bnf/index.htm; Nilsen EV, Fotis

1.3. Farmakoekonominio tyrimo metodika. Šio farmakoekonominio tyrimo tikslas buvo išanalizuoti mažos molekulinės masės heparinų grupės preparatų suvartojimo tendencijas šalyje ir parengti farmakoekonominių sprendimų modelius, kurie padėtų racionaliau panaudoti lėšas heparinų grupės preparatams Lietuvoje.

Rengiant farmakoekonominių sprendimo modelius, buvo remiamasi referentinių kainų nustatymo metodika bei įgyvendinama išlaidų mažinimo metodika. Mažos molekulinės masės heparinų grupė buvo tinkama išlaidų mažinimo analizei ir referentinės kainos taikymui, nes MMMH pademonstravo terapinį ekvivalentiškumą atliktos meta-analizės metu.

1.4. Prospektyvinio biomedicininio tyrimo metodika. Biomedicinio tyrimo tikslas - ištirti heparinų skyrimo tendencijas vidutinėje antrinio lygio klinikinėje ligoninėje šalyje vienerių metų laikotarpiu.

2. Rezultatai

2.1. Heparinų meta-analizės rezultatai. Atliekant meta-analizę buvo vertinamas mažos molekulinės

masės heparinų (Bemiparino, Enoksaparino, Dalteparino, Nadroparino, Tinzaparino) ir nefrakcionuoto heparino efektyvumas ir saugumas bei gydymo baigtys. Pagal šiuos parametrus, visi MMMH buvo pranašesni prieš NFH. Atlikus mažos molekulinės masės heparinų palyginimą, nebuvo nustatytas vienas preparatas, kuris būtų statistiškai reikšmingai pranašesnis prieš kitus tos grupės preparatus. Atsižvelgiant į atliktos meta-analizės rezultatus, mažos molekulinės masės heparinai gali būti laikomi tarpusavyje sukeičiamais preparatais dėl jų farmakologinių savybių ir analogiškų efektyvumo, saugumo rodiklių bei tikėtinų gydymo baigčių[10]. Atliktos meta-analizės rezultatais buvo remiamasi, pasirenkant atitinkamą farmakoekonominio modeliavimo metodiką.

2.2. Heparinų suvartojimo tyrimas Lietuvoje

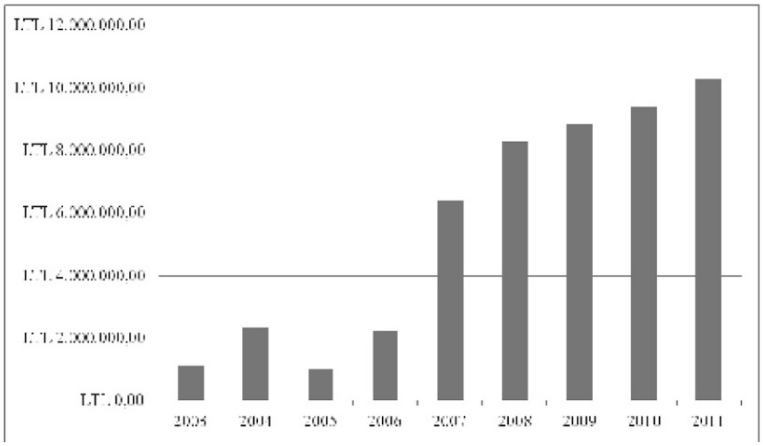
Heparinų suvartojimas Lietuvoje didėjo nuo 322 tūkst. ADD 2003 m. iki 2307 tūkst. ADD 2011 m., t. y. 7,16 karto per devynerių metų laikotarpį. Atitinkamai suvartojimas didėjo nuo 40,12 ADD / 1000 lovadienių 2003 m. iki 309,60 ADD / 1000 lovadienių 2011 m. Didžiausias augimas buvo stebimas 2007 m., kuomet heparinų suvartojimas padidėjo 380 proc., palyginus su 2006 m. rezultatais. Bendri heparinų kaštai Lietuvoje didėjo nuo 1088 tūkst. LTL 2003 m. iki 10284 tūkst. LTL 2011 m., t. y. daugiau nei devynis kartus per devynerių metų laikotarpį. Heparinų kaštai šalyje augo reikšmingai

MA. Developing a model to determine the effects of adverse drug events in hospital inpatients. *Am J Health Syst Pharm* 2007; 64(5): 521-5; RxList. The Internet Drug Index. Available from URL: http://rxlist.com; The publication Guidelines for ATC Classification and DDD Assignment gives further and detailed information about the ATC classification. (WHO Collaborating Centre for Drug Statistics Methodology, 2003; www.whocc.no).

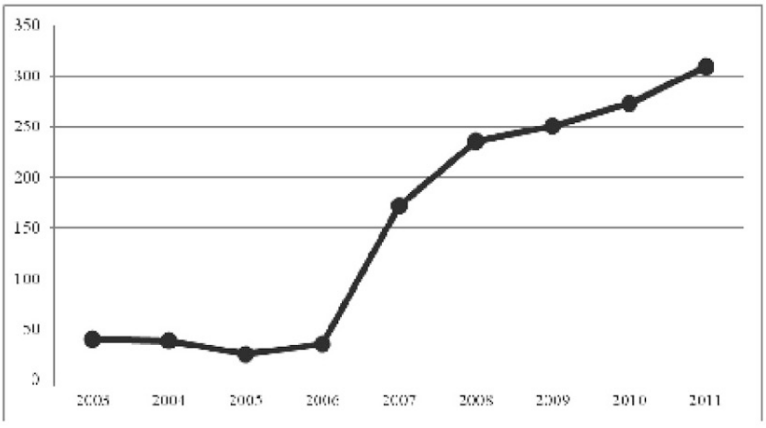
10 Kadusevicius E, Kildonaviciute G, Varanaviciene et al. Low-molecular-weight heparins: pharmacoeconomic decision modeling based on meta-analysis data. *Int J Technol Assess Health Care.* 2010 Jul; 26(3):272-9.

greičiau nei suvartojimo rodikliai, todėl buvo svarbu nustatyti faktorius, kurie lėmė tokį greitą kaštų augimą, pralenkusį suvartojimo rodiklius. (1 pav. ir 2 pav.).

