

Clinical effectiveness analysis of LMWH in the prevention of deep vein thrombosis and pulmonary embolism



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ABSTRACT

Background: The aim of the study was to assess the clinical effectiveness of low molecular weight heparins in prevention of deep vein thrombosis and pulmonary embolism in comparison with physical methods, unfractionated heparin and placebo, by a systematic review of reports in medical literature.

Methods: The assessment of the clinical effectiveness of undertaken interventions was compliant with the principles of systematic review (EBM), based on the Cochrane Collaboration guidelines. Statistical analysis and meta-analysis were performed by means of the RevMan 4.2 software version.

Results: Regarding the risk of postoperative overall deep-vein thrombosis and proximal deep-vein thrombosis, a meta-analysis of obtained results revealed a trend towards low-molecular-weight heparin versus the results of physical methods. However, the difference between the analyzed groups did not reach statistical significance.

Compared to placebo, the results of deep vein thrombosis risk assessment by meta-analysis showed statistically significant differences in favor of low-molecular-weight heparins (RR = 0.50, 95% CI: 0.34, 0.74, P = 0.0004, NNT = 23).

In comparison to the group, receiving unfractionated heparin, the observed differences did not attain statistical significance, neither in thromboembolism prevention nor in deep vein thrombosis treatment.

Regarding the risk of any bleeding episodes, the meta-analysis showed a statistically significant difference in favor of low-molecular-weight heparins administered in the study group vs. placebo results in the control group (RR = 1.55, 95% CI: 1.07, 2.24, P = 0.02) with the NNH equal to 94.

Conclusions: Low molecular weight heparins are effective and safe treatment for venous thromboembolism versus placebo, however, no statistically significant advantages were observed vs. physical methods or unfractionated heparins.

Keywords:

UFH, Venous thromboembolic, Venous thromboembolism, deep vein thrombosis, DVT, intermittent pneumatic compression, IPC, LMWH, low-molecular-weight heparin, PE, pulmonary embolism

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INTRODUCTION

Low molecular weight heparins are used with increasing frequency in the primary prevention and treatment of venous thrombosis and acute myocardial infarction. Low molecular weight heparins (LMWH) are more expensive than unfractionated heparin but associated with additional benefits, such as shorter hospitalization and the possibility of treatment at home.

Due to the increasing popularity of LMWH and the relatively high public reimbursement, allocated for this group of drugs, there are more and more questions about the cost-effectiveness of such procedures. This analysis provides some basis for consideration of the advisability of using low molecular weight heparins. Based on meta-analyses of available clinical evidence, an assessment was conducted of the clinical effects of low molecular weight heparins versus placebo, unfractionated heparin or physical methods.

CLINICAL PICTURE AND EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

The definition of venous thromboembolism includes two diseases: Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), which is often a complication of the former.

Deep vein thrombosis and related complications – pulmonary embolism and the post-thrombotic syndrome – form a very serious interdisciplinary problem of today's medicine, with various risks which may result from these complications. Pulmonary embolism is a severe, life-threatening disease, and the post-thrombotic syndrome, a chronic condition – is often the cause of permanent disability⁴⁷.

According to the Polish data, deep vein thrombosis affects about 50 thousand people per year and pulmonary embolism of varying severity is identified in about 20 thousand people, being the cause of about

10% of all hospital deaths and a leader among preventable causes of mortality. Frequently, deep vein thrombosis has an occult clinical course. It can occur in hospitalized patients, as well as in apparently healthy individuals at any time during their life. Pulmonary embolism is often the first and final sign of deep vein thrombosis. The majority of unrecognized cases of thrombosis lead to the thrombotic syndrome and incidents of pulmonary embolism, later followed by chronic pulmonary hypertension⁴⁸.

The treatment of venous thromboembolism complications is extremely expensive – the costs are comparable to expenditures in oncology, arising not only from the treatment of acute thrombosis or early complications, but also from treatment of the post-thrombotic syndrome and pulmonary hypertension. Indirect costs are associated with days on sick-leave and paid sickness benefits.

PREVENTION OF VENOUS THROMBOEMBOLISM

Physical methods (intermittent pneumatic compression): The aim of physical methods is to reduce venous stasis in the legs, a major contributor to thrombosis formation. These methods are easy, and require relatively cheap measures, while being proven as fairly effective for patients with a moderate risk of thrombotic events. However, in cases of high risk of thrombosis, the outcomes are not satisfactory.

Safety is a great advantage of the physical methods, especially where the risk of bleeding complications, associated with the use of anticoagulants, is unacceptable, for example, after neurosurgical procedures, multiple accidental trauma or surgery within the eyeball.

