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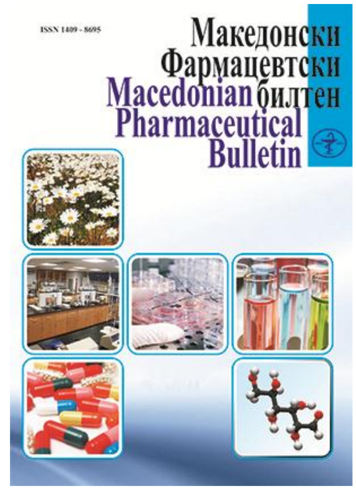

Title: **Cost-effectiveness of LMWHs versus UFH for the prevention of postsurgical venous thromboembolism at orthopedic department in Clinical Hospital Stip**

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Cost-effectiveness of LMWHs versus UFH for the prevention of postsurgical venous thromboembolism at orthopedic department in Clinical Hospital Stip

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Abstract

This study aimed to evaluate the cost-effectiveness of thromboprophylaxis with LMWHs vs UFH in the prevention of venous thromboembolism (VTE) after orthopedic surgery from the perspective of the Clinical hospital in Stip. A model was developed that included both acute VTE (represented as a decision tree) and long-term complications (represented as a Markov process with one-year cycles). Transition probabilities were derived from phase III clinical trials comparing LMWHs with UFH and published literature. Unit costs were taken from the official, publically available hospital and health care insurance data and included direct drug costs for VTE (DVT and PE) prophylaxis (UFH /10000 IU and LMWHs /4000 IU) and hospitalization costs (hospital full board, disposables, medical services, concomitant therapy, healthcare professional time). Costs are reported in Macedonian denars (MKD). When LMWHs and UFH are compared in orthopedic patients, LMWHs dominates UFH and are associated with improved health outcomes , measured by increased quality-adjusted life years (QALYs; 0.05) and with lower cost (savings of 20438.96 MKD) per patient.

LMWHs are a cost-saving alternative to UFH for VTE prophylaxis in patients undergoing orthopedic surgery. Over a one-year horizon, LMWHs dominated UFH in the prevention of VTE events in patients undergoing surgery, providing more quality-of-life benefit at a lower cost.

Keywords: anticoagulants, surgery, thrombosis

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Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major burden on the health care system that caused surgeons to send an action call as early as 2008 (Anderson et al., 2007; Galson et al., 2008). The Health Care and Quality Research Agency stated that the provision of thromboprophylaxis is one of the most important steps to improve patient safety (Galson et al., 2008). Thromboprophylaxis significantly reduces the risk of perioperative VTE. The longer duration of thromboprophylaxis, the lower incidence of VTE. Without anticoagulant prophylaxis, about 50% of patients with symptomatic proximal DVT or PE have a recurrent thrombosis within three months (Torbicki et al., 2008).

The risk of VTE is particularly high in patients who undergo major orthopedic surgical interventions, especially interventions for total hip or knee replacement due to perioperative activation of blood coagulation, the effects of surgical trauma of the femoral and iliac vein or embolism due to prolonged bed stay (Imberti et al., 2011).

Large orthopedic surgical procedures belong to the type of surgery with the highest VTE incidence among cardiothoracic and vascular surgery (Cohen et al., 2007; Geerts et al., 2008; NICE Guidelines http://guidance.nice.org.uk/CG92). Milbrink and Bergqvist assessed the incidence of VTE in orthopedic patients to be approximately 0.6% (Milbrink and Bergqvist, 2008).

Consequences of VTE and its long-term complications can significantly impair the quality of life in terms of patient health, while the treatment of the condition and recurrent complications become significant costs for the health care provider. Costs are also made during the period of hospitalization immediately after surgical interventions for total hip replacement (THR) and total knee replacement (TKR), as well as in months after discharge from the hospital. These complications are not often associated with the operation, as most cases observed in the studies occurred after discharge from the hospital (Geerts et al., 2008).

The most frequently recommended VTE prophylaxis in the 2004 ACCP consensus guidelines is low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). The 2008 ACCP guidelines were released with updated recommendations that include fondaparinux alongside LMWH and UFH for the prevention of VTE in certain patient populations (Geerts et al

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2008). A number of studies have compared the efficacy and safety of LMWH and UFH (Mismetti et al., 2001; Shorr et al., 2008).