Atlikus heparinų suvartojimo įvertinimą, buvo nuspręsta toliau nagrinėti heparinų kaštų augimo tendencijas ir atlikti farmakoekonominį tyrimą, kaštų augimui įvertinti.



1 pav. Heparinų kaštų dinamika Lietuvoje 2003–2011 m.



2 pav. Heparinų suvartojimo dinamika Lietuvoje 2003–2011 m. (ADD / 1000 lovadienių).

2.3. Heparinų farmakoekonominis tyrimas. Mažos molekulinės masės heparinai gali būti tarpusavyje pakeičiami pagal jų naudą sveikatai, todėl ši vaistinių preparatų

grupė buvo tinkama kaštų mažinimo analizės atlikimui ir referentinės kainos taikymui[11].

Farmakoekonominių sprendimų modeliavimą ir referentinės kainos taikymas heparinų grupėje buvo grindžiamas atliktos meta-analizės rezultatais[12].

Atlikus meta-analizę, buvo nuspręsta pasirinkti kaštų mažinimo metodiką ir taikyti ją heparinų grupės preparatams, atsižvelgiant į jų efektyvumo ir saugumo bei gydymo baigčių panašumus[13]. Farmakoekonominiai skaičiavimai buvo atliekami naudojant heparinų pardavimų Lietuvoje duomenis nuo 2003 m. iki 2011 m. Atlikti skaičiavimai apima visus Lietuvoje naudotus mažos molekulinės masės heparinus (angl. *DU100%*) per minėtą laikotarpį. Paskutinių trejų metų laikotarpis (2008 - 2011 m.) buvo pasirinktas kaip tinkamiausias įgyvendinti referentinės kainos nustatymo metodiką. Per šį laikotarpį nebuvo nustatyta neįprastų suvartojimo ir kaštų augimo tendencijų. Taigi buvo gana stabilus laikotarpis, kuris galėjo tinkamai atspindėti referentinės kainos metodikos taikymo naudą.

Atsižvelgiant į referentinės kainos taikymo metodiką, vieno iš preparatų mažiausia ADD kaina buvo pasirinkta kaip referentinė ir pritaikyta pasirinktai mažos molekulinės masės heparinų grupei. Pagal farmakoekonominius skaičiavimus, Dalteparino ADD kaina buvo mažiausias heparinų grupėje nuo 2008 m. iki 2011 m. Reikia pažymėti, kad Dalteparino vienos ADD kaina buvo apytikriai 50 procentų žemesnė nei kito pigiausio heparino ir maždaug du kartus mažesnės nei brangiausio heparino kaina. Atsižvelgiant į ADD kainų svyravimus per trejų metų laikotarpį, vidutinė Dalteparino vienos ADD kaina buvo naudojami kaštų mažinimo skaičiavimams. Be to, mažiausias Dalteparino vienos ADD kaina buvo fiksuota 2010 m., todėl antrasis kaštų mažinimo etapas buvo pagrįstas žemiausios Dalteparino ADD kainos panaudojimu.

Pasirenkant referentine kaina 4,02 Lt (vidutinė Dalteparino vienos ADD kaina), iš viso būtų galima sutaupyti 1,899 – 3,208 tūkst. Lt kasmet (pagal 2008–2011 m. duomenis). Remiantis išlaidų mažinimo modeliu 2008 – 2011 m., referentinės kainos metodikos įgyvendinimas leistų sumažinti bendras išlaidas MMMH 38,66–47,63%. Šis galimas išlaidų sumažėjimas turėtų būti laikoma reikšmingu, nes faktinės išlaidos heparinų grupės preparatams galėtų būti beveik du kartus mažesnės, jei nuoroda referentinės kainos nustatymo metodika buvo įgyvendinta praktikoje.

11 Avritscher EB, Cantor SB, Shih YC, et al. Cost-minimization analysis of low-molecular-weight heparin (dalteparin) compared to unfractionated heparin for inpatient treatment of cancer patients with deep venous thrombosis. Support Care Cancer. 2004 Jul;12(7):531-6. Epub 2004 Feb 21; *Kanavos P, Reinhardt U.* Reference Pricing For Drugs: Is It Compatible With U.S. Health Care? Health Affairs, 22, no.3 (2003):16-30; *Martínez-González J, Rodríguez C.* New challenges for a second-generation low-molecular-weight heparin: focus on bemiparin. Expert Rev Cardiovasc Ther. 2010 May;8(5):625-34; *Staginnus U.* European Pharma industry association (EFPIA) welcomes report on reference pricing. Available at URL://www.healtheconomicsblog.com.

12 Kadusevicius E, Kildonaviciute G, Varanaviciene et al. Low-molecular-weight heparins: pharmacoeconomic decision modeling based on meta-analysis data. *Int J Technol Assess Health Care.* 2010 Jul; 26(3):272-9.