Pharmacological methods: Pharmacological methods rely on the drugs that inhibit blood clotting. Despite a long list of available products, the medicinal products, most readily used in the prophylaxis of venous thromboembolism, are heparin and oral an-

SAFETY IS A GREAT ADVANTAGE OF THE PHYSICAL METHODS, ESPECIALLY WHERE THE RISK OF BLEEDING COMPLICATIONS, ASSOCIATED WITH THE USE OF ANTICOAGULANTS, IS UNACCEPTABLE, FOR EXAMPLE, AFTER NEUROSURGICAL PROCEDURES, MULTIPLE ACCIDENTAL TRAUMA OR SURGERY WITHIN THE EYEBALL.

ticoagulants. Unfractionated heparin (UFH), administered subcutaneously and in small doses (5000 IU every 8-12 hrs.) is a standard method to prevent venous thromboembolism in patients with moderate and high risk of thrombosis. Low molecular weight heparins, administered by subcutaneous injection in small doses, demonstrate a significantly higher bioavailability (> 90%) vs. unfractionated heparin (20-30%). They also present a longer half-life and may be used

idence Based Medicine principles, with the following electronic databases:

- The Cochrane Controlled Trials Register (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Medline (PubMed)
- Embase
- BioMed Central
- and medical electronic portals:

Table 1. Issues vs key words in literature review

ISSUE	KEY WORDS
CLINICAL PROBLEM, POPULATION	(#1) VENOUS THROMBOEMBOLISM (#2) DEEP VEIN THROMBOSIS (#3) PULMONARY EMBOLISM
INTERVENTION	(#4) LOW MOLECULAR WEIGHT HEPARIN (#5) ENOXAPARIN (#6) NADROPARIN (FRAXIPARIN) (#7) DALTEPARIN
COMPARATORS	(#8) MECHANICAL DEVICES (#9) PLACEBO (#10) UNFRACTIONATED HEPARIN
OUTCOMES	(#11) THROMBOPROPHYLAXIS (#12) VTE, DVT PROPHYLAXIS (#13) VTE, DVT PREVENTION (#14) ADVERSE EVENT (#14) BLEEDING COMPLICATION, RISK OF HAEMORRHAGE
STUDY DESIGN	(#15) RANDOMIZED CONTROLLED TRIAL (#16) RANDOMIZED CLINICAL TRIAL (#16) RCT (#17) CLINICAL TRIAL

in single daily doses. They do not require laboratory monitoring of their anticoagulant activity, due to their improved pharmacokinetic properties.

Other pharmacological therapies include oral anticoagulants, dextran, heparinoids and specific inhibitors of enzymes.

METHODS

The search strategy was based on the Ev-

- BIOSIS Previews
- CINAHL Database
- PsycINFO
- European Public Assessment Report (EPAR)
- Health Canada
- Netherlands Pharmacovigilance Centre Lareb
- The Uppsala Monitoring Centre, and
- Thompson Micromedex

Additionally, to find more reliable data, a secondary search was carried out (systematic reviews and meta-analyses) in medical databases and existing independent HTA reports, available on the websites of institutions, cooperating with the Agency for Health Technology Assessment: International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment International (HTAi) and the Centre for Reviews and Dissemination (CRD

obtained by manual search of selected journals, the use of search engines and by contacts with authors of clinical trials.

Date from the last search of medical databases: 10 September 2007

The decision issue was defined according to the PICOS pattern (population, intervention, comparator, outcomes, study design) (Table 1).

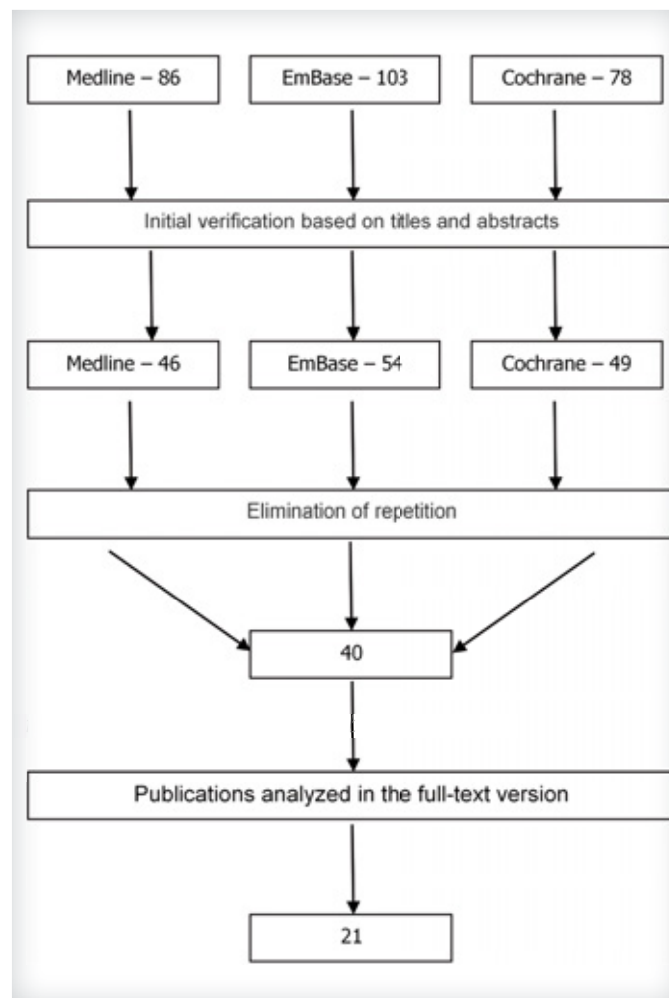


Figure 2. Overall episodes of deep vein thrombosis

Scientific papers were also sought in sources other than medical information databases: in bibliographies of published literature reviews and references, used in clinical research publications, reports and abstracts from scientific conferences and clinical trial registries. Clinical experts were also invited to consult. Additional information was

RESULTS

In result of searching medical databases, 267 publications were found on the use of low molecular weight heparins in prevention of venous thromboembolism (Figure 1).