Therefore, routine primary prophylaxis in patients at risk with VTE is designated as a recommendation of grade 1A in international guidelines. (Geerts et al., 2008) For patients who undergo elective arthroplasty on hip or knee, the American College of Chest Physicians recommends LMWHs, low doses of UFH, fondaparinux, or vitamin K antagonist up to 35 days after surgery. The most common approach for the application of VTE thromboprophylaxis in the Clinical Hospital Stip is pharmacological thromboprophylaxis for a minimum of 7-10 days with LMWHs or UFH or until the patient is mobilized.

Our primary objective was to evaluate the cost effectiveness of LMWHs compared to UFH for the prevention of VTE in orthopedic surgical patients.

Materials and methods

We used cost-effectiveness analysis in which the costs are reported in MKD values, and health outcomes are converted into Quality Adjusted Life Years (QALYs), incorporating the measure of quality of life (utility) in health outcomes. We revised cost-effectiveness between the two thromboprophylactic regimens - LMWHs and UFH used in orthopedic surgical patients hospitalized at the orthopedic department in Clinical Hospital Stip. We have developed our analysis according to the pre-existing guidelines for economic evaluations (American Thoracic Society, 2002; Canadian Agency for Drugs and Technologies in Health, 2013; Gold et al., 1996).

At the time of the analysis, there was no preferred anticoagulant that complies with the recommendations of the American College of Chest Physicians (ACCP) (Geerts et al., 2008). The choice of thromboprophylaxis was dependent solely on the surgeon's decision. In the case of a shortage of some of the first line anticoagulants, the one that was available at the hospital pharmacy was used.

The protocol for the administration of thromboprophylaxis is described in Table 1.

Table 1.

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Decision tree model

A decision-analytic model was developed to evaluate the cost-effectiveness and results of prophylaxis of DVT with LMWHs SC once daily compared to UFH 5,000 IU twice daily in high-risk patients who underwent orthopedic surgery

The decision tree model is developed using proprietary software (Tree Age Pro 2013 software, Williamstown, MA).

The clinical starting point of the model is the admission for surgical treatment of serious orthopedic conditions. The transition model involves the development or non-development of VTE and simulated the movement of a hypothetical cohort of patients through four health states—'Stabile (no VTE); patients discharged from hospital', 'Not stabile; patients who continue hospitalization', 'PE', and DVT (Fig. 1). Because of the relative low frequency, simultaneous PE and DVT are not considered and the progression of DVT to VTE is not included in the analysis. One arm of the model considered treatment with LMWH, while the other arm considered a UFH regimen.

Patients were evaluated for VTE in the post-operative period up to 11 days, up to 20 days and over 21 days from the time of admission to the hospital where they were given thromboprophylaxis with LMWH or UFH. This time period was selected to cover DVT and PE occurring at the time of hospitalization, and the period after discharge was not covered even the increased risk of VTE may continue in some patients. The time horizon of the analysis was 1 year.

The model can be used for patients of different ages and sexes. For our analysis, we used data from the medical records of 280 hospitalized patients who underwent various surgical orthopedic interventions who received thromboprophylaxis (Geerts et al., 2008).

Fig. 1

Unit cost

The basic scenario is large orthopedic surgical interventions in all hospitalized patients regardless of age. The analysis is from an institutional perspective, the hospital as a healthcare payer and covers all hospital costs, including costs for doctors and other staff.

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Unit costs (Table 2) were taken from the official, publically available hospital and health care insurance data and included direct drug costs for VTE (DVT and PE) prophylaxis (UFH /10000 IU and LMWHs /4000 IU) and hospitalization costs (hospital full board, disposables, medical services, concomitant therapy, healthcare professional time).

The cost of medicines was estimated from the purchase price of the drug, and also the costs associated with the materials used for drug application were obtained from the purchase price of the materials used. Costs for laboratory procedures for monitoring anticoagulant therapy are calculated in hospital day services, while the cost of engagement of health workers includes the costs of engaging a nurse and a doctor including a doctor's visit. Costs for diagnosis and treatment of proximal and distal DVT, PE, are derived from the costs calculated by the diagnosis related group (DRG) and the official refound rate from the Health Insurance Fund of Macedonia. Direct medical costs arising from prophylaxis and management of adverse effects, including continued hospitalization, were modeled and expressed in Macedonian Denars (MKD).