13 *Ibid.*

Pasirenkant referentinę kaina 2,75 Lt (mažiausias Dalteparino vienos ADD kaina), iš viso būtų galima racionaliau panaudoti 3,218 – 4,679 tūkst. Lt kasmet (pagal 2008 - 2011 m. duomenis). Remiantis išlaidų mažinimo modeliu 2008–2011 metams, referentinės kainos metodikos taikymas leistų sumažinti išlaidas heparinams 59,82–69,59%. Šis galimas išlaidų sumažėjimas taip pat turėtų būti laikoma reikšmingu, nes faktinės išlaidos heparinams gali būti sumažintos daugiau nei du kartus, jei nuoroda referentinės kainos nustatymo metodika buvo įgyvendinta praktikoje. (1 lentelė, 2 lentelė, 3 lentelė).

Kaip siūlė 2008–2011 m. kaštų mažinimo modelis, referentinės kainos nustatymo metodikos įgyvendinimas reikšmingai prisidėtų prie tinkamo ir efektyvaus išlaidų valdymo mažos molekulinės masės heparinų grupėje.

1 lentelė. Heparinų suvartojimo ir kaštų pokytis Lietuvoje nuo 2003 m. iki 2011 m.

		Bemiparinas	Dalteparinas	Enoksa-parinas	Nadroparinas	Tinzapa-rinas	NHF	VISO
2003	Kaštai (Lt)	- Lt	41.620,00 Lt	260.514,00 Lt	483.729,00 Lt	75.544,00 Lt	226.869,00 Lt	1.088.276,00 Lt
	Suvartojimas (ADD)	---	5649	31034	53811	7620	233975	**332089**
2004	Kaštai (Lt)	- Lt	52.826,00 Lt	142.037,00 Lt	581.020,00 Lt	50.966,00 Lt	201.024,00 Lt	1.027.873,00 Lt
	Suvartojimas (ADD)	---	4983	16490	64714	3680	235282	**325149**
2005	Kaštai (Lt)	- Lt	79.384,00 Lt	109.538,00 Lt	857.335,00 Lt	- Lt	90.655,00 Lt	1.136.912,00 Lt
	Suvartojimas (ADD)	---	10160	11908	80105	0	108755	**210928**
2006	Kaštai (Lt)	- Lt	171.366,00 Lt	114.678,00 Lt	1.839.660,00 Lt	- Lt	178.232,00 Lt	**2.303.936,00 Lt**
	Suvartojimas (ADD)	---	21740	12260	168440	0	81050	**283490**
2007	Kaštai (Lt)	- Lt	486.041,05 Lt	2.099.463,36 Lt	3.137.551,37 Lt	- Lt	681.834,90 Lt	**6.404.890,68 Lt**
	Suvartojimas (ADD)	---	98620	330850	359650	0	584661	**1373781**
2008	Kaštai (Lt)	511.639,72 Lt	769.864,83 Lt	3.010.702,10 Lt	3.291.548,69 Lt	- Lt	772.147,02 Lt	**8.355.902,36 Lt**
	Suvartojimas (ADD)	58760	157920	476198	395657	0	749958	**1838493**
2009	Kaštai (Lt)	1.087.386,00 Lt	898.817,00 Lt	4.045.505,00 Lt	2.206.068,00 Lt	- Lt	619.989,75 Lt	8.857.765,75 Lt
	Suvartojimas (ADD)	141795	201840	663436	287080	0	612940	**1907091**

2010	Kaštai (Lt)	933.055,00 Lt	1.586.553,00 Lt	2.952.496,00 Lt	2.189.751,00 Lt	- Lt	1.733.442,94 Lt	9.395.297,94 Lt
	Suvartojimas (ADD)	148630	576500	492204	398040	0	458463	**2073837**
2011	Kaštai (Lt)	1.1195.621,47 Lt	2.514.636,70 Lt	3.055.190,91 Lt	2.288.855,52 Lt	- Lt	1.229.159,63 Lt	10.283.464,23 Lt
	Suvartojimas (ADD)	231395	899480	504614	449590	0	221450	**2306529**

2 lentelė. Heparinų suvartojimo (ADD/1000 lovadienių) ir kaštų dinamika (vienos ADD kaina) Lietuvoje (2003 – 2011)