Initially, 40 publications were selected with data meeting inclusion criteria. Full texts of scientific reports were analysed to assess their reliability, providing, 21 publications, out of the original set of randomized clinical trials, which met the criteria and were eligible for later analysis in compliance with predefined assumptions.

Additionally, four secondary studies were found, being meta-analyses of the clinical efficacy and safety of low molecular weight heparins in prevention and treatment of venous thromboembolism, as compared with the physical methods, placebo or unfractionated heparin.

At all stages, the selection was made independently by two analysts. In any case of disagreement in verification, based on full text analysis of scientific reports, a final position was attained by consensus.

META-ANALYSIS RESULTS

LMVH vs physical methods (Fig. 2, Fig. 3)

Treatment – LMWH

Control – physical methods (foot pump)

Outcome – overall episodes of deep vein thrombosis

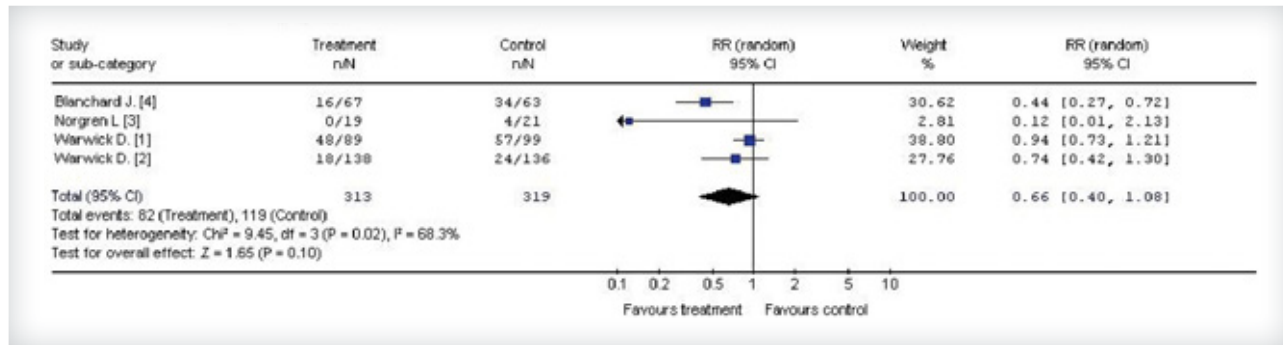


Figure 2. Overall episodes of proximal deep vein thrombosi

Treatment – LMWH

Control – physical methods (foot pump)

Outcome – episodes of proximal deep vein thrombosis

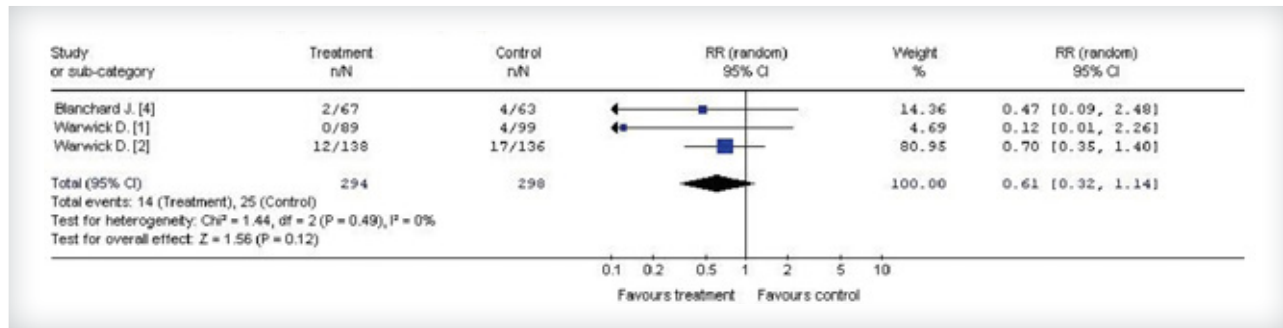


Figure 3. Overall episodes of proximal deep vein thrombosi

Table 2. Episodes of deep vein thrombosis vs. episodes of proximal deep vein thrombosis in metaanalysis studies

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (FOOT PUMP)	RR [95% CI]	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	4	26.2%	37.3%	0.66 [0.40; 1.08] NS	HIGH
EPISODES OF PROXIMAL DEEP VEIN THROMBOSIS	3	4.8%	8.4%	0.61 [0.32, 1.14] NS	HIGH