Table 2.

Transition probabilities and utility values

The study monitored all patients from admission to discharge from the hospital and therefore, our time period was from the randomization period to the discharge from the hospital, which for most of the patients was up to 11 days. All patients involved in the analysis are at risk, so the thromboprophylaxis started from the first day of hospitalization and lasted until the discharge from the hospital. Outcome parameters (occurrence of DVT and PE) were derived from larger meta-analysis to evaluate LMWH *vs* UFH.

The probabilities event for the relative rates of PE and DVT were taken from the literature data (Zeidan et al., 2013). Since the probability event, utility and costs were based on symptomatic events, the estimated reduction in VTE was based on the relative reduction of symptomatic events. The VTE risk was considered constant throughout the additional 21 days of prophylaxis. (Rasmussen et al., 2006) QALYs for these health outcomes were based on the results of utilities presented in the literature.

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Table 3.

The analysis was done from in-hospital health care payer perspective and to encompass hospital costs, including physician and other personnel costs. Time horizon for this analysis was from the period of randomization to one year after hospital discharge. The main measure of the outcome was the incremental cost-effectiveness ratio (ICER), presented as an incremental cost for the quality adjusted life years (MKD / QALY). Because of the short time horizon of the model, no discounting of the costs and outcomes was applied.

Sensitivity analysis

In order to account for uncertainty in parameter estimates, we conducted several sensitivity analyses by varying individual parameters (one-way sensitivity analysis-Tornado diagram) or several parameters simultaneously (probabilistic sensitivity analysis-PSA). Analyses were conducted to account for uncertainty surrounding costs, duration of hospital stay and quality-of-life. The base-case values were varied by ±25% (±2SD) to understand how sensitive the model was to changes in the input these parameters. In the PSA (1000 iterations) we used betta distribution for utilities and probabilities associated with duration of stay and gamma distribution for costs.

Results

Cost-effectiveness analysis plays a role in identifying, measuring and comparing costs (for example, resource consumption) and the consequences (for example, clinical and humanistic results) of different interventions, in order to optimize the allocation of limited resources in health care system. This analysis optimizes the distribution of limited resources in health care.

VTE is a serious threat to the health of patients which may persist for a long period following the patients discharge from a hospital. For these reasons, analyzing the data is also made for longer periods of time.

According to the results from cost-effectiveness analysis of LMWHs versus UFH, it can be concluded that LMWHs with respect to UHF is a cost-saving strategy for thromboprophylaxis in patients hospitalized at the orthopedic department. The cost of thromboprophylaxis for the

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hospitalized patients with UFH is higher by 20438.96 MKD compared to LMWH (82346.81 MKD vs 61907.85 MKD), and it is associated with lower efficacy compared to LMWHs of 0.05 QALY (9.69 QALY *vs* 9.73 QALY) (Table 3 and Fig. 2). All of this results in a negative value of ICER which is – 453166.21 MKD / QALY.

Key costs-effectiveness drivers are improved health outcomes with LMWHs, which result in a cost reduction for adverse events treating and provision in QALYs and reduced costs due to the one-day LMWHs application. Although the only major cost is the cost of prophylaxis as determined by the assumed duration of prophylaxis and the different drug prices, the reduction in the costs of treating symptomatic events and subcutaneous administration of LMWHs partly or fully compensates the higher costs of prophylaxis.

Table 4.

Fig. 2.

The results from the one-way sensitivity analysis are shown in Fig. 3. According to the obtained results, ICER from the basic cost-effectiveness analysis model mostly depends on the quality of life associated with DVT (variable range 0.507 to 0.846), pulmonary embolism (variable range 0.459 to 0.765) and prolonged hospitalization as a result of the treatment of these two conditions (variable range 0.604 to 1.007). The results from the sensitivity analysis shows that the cost associated with the treatment of deep vein thrombosis (Variable range 25.591 to 42.652 MKD) has the least impact on ICER from the baseline model of analysis.

Fig. 3.

The obtained results from PSA confirm the stability of the model (Fig. 4) and show that in 60% of all possible cost-effectiveness changes associated with LMWHs and UFH, thromboprophylaxis with is a valid strategy for VTE prophylaxis (DVT and PE) in orthopedic surgery (Fig. 5).