		Bemiparinas	Dalte-parinas	Enoksaparinas	Nadroparinas	Tinza-parinas	NFH	VISO
2003	ADD/1000 lovadienių	----	0,68	3,75	6,50	0,92	28,27	**40,12**
	Vienos ADD kaina	- Lt	7,37 Lt	8,39 Lt	8,99 Lt	9,91 Lt	0,97 Lt	**3,28 Lt**
2004	ADD/1000 lovadienių	----	0,60	1,98	7,76	0,44	28,20	**38,97**
	Vienos ADD kaina	- Lt	10,60 Lt	8,61 Lt	8,98 Lt	13,85 Lt	0,85 Lt	**3,16 Lt**
2005	ADD/1000 lovadienių	----	1,24	1,45	9,76	----	13,25	**25,70**
	Vienos ADD kaina	- Lt	7,81 Lt	9,20 Lt	10,70 Lt	- Lt	0,83 Lt	**5,39 Lt**
2006	ADD/1000 lovadienių	----	2,75	1,55	21,27	----	10,24	**35,81**
	Vienos ADD kaina	- Lt	7,88 Lt	9,35 Lt	10,92 Lt	- Lt	2,20 Lt	**8,13 Lt**
2007	ADD/1000 lovadienių	----	12,33	41,38	44,98	----	73,12	**171,82**
	Vienos ADD kaina	- Lt	4,93 Lt	6,35 Lt	8,72 Lt	- Lt	1,17 Lt	**4,66 Lt**
2008	ADD/1000 lovadienių	7,54	20,25	61,07	50,74	----	96,19	**235,79**
	Vienos ADD kaina	8,71 Lt	4,88 Lt	6,32 Lt	8,32 Lt	- Lt	1,03 Lt	**4,54 Lt**
2009	ADD/1000 lovadienių	18,65	26,55	87,26	37,76	----	80,61	**250,82**
	Vienos ADD kaina	7,67 Lt	4,45 Lt	6,10 Lt	7,68 Lt	- Lt	1,01 Lt	**4,64 Lt**
2010	ADD/1000 lovadienių	19,55	75,82	64,73	52,35	----	60,30	**272,75**
	Vienos ADD kaina	6,28 Lt	2,75 Lt	6,00 Lt	5,50 Lt	- Lt	3,78 Lt	**4,53 Lt**
2011	ADD/1000 lovadienių	31,06	120,74	67,73	60,35	----	29,72	**309,60**
	Vienos ADD kaina	5,17 Lt	2,80 Lt	6,05 Lt	5,09 Lt	- Lt	5,55 Lt	**4,46 Lt**

3 lentelė. Pagal referentinės kainos metodiką perskaičiuoti heparinų kaštai Lietuvoje (2008–2011)

		Bemiparinas	Dalteparinas	Enoksaparinas	Nadroparinas	VISO
Referentinė kana (vienos ADD kaina) - 2,75 Lt						
2008	Pagal referentinę kainą perskaičiuoti kaštai (Lt)	161.590,00 Lt	434.280,00 Lt	1.309.544,50 Lt	1.088.056,75 Lt	**2.993.471,25 Lt**
	Racionaliau panaudojama kaštų dalis (Lt)	350.049,72 Lt	335.584,83 Lt	1.701.157,60 Lt	2.203.491,94 Lt	**4.590.284,09 Lt**
Referentinė kana (vienos ADD kaina) - 2,75 Lt						
2009	Pagal referentinę kainą perskaičiuoti kaštai (Lt)	389.936,25 Lt	555.060,00 Lt	1.824.449,00 Lt	789.470,00 Lt	**3.558.915,25 Lt**
	Racionaliau panaudojama kaštų dalis (Lt)	697.449,75 Lt	343.757,00 Lt	2.221.056,00 Lt	1.416.598,00 Lt	**4.678.860,75 Lt**
Referentinė kana (vienos ADD kaina) - 2,75 Lt						
2010	Pagal referentinę kainą perskaičiuoti kaštai (Lt)	408.732,50 Lt	---	1.353.561,00 Lt	1.094.610,00 Lt	**2.856.903,50 Lt**
	Racionaliau panaudojama kaštų dalis (Lt)	524.322,50 Lt	---	1.598.935,00 Lt	1.095.141,00 Lt	**3.218.398,50 Lt**
Referentinė kana (vienos ADD kaina) - 2,75 Lt						
2011	Pagal referentinę kainą perskaičiuoti kaštai (Lt)	636.336,25 Lt	2.473.570,00 Lt	1.387.688,50 Lt	1.236.372,50 Lt	**5.733.967,25 Lt**
	Racionaliau panaudojama kaštų dalis (Lt)	559.285,22 Lt	41.066,70 Lt	1.667.502,41 Lt	1.052.483,02 Lt	**4.549.496,98 Lt**

2.4. Biomedicininio tyrimo rezultatai

Tyrimas buvo atliekamas siekiant ištirti heparinų skyrimo tendencijas vidutinėje antrinio lygio klinikinėje ligoninėje šalyje, kadangi heparinai daugiausiai yra skiriami ir vartojami stacionaro sąlygomis. Atliekant biomedicininį tyrimą, buvo įvertintos 339 pacientų ligos istorijos. Šie pacientai buvo gydomi antrinio lygio klinikinėje ligoninėje nuo 2009 - 2010 m. Šis tyrimas buvo vykdomas kardiologijos, urologijos, vidaus ligų, chirurgijos ir infekcinių ligų ir intensyvios terapijos skyriuose, kur heparinai buvo nuolat skiriami pacientams gydymo ir profilaktikos tikslais.

Svarbiausios pacientų charakteristikas: pacientai dažniau buvo vyrai (n=177; 52,2%); senyvo amžiaus (vidutinis amžius 69,6 m.). Vidutinė hospitalizacijos trukmė buvo 9,6 d., o vidutinė heparinų vartojimo trukmė buvo šiek tiek ilgesnė nei 4 d. (4 lentelė).