With regard to the risk of postoperative deep vein thrombosis in both the total number of cases and the number of cases with proximal deep vein thrombosis, meta-analysis studies^{1,2,3,4} showed a trend in favour of low molecular weight heparins versus the physical methods (intermittent pneumatic

compression). The difference between the analyzed groups, however, did not reach statistical significance (RR = 0.66, 95% CI: 0.40, 1.08, p = 0.10). (RR = 0.61, 95% CI: 0.32, 1.14, p = 0.12) (Table 2). *LMWH vs placebo (Fig. 4, Fig.5, Fig.6, Fig.7)*

Treatment – LMWH

Control - placebo

Outcome – episodes of deep vein thrombosis

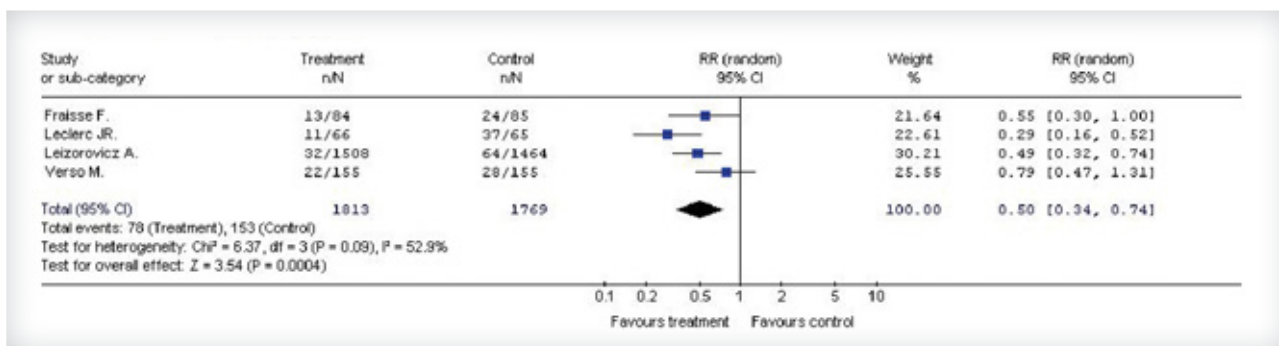


Figure 4. Episodes of deep vein thrombosis

With regard to the risk of deep vein thrombosis, meta-analysis results of four primary clinical trials showed a statistically significant difference between the benefits of low molecular weight heparins in the study group vs. the placebo-treated control group. (RR = 0.50, 95% CI: 0.34, 0.74, p = 0.0004).

The NNT (the Number Needed to Treat) was 23, which means that the administration of low molecular weight heparins instead of placebo to 23 patients, during the period of follow-up, was associated with avoiding deep vein thrombosis in one of them.