Fig. 4.

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The following ICE scatterplot graph (Fig. 5) shows simulation iterations plotted for incremental cost and incremental effectiveness. The plots to the right of the line confirm the base case analysis. ICE scatter plot shows that the model is stable and variations do not affect the final result of the base model.

Fig. 5.

Discussion

In hospitalized surgical patients, VTE prophylaxis with UFH or LMWHs seems to be effective, well-tolerated and cost-effective compared to the absence of thromboprophylaxis (Pineo et al., 2009). LMWHs are more cost-effective when used in the prevention and treatment of VTE compared to UFH because of their advantages over less laboratory monitoring and mild application (subcutaneous versus intravenous application), which facilitates hospitalization and the use of these drugs in an outpatient environment (Hawkins et al., 2004).

Compared with UFH, LMWHs are more effective in preventing VTE and death, but with increased costs. Minor additional costs after avoided VTE or after avoidance of death implies that LMWHs are considered cost-effective compared to UFH. The cost-effectiveness of LMWHs depends on the risk of developing VTE, medical costs, monitoring costs, and large bleeding costs. Compared with UFH, LMWHs are more cost-effective in patients at high risk of developing VTEs such as our patients undergoing orthopedic surgery than in patients with moderate risk (Matzsch et al., 2000).

In this paper we examined the cost-effectiveness of administering LMWH instead of UFH for prophylaxisof VTE after orthopedic surgery, taking a hospital perspective of analysis and considering the outcomes of the prophylaxis. By a decision analysis model, we assessed the clinical and economic burden of prophylaxis itself and of short-term effects of unprevented VTD.

The expected economic outcome of the analysis was a cost saving with LMWH of about 20468.96 MKD per treated patient. The expected health outcome of prophylaxis was 9.73 QALYs by LMWH for the orthopedic patients population

This is the first economic evaluation for LMWHs cost-effectiveness in a Macedonian healthcare institution. A special aspect of our analysis is that we simultaneously evaluated two

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perspectives: the hospital's perspective and the perspective of the health insurance fund. This choice was made due to the Macedonian system for reimbursement of the hospital budget. The use of LMWHs resources is included in the DRG calculation scheme. Despite this potentially cost recovery, hospitals require stimulation to change behavior when administering therapy or prophylaxis.

In our analysis, LMWHs were found to be more effective in preventing VTE events compared to UFH. With these results, it is confirmed that the hospital can be financially improved by avoiding VTE events and will save money if it continues to prescribe LMWHs for thromboprophylaxis. The cost-effectiveness graph we presented could help the hospital in measuring loss of image vs loss of profit. In terms of the effectiveness of LMWHs, our findings are similar to those of other published economic models (Briggs et al., 2006; Diamantopoulos et al., 2010; Greets et al., 2008; Lynd et al., 2007; Stollenwerk et al., 2010; Tilleul et al., 2006). However, these models refer to different settings (ie, Canada, France) and use different results for effectiveness (QALYs and LYG). In terms of costs, the analysis concluded that prophylaxis with LMWHs leads to cost savings in orthopedic surgery from a health perspective.

In the current study, effects and costs were based on actual patient level data, not on a decision-analytic model with hypothetical cohorts and data integrated from other literature that may be less representative of the relevant groups in this comparison. Further, cost and effects had known distributions and variance in this analysis, allowing a more precise estimate of between-group differences than with most economic analyses. Our study was not funded by the manufacturer of either LMWH or UFH.

On the basis of our study we strengthen the recommendations of the European Consensus Statement to use LMWH prophylaxis in elective hip replacement. Attention should be paid by policy makers even to procedures which are expensive in themselves, but capable of reducing the overall expenditures of the health care system and the burden of chronic diseases on patients and society.

Conclusion

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Cost-effectiveness analysis of LMWHs versus UFH in major orthopedic surgery shows that LMWHs dominate, providing greater effectiveness at lower costs. In addition to providing increased QALYs comparing to UFH, LMWHs also lead to less symptomatic VTE events than UFH. The use of LMWHs in this prophylactic indication contributes to the effective use of limited resources, as it is associated with better clinical results at a lower cost.