4 lentelė. Bendrosios biomedicininio tyrimo pacientų charakteristikos

Bendrosios charakteristikos	Reikšmė
Tyrimo subjektų skaičius	339
Lytis	
Moterys (*n ir %*)	162 (47,8%)
Vyrai (*n ir %*)	177 (52,2%)

	Vidurkis, SN	Mediana	Minimali reikšmė	Maksimali reikšmė
Amžius (metai)	69,6 (13,3)	72.0	21	101
Hospitalizacijos trukmė (dienos)	9,6 (9,1)	8.0	1	87
Heparinų vartojimo trukmė (dienos)	4,3 (4,4)	3.0	1	53

Šie heparinai buvo vartojami antrinio lygio klinikinėje ligoninėje tyrimo metu: Enoksaparinas (*Clexane*), Nadroparinas (*Fraxiparin*), Dalteparinas (*Fragmin*) ir Bemiparinas (*Zibor*). Kaip buvo nustatyta tyrimo metu, dažniausiai heparinai buvo vartojami VT (venų tromboembolijos) profilaktikai chirurginių intervencijų metu, 39,8% (n = 135) ir nestabilios krūtinės anginos arba miokardo infarkto gydymui, 49,0% (n = 166). Kitų indikacijų pacientų skaičiai buvo reikšmingai mažesni: GVT (gilių-jų venų trombozė) - 4,1% (n = 14) ir profilaktika mažai judantiems pacientams 6,5% (n = 22). Dalteparinas buvo dažniausiai vartojamas heparinas, jis buvo skiriamas 70,2%. atvejų.

Santykinių kontraindikacijų dažnis buvo 69,0% (n = 234). Dažniausia santykinė kontraindikacija buvo senyvas amžiaus, t. y. heparinai buvo skiriami vyresniems nei 65 metų amžiaus pacientams.

90,27% visų gydymo baigčių buvo teigiamos (n = 306), t. y. šie pacientai pasveiko. Iš viso, 9,14 % gydymo rezultatų buvo neigiami, t. y. mirtis (6,49%, n = 22), nepasveiko (1,77%, n = 6), pasveiko su pasekmėmis (1,47%, n = 5). Dažniausios mirties priežastys buvo GVT (giliųjų venų trombozė) ar PE (plaučių embolija) ir įvairūs širdies ir kraujagyslių sistemos sutrikimai.

Bendras nepageidaujamų reakcijų, nurodytų pacientų ligos istorijose, dažnis buvo 13,57%. (n = 46). Šis skaičius nesiskyrė nuo nepageidaujamos reakcijos dažnio, nurodyto gamintojo instrukcijose (preparatų charakteristikų santraukose)[14].

Nepageidaujamų reakcijų raportavimas laiku, užtikrina tinkamą pacientų medicininę priežiūrą, leidžia pateisinti būsimus terapijos pakeitimus ir padeda išvengti nepageidaujamų reakcijų pasikartojimo ateityje[2,3,8,17].

Svarbu dar kartą pabrėžti saugumo stebėjimo svarbą, skiriant heparinus pacientams. Stebėjimas ypač svarbus, kai heparinus vartoja pacientai, kuriems heparinai skirti ilgalaikiam gydymui; pacientams, kurių hospitalizacijos trukmė yra ilgesnė nei įprasta; ir pacientams, kurių tikėtina gydymo baigtis yra neigiama.

Biomedicininio tyrimo metu buvo vertinamas heparinų skyrimo atitikimas *NHS Devon'o* klinikinėms rekomendacijoms (Mažos molekulinės masės heparinais – naudojimas ir priežiūra bendruomenės ligoninėse). Tyrimo duomenys buvo dar kartą įvertinti, siekiant nustatyti, kaip skyrėsi heparinų saugumo stebėjimo praktika antrinio lygio klinikinėje ligoninėje palyginus su tarptautinėmis rekomendacijomis.

14 Martínez-González J, Rodríguez C. New challenges for a second-generation low-molecular-weight heparin: focus on bemiparin. Expert Rev Cardiovasc Ther. 2010 May;8(5):625-34; Leclerc-Foucras S, Bagheri H, Samii K, et al. Modifications of low-molecular weight heparin use in a French university hospital after implementation of new guidelines. *Drug Saf.* 2007;30(5):409-17.

Atliekant biomedicininį tyrimą, pacientų ligos istorijose nebuvo rasta jokios informacijos, susijusios su VTE rizikos vertinimu, kartu vartojamų vaistinių preparatų, didinančių kraujavimo riziką vertinimu ir kontraindikacijų rizikos vertinimu. Dėl šio priežasties kasdieninė medicininė praktika turėtų būti koreguojama, kad atitiktų tarptautines heparinų skyrimo gaires (4 lentelė).

Svarbu pabrėžti, kad laboratorinių tyrimų rezultatų stebėjimas turėtų būti atliekamas prieš skiriant heparinus, tačiau atitinkami laboratoriniai tyrimai nebuvo atlikti antrinio lygio klinikinėje ligoninėje 60,77% visų atvejų (n = 206). Remiantis tyrimo duomenimis, laboratorinių tyrimų rezultatai buvo stebimi 39,23% visų atveju (n = 133). Taip pat labai skyrėsi atliktų laboratorinių tyrimų apimtis, todėl visi reikiami laboratoriniai tyrimai buvo atlikti gerokai mažesniam pacientų skaičiui. Pavyzdžiui, elektrolitų stebėjimas buvo atliekamas dažniausiai, t. y. buvo ištirta 33,33% pacientų (n = 113). Kepenų funkcijos tyrimai buvo atlikti 65 pacientams (19,17%). 89 pacientams buvo stebima inkstų funkcijos *urea* parametrai (26,25%) Trombocitų skaičius, kartu su INR ir DATL parametrais buvo stebimi 27,43% atvejų (n = 93). (5 lentelė).