Treatment – LMWH

Control – placebo

Outcome – any bleeding episodes

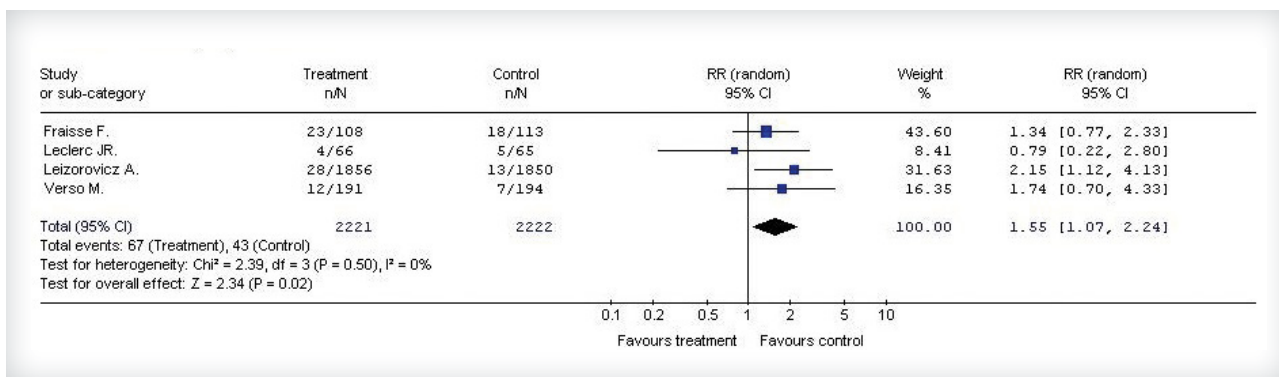


Figure 5. Any bleeding episodes

Treatment – LMWH
 Control – placebo
 Outcome – major bleeding episodes

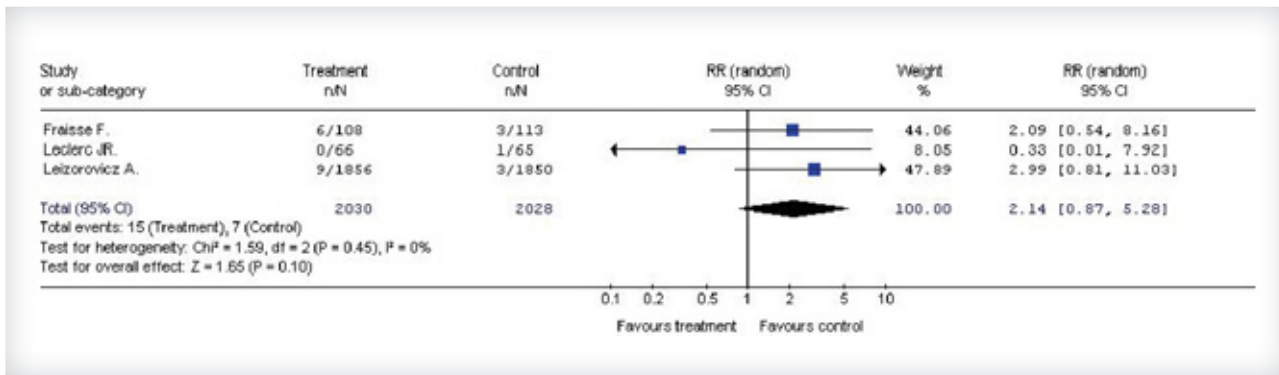


Figure 6. Major bleeding episodes

Treatment – LMWH
 Control – placebo
 Outcome – death

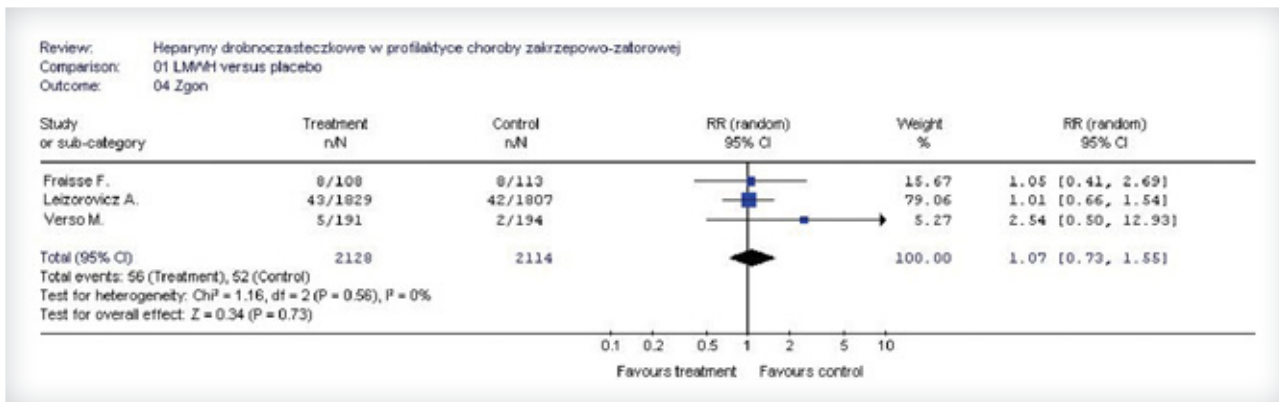


Figure 7. Mortality rates

Regarding the risk of any incidents of bleeding, the meta-analysis showed a statistically significant difference in favour of low molecular weight heparins, administered in the study group and compared to placebo in the control group (RR = 1.55, 95% CI: 1.07, 2.24, P = 0.02).

The NNH parameter (the Number Needed to Harm) was 94, which means that the administration of LMWH instead of placebo to 94 patients during the follow-up period was associated with bleeding events in one of them.

With regard to the risk of death from any cause, and clinically significant bleeding, the meta-analysis showed no statistically sig-

nificant differences between the compared groups (RR = 2.14, 95% CI: 0.87, 5.28, P = 0.10); (RR = 1.55, 95% CI: 0.73, 1.55, P = 0.73) (Table 3).

The meta-analysis showed a 50% decrease in the risk of deep venous thrombosis after low molecular weight heparins, compared to placebo, and NNT = 23. Only one study of pulmonary embolism did not confirm the statistically significant activity of LMWH versus placebo. There were no significant differences between the groups regarding the risk of clinically significant bleeding, which indicates an acceptable safety profile of low molecular weight heparins. Their high antithrombotic efficacy is much higher than any of the risks of bleeding events.

Table 3. Risk of any incidents of bleeding (LMWH vs. placebo)

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (PLACEBO)	RR [95% CI] NNT/NNH*	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	4	4,3%	8,6%	0,50 [0,34, 0,74] NNT = 23	HIGH
MINOR BLEEDING EPISODES	4	3%	1,9%	1,55 [1,07, 2,24] NNH = 94	HIGH
MAJOR BLEEDING EPISODES	4	0,7%	0,3%	2,14 [0,87, 5,28] NS	HIGH
DEATH	4	2,6%	2,5%	1,07 [0,73, 1,55] NS	HIGH

* NNT and NNH parameters were calculated for statistically significant differences between the compared groups

** not significant

LMWH vs. UFH (Fig. 8, Fig. 9, Fig.10, Fig.11)