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Резиме

Трошок-ефективност на хепарини со мала молекулска тежина наспроти нефракциониран хепарин за превенција на постхируршки венски тромбоемболизам на ортопедското одделение во Клиничка болница Штип

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Клучни зборови: антикоагуланси, хирургија, тромбоза

Оваа студија имаше за цел да ја процени трошк-ефективност на тромбопрофилаксата со хепарини со мала молекулска тежина наспроти нефракционираниот хепарин во превенција на венски тромбоемболизам (ВТЕ) по ортопедска хирургија од перспектива на Клиничката болница во Штип. Беше развиен модел кој вклучуваше и акутен ВТЕ (претставен како дрво на одлуки) и долгорочни компликации (претставени како марков процес со едногодишни циклуси). Веројатностите за транзиција беа изведени од фаза III на клиничките испитувања преку споредување на хепарините со мала молекулска тежина наспроти нефракционираниот хепарин и објавената литература. Единечните трошоци беа земени од официјалните, јавно достапни болнички и здравствени осигурителни податоци и вклучуваат директни трошоци за лекови за профилакса на ВТЕ (ДВТ и ПЕ) (нефракциониран хепарин/10000 ИЕ и хепарини со мала молекулска тежина/4000 ИЕ) и трошоци за хоспитализација (болнички пансион, потрошен материјал за еднократна употреба, медицински услуги, истовремена терапија, време на здравствени професионалци–лекар и сестра). Трошоците се пријавени во македонски денари. Кога хепарините со мала молекулска тежина и нефракционираниот хепарин се споредуваат кај

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ортопедските пациенти, хепарините со мала молекулска тежина доминираат над нефракционираниот хепарин и се поврзани со подобрени здравствени резултати, мерени со зголемување на годините на квалитетно прилагоден живот (QALYs; 0,05) и со пониски трошоци (заштеда од 20438,96 МКД) по пациент.

Хепарините со мала молекулска тежина се алтернатива на нефракционираниот хепарин за намалување на трошоците за ВТЕ профилакса кај пациенти подложени на ортопедска хирургија. Во текот на едногодишниот хоризонт, хепарините со мала молекулска тежина доминираа над нефракционираниот хепарин во спречувањето на ВТЕ-настани кај пациенти кои биле подложени на хируршка интервенција, обезбедувајќи поголема придобивка преку квалитетен живот по пониска цена.

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Table 1. Protocol for the thromboprophylaxis administration

	Thromboprophilaxis protocol	
Drug	Preoperative	Postoperative
UFH	-The first dose of 5000 IU, given about 16 hours before surgery.	-The first postoperative dose of 5000 IU given 12 hours after the surgery.
	-Activated thromboplastin time, measured four hours later, so that if needed, the next dose of heparin given two hours before surgery, may be adjusted.	-Subsequent doses of 5000 IU administered subcutaneous at an interval of 12 hours.
LMWH	-4000 IU Enoxaparin/Fraxiparine, subcutaneously, 12 hours before surgery.	-4000 IU, 12 hours after surgery and then every morning the following days during hospitalization period.

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Table 2. Unit costs used to evaluate the total costs per patient associated with pharmacological thromboprophylaxis option

Unit	Average cost per day (MKD)
Hospital day (Medical services, Hospital full board, Disposables)	1168.66
Concomitant therapy*	185609
Health care time	
nurse	900
specialist (visits included)	2250
Anticoagulant therapy	
LMWH (4000 IU)	131.36
Heparin (10 000 IU)	83.96
Disposables associated with anticoagulant treatment	
LMWH (4000 IU)	0
Heparin (10 000IU)	30

*antibiotics and analgetics

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Table 3. Literature data for probabilities event for the relative rates of PE and DVT

Health state	Utility Adjusted for THR	Utility Adjusted for TKR	Source
No VTE event	712	0.66	Brunenburg et al., 2005
Prophylaxis related	706	655	Brunenburg et al., 2005
Asymptomatic DVT	712	0.66	Brunenburg et al., 2005
Symptomatic DVT	0.68352	0.6336	Haentjens et al., 2004 Brunenburg et al., 2005
PE	0.62656	0.5808	Haentjens et al., 2004 Brunenburg et al., 2005
Recurrent VTE	0.8237	0.8074	Haentjens et al., 2004
Long-term utility	858	841	Räsänen et al., 2007
Death	0	0	Assumption