Pagal tarptautines rekomendacijas, laboratorinių tyrimų rezultatai turėtų būti stebimi vartojant heparinus hospitalizacijos metu. Remiantis tyrimo duomenimis, laboratorinių tyrimų rezultatai buvo stebimi 53,98% visų atveju (n = 183). Atitinkami laboratoriniai tyrimai nebuvo atlikti antrinio lygio klinikinėje ligoninėje 46,02% visų atvejų (n = 156). Taip pat labai skyrėsi atliktų laboratorinių tyrimų apimtis. Pavyzdžiui, elektrolitų stebėjimas buvo atliekamas dažniausiai, t. y. buvo ištirta 25,96% pacientų (n = 88). Kepenų funkcijos tyrimai buvo atlikti 60 pacientų (17,70%). 66 pacientams buvo stebima inkstų funkcija (19,47%). (5 lentelė).

5 lentelė. Medicininės praktikos, skiriant MMMH, atitikimas tarptautinėms gairėms antrinio lygio klinikinėje ligoninėje

Pacientų saugumo stebėjimo reikalavimai		**Kasdieninės praktikos atitikimas tarptautinėms gairėms**
Reliatyvių kontraindikacijų vertinimas	Senyvas amžius	223 iš 339 (65,78%)
	Mažas kūno svoris	339 iš 339 (100%)
	Inkstų funkcijos nepakankamumas	89 iš 339 (26,25%)
	Kraujavimo rizika	0 iš 339 (0%)
VTE rizikos vertinimas		0 iš 339 (0%)
Gretutinių vaistiniai preparatų, kurie veikia trombocitų funkciją, vertinimas		0 iš 339 (0%)
Gretutinių susirgimų vertinimas		0 iš 339 (0%)
Dozės korekcija, atsižvelgiant į reliatyvias kontraindikacijas		0 iš 339 (0%)
Laboratorinių parametrų stebėjimas hospitalizuojant		133 iš 339 (39,23%)
Laboratorinių parametrų stebėjimas hospitalizacijos metu		183 iš 339 (53,98%)

Atsižvelgiant į biomedicininio tyrimo rezultatus, buvo suformuluotas farmakoekonominių sprendimų modelis antrinio lygio klinikinės ligoninės heparinų kaštų mažinimo galimybėms įvertinti. Pasirenkant referentine kaina 2,75 Lt (mažiausias Dalteparino vienos ADD kaina), iš viso būtų galima racionaliau panaudoti 2155,79 Lt. Remiantis išlaidų mažinimo modeliu, referentinės kainos metodikos taikymas leistų sumažinti išlaidas heparinams 29,20%. Šis galimas išlaidų sumažėjimas turėtų būti laikoma reikšmingu (6 lentelė).

6 lentelė. Pagal referentinės kainos metodiką perskaičiuoti heparinų kaštai antrinio lygio klinikinėje ligoninėje

	Bemiparin	**Dalteparin**	**Enoxaparin**	Nadroparin	IŠ VISO
Heparinų kaštai	1526,04 Lt	3300,00 Lt	462,00 Lt	2095,50 Lt	**7383.54 Lt**
Heparinų suvartojimas (ADD)	243	1200	77	381	**1901**
Referentinė vienos ADD kaina - 2.75 Lt					
Perskaičiuoti kaštai	668,25 Lt	3300,00 Lt	211,75 Lt	1047,75 Lt	5227,75 Lt
Kaštų sumažėjimas	857,79 Lt	0	250,25 Lt	1047,75 Lt	**2155,79 Lt**

Diskusija

Heparinų suvartojimas Lietuvoje pastaruosius devynerius metus reikšmingai didėjo. Pagrindinis suvartojimo rodiklis, t. y. ADD skaičius tenkantis 1000 lovadienių, išaugo daugiau nei septynis kartus, nuo 40,12 ADD / 1000 lovadienių 2003 m. iki 309,60 ADD / 1000 lovadienių 2011 m. Bendri heparinų kaštai Lietuvoje didėjo nuo 1088 tūkst. LTL 2003 m. iki 10283 tūkst. LTL 2011 m., t. y. daugiau nei devynis kartus per devynerių metų laikotarpį. Heparinų kaštai augo reikšmingai greičiau nei suvartojimo rodikliai. Tai rodo, jog būtina tyrinėti šią vaistinių preparatų grupę ir taikyti farmakoekonominį sprendimų modelį išlaidoms reguliuoti.

Manoma, kad heparinų suvartojimo augimą lėmė kelios pagrindinės priežastys, t. y. platesnis heparinų indikacijų spektras, dažnesnis skyrimas pacientams profilaktikos ir gydymo tikslais, ilgėjantis heparinų sąrašas ir didėjantis jų pasirinkimas, informacijos sklaida apie heparinų poveikį ir kt.

Atlikus heparinų suvartojimo įvertinimą, buvo nuspręsta toliau nagrinėti heparinų kaštų augimo tendencijas ir atlikti farmakoekonominį tyrimą, kaštų augimui įvertinti.