Treatment – LMWH

Control - UFH

Outcome – episodes of deep vein thrombosis

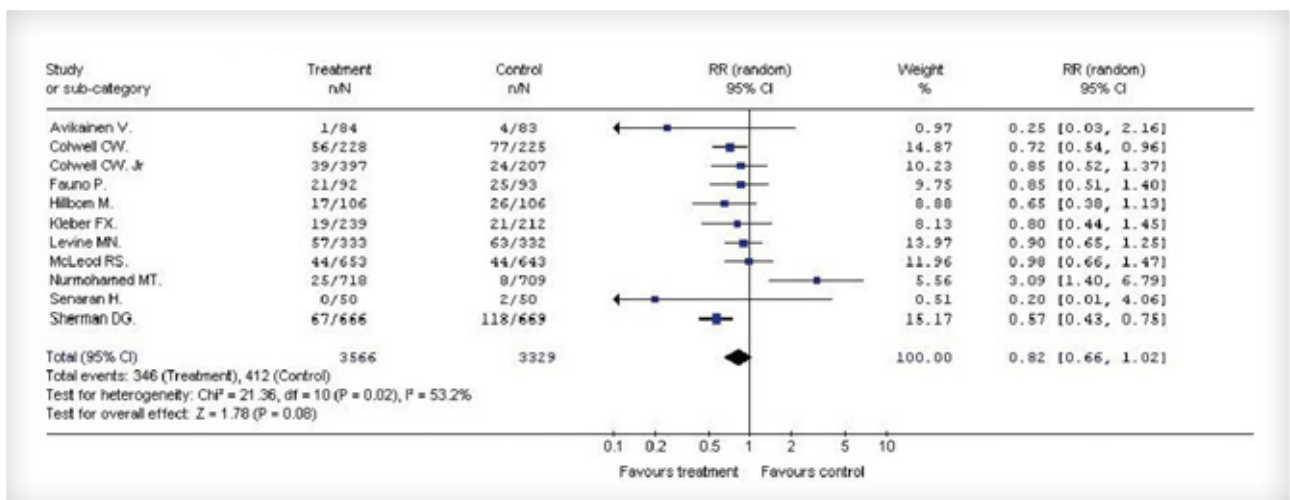


Figure 8. Episodes of deep vein thrombosis

Treatment – LMWH
 Control - UFH
 Outcome – episodes of pulmonary embolism

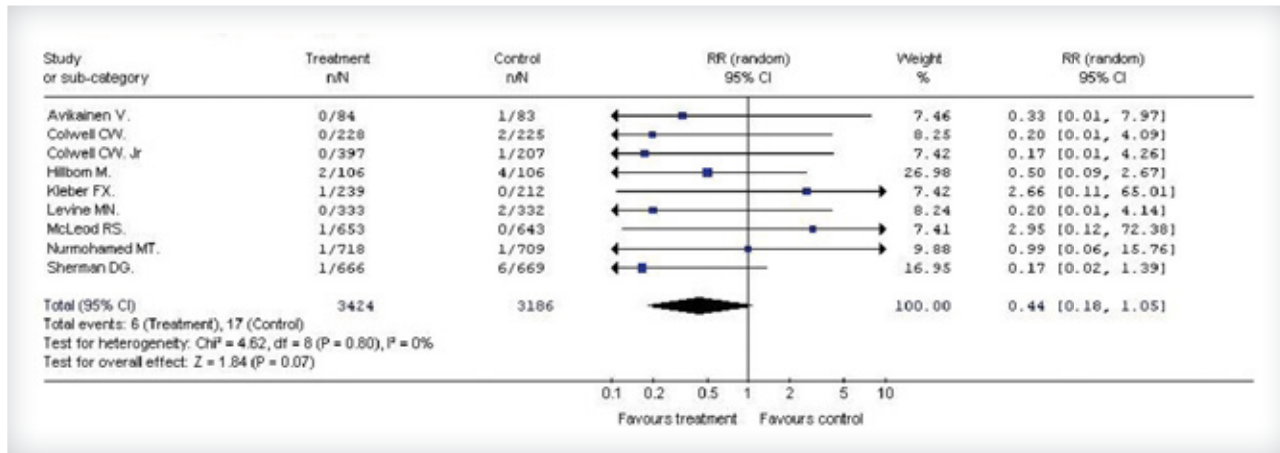


Figure 9. Episodes of pulmonary embolism

Treatment – LMWH
 Control – UFH
 Outcome – any bleeding episodes

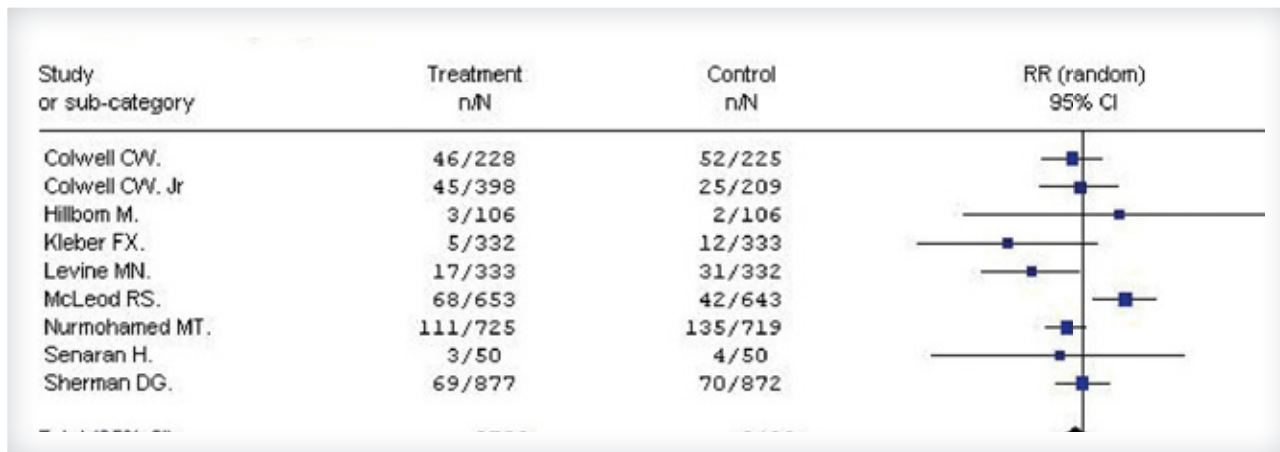


Figure 10. Any bleeding episodes

A meta-analysis of clinical efficacy showed a trend in favor of LMWHs vs UFH in the prevention of thromboembolism. However, differences in the incidence of deep vein thrombosis and pulmonary embolism,