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Table 4. Cost-effectiveness outcome analysis of LMWHs versus UFH in orthopedic surgical patients

	LMWHs	UFH
Cost (MKD)	61907.85	82346.81
Effectiveness (QALY)	9,73	9,69
Incremental Cost		20438.96
Incremental effectivness		-0.05
ICER		-453166.21

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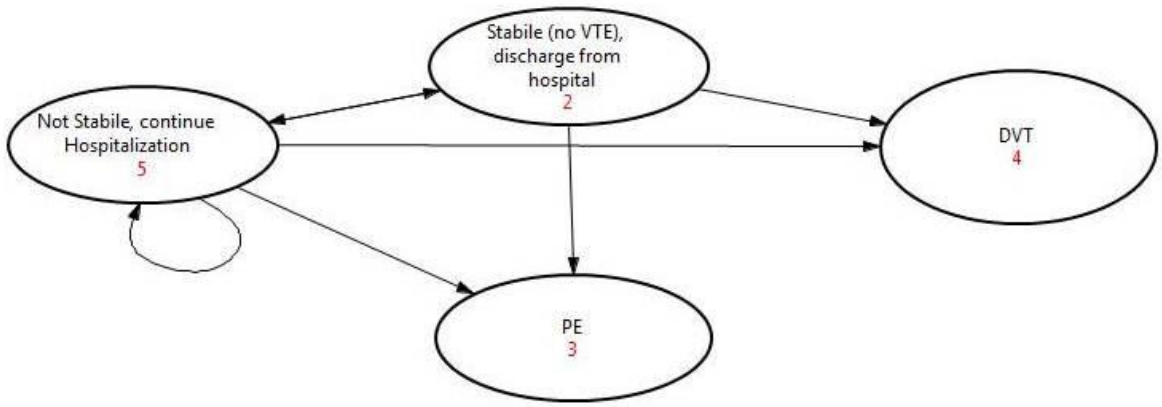

Fig. 1. Simplified schematic of the model. The model included four health states: Stabile (no VTE - venous tromboembolism), Not stabile, PE - pulmonary embolism and DVT - deep vein thrombosis.

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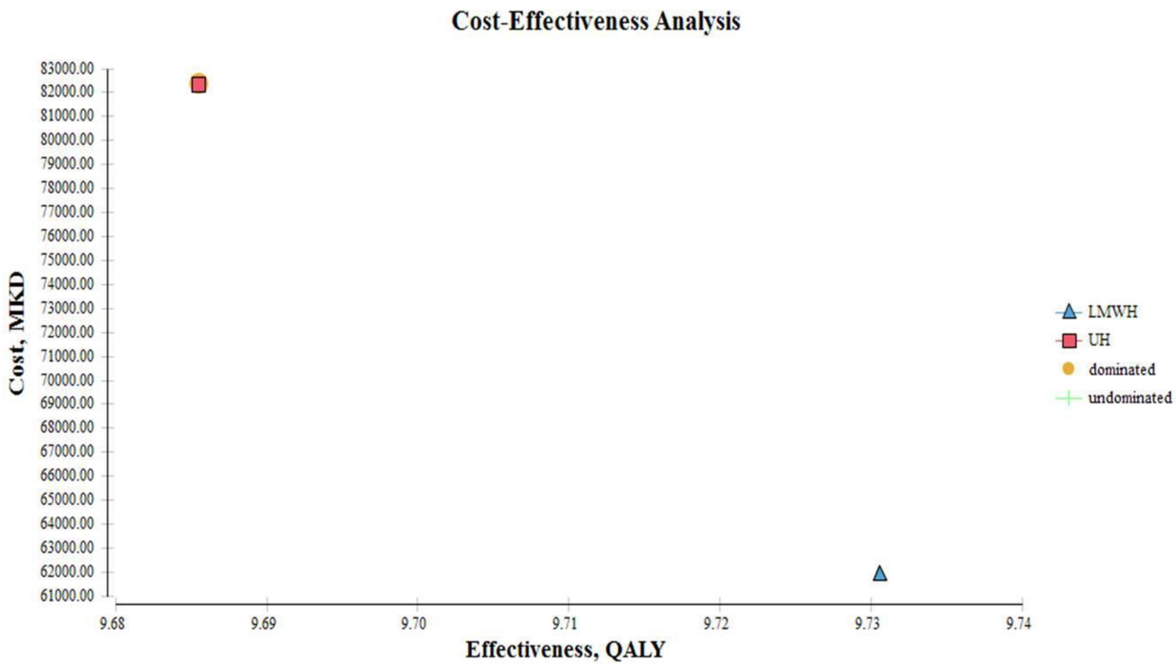

Fig. 2. Cost-effectiveness graph for LMWH vs UFH for 1year period.