Remiantis meta-analizės rezultatais, buvo pasirinkta kaštų mažinimo metodika MMMH farmakoekonominės analizės sprendimų modeliui sukurti. Kaštų mažinimo metodikos pasirinkimas buvo grindžiamas vienodais MMMH efektyvumo ir saugumo parametrais bei gydymo baigtimis. Kaštų mažinimo metodika buvo įgyvendinta pasinaudojant referentinės kainos taikymo principais. Pasirenkant referentine kaina

žemiausią vienos Dalteparino ADD kainą (2,75 LTL), kasmet būtų galima racionaliau panaudoti 3218 – 4679 tūkst. LTL (2008 – 2011 m. duomenys). Tokiu būdu būtų galima sumažinti heparinų kaštus 60%. Šis galimas išlaidų sumažėjimas turėtų būti laikoma reikšmingu, nes faktinės išlaidos heparinų grupės preparatams galėtų būti beveik du kartus mažesnės, jei nuoroda referentinės kainos nustatymo metodika buvo įgyvendinta praktikoje. Kaip siūlė 2008 – 2011 m. kaštų mažinimo modelis, referentinės kainos nustatymo metodikos įgyvendinimas reikšmingai prisidėtų prie tinkamo ir efektyvaus išlaidų valdymo mažos molekulinės masės heparinų grupėje. Kasmet galimai racionaliau panaudojamų lėšų dalis galėtų būti perskirstoma ir panaudojama kitoms sveikatos priežiūros sistemos išlaidoms kompensuoti.

Heparinai pasaulyje ir Lietuvoje dažniausiai yra skiriami stacionare gydomiems pacientams, todėl tinkamas heparinų skyrimas padėtų racionaliau panaudoti sveikatos priežiūros įstaigų lėšas. Apskaičiuota, kad vidutiniškai 10 proc. ligoninės išlaidų yra skiriama heparinų kaštams padengti. Todėl svarbu nuolat analizuoti heparinų skyrimo ir suvartojimo tendencijas ligoninėse, o tai šiuo metu nėra atliekama Lietuvos sveikatos priežiūros įstaigose.

Biomedicininio tyrimo rezultatai parodė, kad saugumo parametrų stebėjimo ligoninėje labai dažnai neatitinka tarptautinių heparinų skyrimo rekomendacijų. Atliekant biomedicininį tyrimą, pacientų ligos istorijose nebuvo identifikuota ar buvo atliekamas venų tromboembolijos rizikos vertinimas, gretutinių vaistinių preparatų, didinančių kraujavimo riziką, skyrimo rizikos vertinimas, galimos kontraindikacijos. Galima daryti išvadą, kad saugumas stebimas nepakankamai, kaip nurodo tarptautinės heparinų skyrimo rekomendacijos ir gairės[15].

Heparinų suvartojimas ir kaštai Lietuvoje reikšmingai didėjo, tai rodo, jog būtina taikyti farmakoekonominį modelį išlaidoms reguliuoti. Heparinų efektyvumo ir saugumo monitoravimas tik maža apimtimi atitinka tarptautines rekomendacijas, todėl nacionalinės gydymo rekomendacijos ir gydymo auditas turėtų būti prioritetiniai siekiniai skatinant racionalų heparinų vartojimą.

15 Leclerc-Foucras S, Bagheri H, Samii K, et al. Modifications of low-molecular weight heparin use in a French university hospital after implementation of new guidelines. *Drug Saf.* 2007;30(5):409-17; Klein W, Kraxner W, Hödl R, et al. Patterns of use of heparins in ACS. Correlates and hospital outcomes: the Global Registry of Acute Coronary Events (GRACE). *Thromb Haemost.* 2003 Sep;90(3):519-27; Lanthier L, Bechard D, Viens D, et al. Evaluation of thromboprophylaxis in patients hospitalized in a tertiary care center: an applicable model of clinical practice evaluation. Revision of 320 cases. *J Mal Vasc* 2011. 36(1): 3-8; NICE clinical guideline. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital. Available at URL://www.nice.org.uk/guidance/CG92; NICE clinical guideline 46. Venous thromboembolism. April 2007. Available from URL: http://www.nice.org.uk; Prandoni P. Prevention and treatment of venous thromboembolism with low-molecular-weight heparins: Clinical implications of the recent European guidelines. *Thromb J.* 2008; 6: 13. Published online 2008 September 9. doi: 10.1186/1477-9560-6-13; Schünemann H.J., Hirsh J, Guyatt G, et al. Antithrombotic and Thrombolytic Therapy: Evidence-Based Clinical Practice Guidelines American College of Chest Physicians (8th Edition). *Chest* 2008;133;110S-112S; Vats V, Nutescu EA, Theobald JC, et al. Survey of hospitals for guidelines, policies, and protocols for anticoagulants. *Am J Health Syst Pharm.* 2007 Jun 1;64(11):1203-8.

Išvados ir pasiūlymai

Remdamiesi atliktu tyrimu, pateikiame keletą pasiūlymų, kaip būtų galima skatinti racionalią mažos molekulinės masės heparinų vartojimo politiką Lietuvoje. Siūlytume sveikatos priežiūros įstaigoms paruošti ir patvirtinti heparinų skyrimo ir saugumo stebėjimo gaires, kuriomis būtų vadovaujamasi, skiriant heparinus pacientams profilaktikos ar gydymo tikslais. Atitinkamai ligoninėse turėtų būti atliekami auditai, kurie įvertintų heparinų skyrimo praktiką pacientams ir šios praktikos atitikimą patvirtintoms gairėms. Mažos molekulinės masės heparinų grupės vaistiniams preparatams galėtų būti taikoma referentinė kaina, kuri būtų naudojama sveikatos priežiūros įstaigoms organizuojant viešuosius pirkimus. Pritaikius referentinės kainos metodiką organizuojant heparinų viešinusius prikimus, būtų galima gerokai sumažinti gydymo įstaigų kaštus šios grupės vaistiniams preparatams. Sutaupytos lėšos galėtų būti panaudojamos išlaidoms, atsirandančioms naujus vaistinius preparatus įtraukiant į gydymui naudojamų vaistų sąrašus, kompensuoti.