did not achieve statistical significance (RR = 0.82, 95% CI: 0.66, 1.02, p = 0.08); (RR = 0.44, 95% CI: 0.18, 1.05, p = 0.07).

Clinical effectiveness analysis of LMWH in the prevention of deep vein thrombosis and pulmonary embolism

Treatment – LMWH

Control – UFH

Outcome – major bleeding episodes – clinically significant

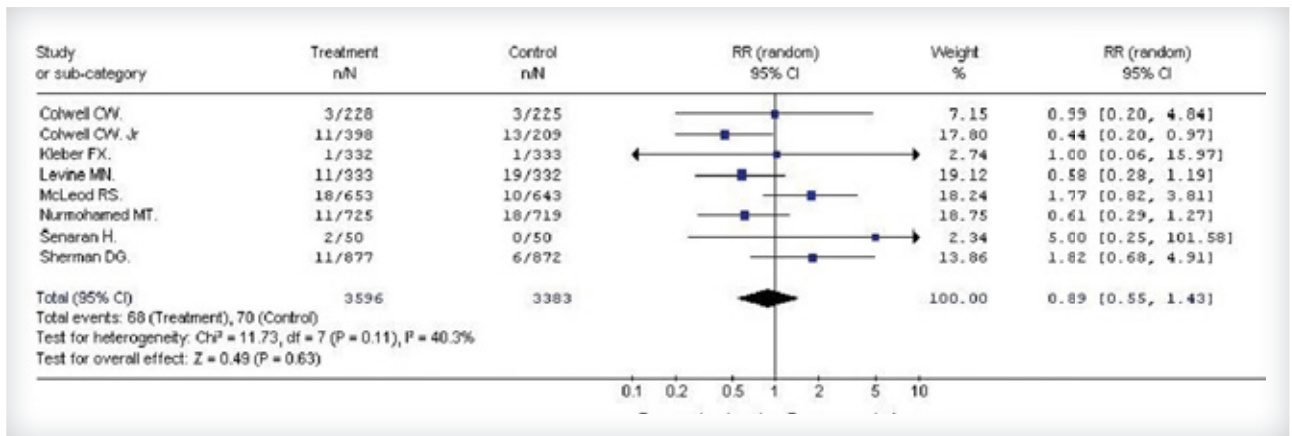


Figure 11. Major bleeding episodes

Treatment – LMWH

Control – UFH

Outcome – death

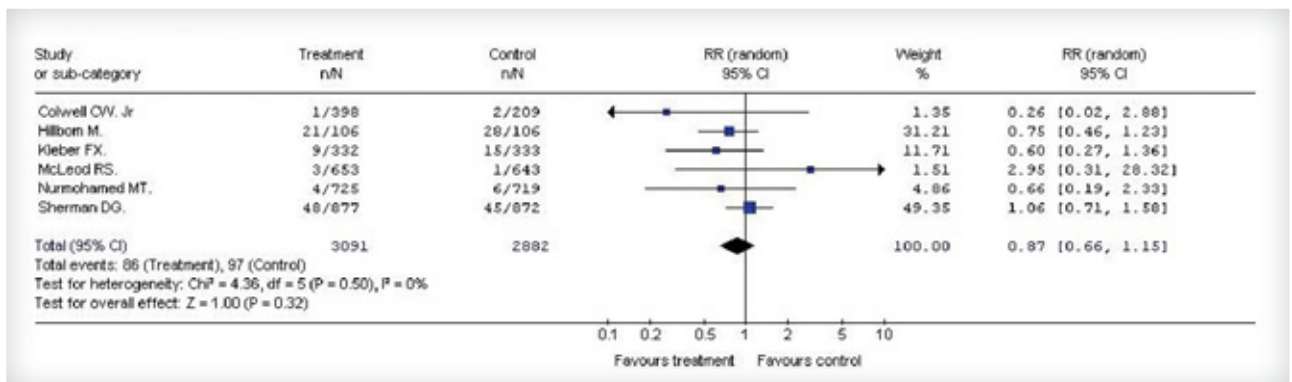


Figure 12. Mortality rates

In all the measured safety parameters after LMWH vs. UFH, the risk of minor and major bleeding and the mortality rates were slightly lower in the groups, receiving low molecular weight heparins, compared to the control group. However, the differences