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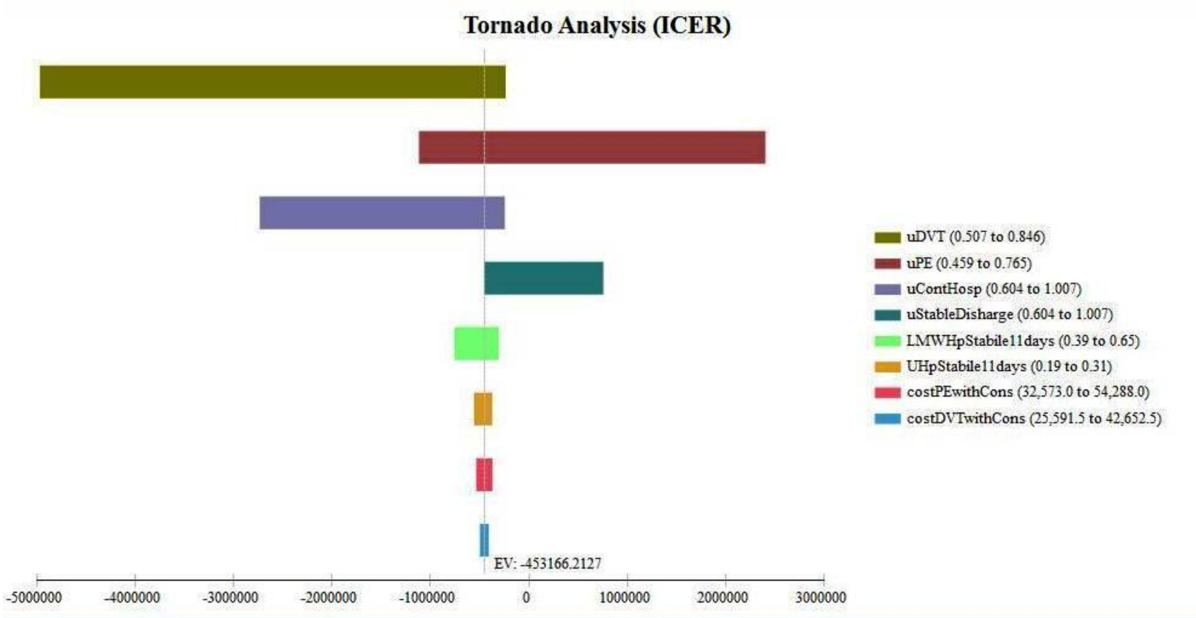

Fig. 3. Tornado diagram.

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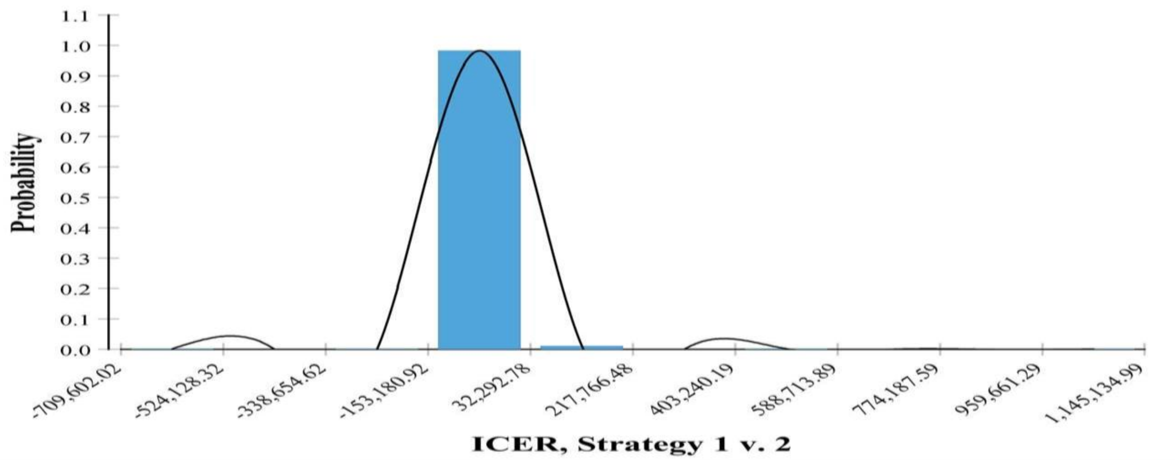