Pharmacoepidemiologic and pharmacoeconomic research significance promoting rational low-molecular-weight heparins utilization policy in Lithuania

Gabrielė Kildonavičiūtė
JSC Quintiles, Manager Clinical Operations, Lithuania

Vilma Morkūnienė
Department of Technical Science, Kauno kolegija / University of applied Science, Lithuania

Edmundas Kaduševičius
Lithuanian University of Health Sciences, Institute of Physiology and Pharmacology, Lithuania

Summary

Aim of this research *– to investigate the significance of pharmacoeconomic and pharmacoepidemiologic research data promoting rational low-molecular-weight heparins utilization policy.*

Methodology *– drug utilization research was based on WHO ATC/DDD (Defined Daily Dose) methodology; pharmacoeconomic cost-minimization research was based on reference pricing methodology; prospective biomedical research was conducted to investigate the practical aspects of heparins prescription and administration at the in-patient setting.*

Results *– utilization of heparins in Lithuania increased for 40.12 DDD/1000 hospitalization days (HD) in 2003 up to 309.60 ADD/1000 HD in 2011. Total expenditures on heparins increased from 1,088 thousand LTL in 2003 up to 10,284 thousand LTL in 2011, i.e. more than nine-fold during the nine-year period. Setting the reference price of 2.75 LTL (lowest Dalteparin single DDD price) for low-molecular-weight heparins group would result in total savings of 3,218–4,679 thousand LTL in Lithuania yearly (as per 2008 - 2011 data). Reference pricing implementation would enable to decrease the total expenditures on LMWHs by nearly 60%. This potential decrease of expenditures should be considered significant as actual costs of heparins could be reduced more than two-fold. Heparins safety and efficacy monitoring practices at the in-patient setting*

just partially adhered to international guidelines. Before heparins administration, laboratory data safety monitoring was performed for 39.23% of subjects (n=133). Laboratory data safety monitoring was only performed for 53.98% of subject (n=183) during their treatment course.

***Conclusions** – heparins costs and utilization rates have significantly increased in the last decade. Such a dramatic increase justifies the implementation of pharmacoeconomic models and policies for costs management. Heparins safety and efficacy monitoring practices just partially adhered to international recommendations, thus national treatment guidelines and medical auditing should be prioritized promoting the rational use of heparins in the country.*

***Keywords**: low-molecular-weight heparins, pharmacoeconomics, reference pricing, cost-minimization.*

Gabrielė Kildonavičiūtė, Lietuvos sveikatos mokslų universiteto absolventė, Farmacijos magistrė. UAB Quintiles (Sutartinėje mokslinių tyrimų organizacijoje – SMTO) dirba vadovės klinikinėms operacijos pareigose.

Vilma Morkūnienė, socialinių mokslų daktarė, Kauno kolegijos Bendratechninių mokslų katedros docentė.

Edmundas Kaduševičius, klinikinis farmakologas, Lietuvos sveikatos mokslų universiteto biomedicinos mokslų daktaras, Fiziologijos ir farmakologijos instituto, Klinikinės farmakologijos katedros docentas.

Gabrielė Kildonavičiūtė, Master of Pharmacy degree obtained at Lithuanian University of Health Sciences. Currently holds a position of Manager Clinical Operations at JSC Quintiles (Clinical Research Organization – CRO).

Vilma Morkūnienė, Doctor of Social Science, Assoc. professor at the Department of Technical Science, Kauno kolegija / University of Applied Science.

Edmundas Kaduševičius, clinical pharmacologist, PhD, Assoc. Professor at Department of Clinical Pharmacology, Institute of Physiology and Pharmacology, Lithuanian University of Health Science.

RESEARCH

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

Gabriele Pranckeviciene, MPharm; Edmundas Kadusevicius, MPharm, MD, PhD; and Asta Putniene, MPharm

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.

J Manag Care Pharm. 2013;19(6):478-86

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 authors[11-14] 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 (±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 ± 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 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).

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.

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

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
		0.0%	0.0%	44.4%	55.6%	0.0%
Total		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
		0.0%	95.8%	0.0%	4.2%	0.0%
Total		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 ± 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

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	—

[a]*All 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 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)

[a]*All 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, χ^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, χ^2 = 69.3, P < 0.0005), an increased risk for the development of ADRs (r_s = 0.277, χ2 = 17.5, P < 0.0005), an increased risk for negative treatment outcomes (r_s = 0.236, χ^2 = 50.5, P < 0.0005), and an increased risk for a prolonged hospitalization period (r_s = 0.169, χ^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, 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).

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.

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, χ^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, χ^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-

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 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]

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.

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.[10] 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

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.

Authors

GABRIELE PRANCKEVICIENE, MPharm, is Manager, Clinical Operations, Quintiles, JSC, Kaunas, Lithuania. EDMUNDAS KADUSEVICIUS, MPharm, MD, PhD, is Associate Professor, and ASTA PUTNIENE, MPharm, is Assistant, Institute of Physiology and Pharmacology, Department of Clinical Pharmacology, Lithuanian University of Health Sciences, Kaunas, Lithuania.

AUTHOR CORRESPONDENCE: Gabriele Pranckeviciene, MPharm, Manager, Clinical Operations, Quintiles, JSC, Savanoriu av. 349, LT-49425 Kaunas, Lithuania. Tel.: +370.611.24373; Fax: +370.37.312775; E-mail: gabrielekil@yahoo.com.

DISCLOSURES

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

Concept, design, data collection, data analysis, and manuscript writing were performed by all authors.

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