between the analyzed therapeutic options were not statistically significant. (RR=0.91; 95% CI: 0.73, 1.13; p=0.39); (RR = 0.89; 95% CI: 0.55, 1.43; p = 0.63); (RR = 0.87; 95% CI: 0.66, 1.15; p = 0.32) (Table 4).

Table 4. Risk of minor and major bleeding and the mortality rates (LMWH vs. UFH)

MEASURED ENDPOINT	NUMBER OF STUDIES	PATIENTS % (LMWH)	PATIENT % (UFH)	RR [95% CI] NNT/NNH*	GRADE SCORE
EPISODES OF DEEP VEIN THROMBOSIS	11	9,7%	12,4%	0,82 [0,66, 1,02] NS	HIGH
EPISODES OF PULMONARY EMBOLISM	9	0,20%	0,53%	0,44 [0,18, 1,05] NS	HIGH
MINOR BLEEDING EPISODES	9	9,9%	10,7%	0,91 [0,73, 1,13] NS	HIGH
MAJOR BLEEDING EPISODES	8	1,9%	2,1%	0,89 [0,55, 1,43] NS	HIGH
DEATH	6	2,8%	3,4%	0,87 [0,66, 1,15] NS	HIGH

The Meta-analysis showed no statistically significant differences between LMWH and UFH in all the assessed endpoints. A trend was identified, suggesting a higher clinical efficacy of low molecular weight heparins.

DISCUSSION

The increasing prevalence of risk factors for venous thromboembolism, as well as the progress in diagnostic methods, leads to an increasing number of diagnosed cases. Along with an elevated risk of disease, the sales rates of low molecular weight heparins are steadily rising. In some countries, the costs of low molecular weight heparins is among the highest of all reimbursed drugs.

This analysis attempts to complement the studies, forming a base for consideration of the rationality of the use of low molecular weight heparins. The results of the meta-analyses enable a more accurate assess-

ment of the clinical effectiveness of low molecular weight heparins, in comparison to individual studies. The results confirm the effectiveness and safety of LMWH in prevention of venous thromboembolism, while drawing attention to the fact that most of the assessed endpoints did not achieve statistically significant difference, compared to cheaper treatments, such as the physical methods or unfractionated heparin. This fact should be taken into consideration in the conditions, where cheaper therapies (as the above-mentioned UFH and the physical methods) are readily available.

The use of LMWH in the prevention and treatment of venous thromboembolism, when compared with unfractionated heparin, is more convenient in practice. It does not require the activated partial thromboplastin time (APTT) to be determined nor the use of infusion pumps. The easy use of LMWH, combined with their pharmacoki-

netic properties, allows for administration of the drug in outpatient settings or even at home. There is also a financial aspect of hospitalization, which has been omitted in this analysis. The most advantageous feature of low molecular weight heparins, compared to heparin, is the predictable relationship between dose and effect of anticoagulant, which translates into a dosage based on the weight of the patient, without laboratory monitoring.

The most common and also the most feared complication of both unfractionated heparin and low molecular weight heparins is bleeding. The risk of bleeding is higher in case of unfractionated heparin, however, the difference in the reported study was not statistically significant.

The present analysis leads to a surprising conclusion that the physical methods are highly effective, when compared to LMWH. Trials assessing the end point of deep vein thrombosis risk, included studies with ambiguous results. On the other hand, the meta-analysis did not confirm statistically significant superiority of LMWH. In case of a high probability of complications, including bleeding, and of the coexistence of additional risk factors, the use of physical methods is recommended as an effective thromboprophylaxis. They can be an alternative when contraindications to anticoagulants exist.

In the analyzed studies, there were no other significant, treatment-associated, adverse effects, other than bleeding incidents. This demonstrates an acceptable safety profile of low molecular weight heparins, compared to placebo³⁻⁶, and a significantly better safety profile, compared to unfractionated heparin⁷⁻¹⁵. Significant clinical benefits, arising from their use, outweigh the potential risk of adverse effects, such as bleeding.

CONCLUSIONS

The results of this analysis demonstrate the effectiveness of low molecular weight heparins and safety of their use in prevention of deep vein thrombosis and pulmonary embolism. However, they also draw attention to the lack of statistical significance in a number of parameters versus other, less expensive methods, such as unfractionated heparin or physical methods (foot pump). Additionally, it should be noted that all the results of the meta-analyses take into account the realities of presented clinical trials and cannot be directly transferred into the reality of the Polish medical practice. ■



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