Fig. 4. Monte Carlo probability distribution; ICER, Strategy 1 (LMWHs) vs. strategy 2 (UFH).

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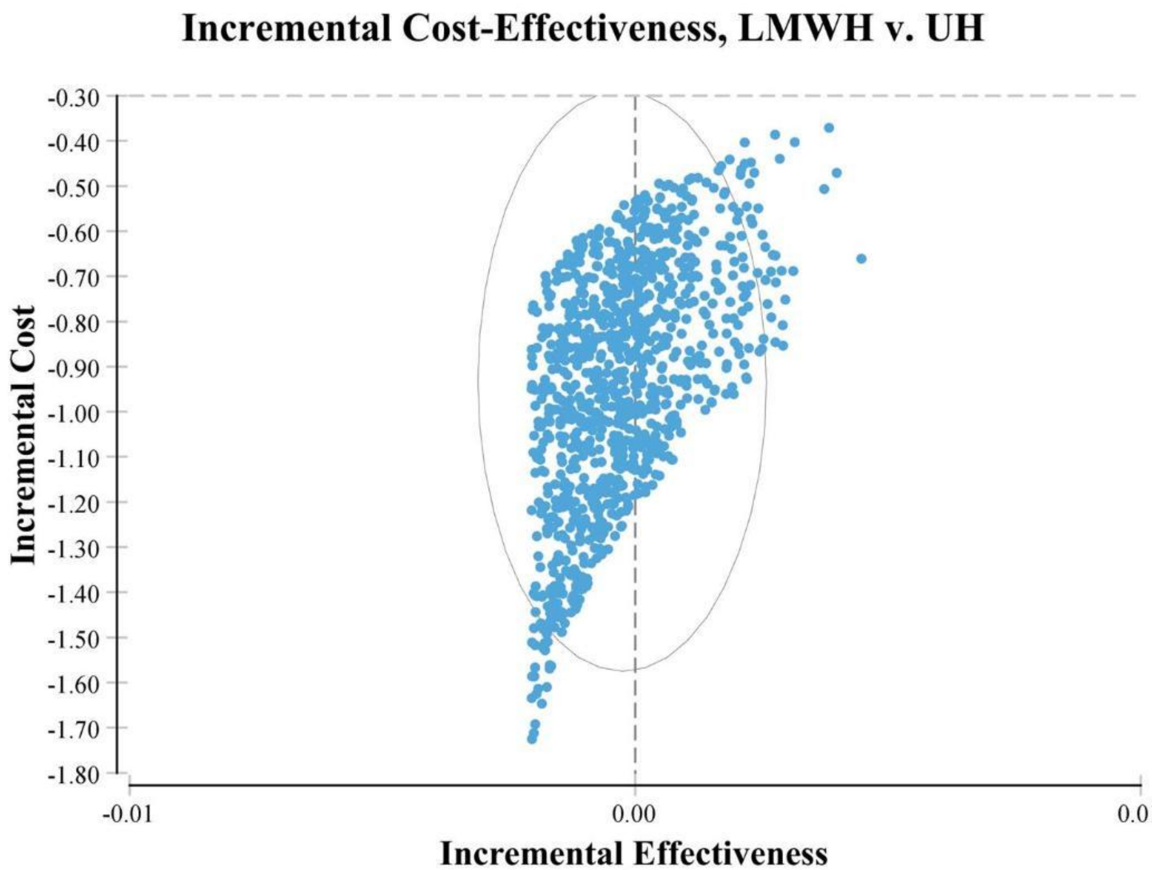

Fig. 5. Scatter plots showing the results of the incremental costs and incremental QALYs for 1000 runs, most results fell within the South-East quadrant, suggesting that the LMWH treatment results in increased efficacy and lower costs.

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