Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement

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ABSTRACT

Background and Objective. **Either low molecular weight heparin (LMWH) or unfractionated heparin (UH) may be used for the prophylaxis of post-operative venous thromboembolic disease (VTD) in elective hip replacement. This study was aimed at assessing the cost-effectiveness of LMWH over UH from the society perspective, which considers all the outcomes occurring in the life-long time horizon.**

Design and Methods. **A decision tree modeled the clinical outcomes and resources used in consequence of restricted (2 weeks) and extended (4 weeks) prophylaxis of VTD with LMWH or UH.**

Results. **In the studied population, that of 67 year-old patients, restricted prophylaxis with LMWH saved 25 quality-adjusted days and $75 over UH. Extended prophylaxis provided a small additional benefit with additional cost savings. The incremental outcomes of the model proved independent of most parameters.**

Interpretation and Conclusions. **We conclude that LMWH has considerable advantages over UH in the prophylaxis of VTD following elective hip replacement, and should be recommended in clinical practice.**

Key words: decision trees, decision support techniques, cost benefit analysis, heparin, low molecular weight therapeutic use, heparin economics, arthroplasty, replacement, hip adverse effects, thrombosis prevention and control

Over the last decade low molecular weight heparin (LMWH) has been established to be effective and well-tolerated drug for preventing and treating venous thromboembolic disease (VTD). Theoretical advantages of LMWHs over unfractionated heparin (UH) are longer half-life, greater bioavailability, anti factor Xa activity and anti factor IIa activity. Practical advantages are lower incidences of thrombosis and bleeding, less need for laboratory monitoring, and decreased incidences of heparin-induced thrombocytopenia and heparin resistance. Several economic analyses in the US, Canada, and the UK have been carried out for policy recommendations, concluding that, despite the higher acquisition cost of LMWH over UH, the cost-effectiveness ratio of short term prophylaxis with a LMWH compares favorably with that of other generally accepted medical interventions.[1-4] The existing evidence of therapeutic effectiveness and cost-acceptability prompted the European Consensus Statement[5] to identify LMWHs as the recommended prophylaxis against VTD, and European orthopedic and surgical units to adopt it widely as the standard prophylaxis for their patients.[6]

In spite of existing evidence of the therapeutic effectiveness and economic acceptability, however, neither the *American College of Chest Physicians*,[7] nor the latest *International Consensus Conference*[8] recommended LMWH as the best drug for VTD prophylaxis in the USA. Moreover, policies from the public health services have not universally agreed on reimbursement of LMWH for home prophylaxis, being only partially reimbursed in Italy (up to April 1999) and France. This may be due to some unresolved issues about the optimal use of the drug and to inadequacy of the existing economic evaluations. As a matter of fact, it has been claimed that the risk of post-operative VTD persists for a considerable time following discharge from hospital,[9] consequently extended prophylaxis with a LMWH is more effective, and is not associated with an increased risk of bleeding complications or other adverse events.[10,11] However, extending prophylaxis increases expenditures on the drug, while it limits those for VTD, making the short-term economic advantage of such a strategy uncertain. Moreover, post-operative VTD also carries long-term costs and morbidity, but no study has assessed the impact that the sequelae of unprevented VTD would have on both costs and quality-adjusted life expectancy. A temporally extended perspective of the analysis might, therefore, reinforce the economic issues on the universal recommendation for use of the drug.

This study was undertaken with two aims: first, to yield further evidence on cost-effectiveness of LMWH

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with respect to UH in the case of prolonged prophylaxis for VTD; second, to calculate, under a society perspective analysis, the whole marginal financial gain for the use of the drug for elective hip replacement.

Design and Methods

The model

We created a decision tree comparing LMWH with UH for the prophylaxis of VTD in patients undergoing elective hip replacement (Figure 1). Despite prophylaxis, some patients develop deep vein thrombosis (DVT), either proximal or distal, which may be clinically apparent or silent. Since there are no recommendations to perform invasive investigations routinely to detect VTD, the model considered usual clinical practice, that is to investigate only clinically symptomatic patients. Thus, patients who do not develop DVT may receive a false positive clinical diagnosis of DVT and patients who develop DVT may not receive a diagnosis (false negatives). Patients who develop clinical symptoms of DVT were assumed to undergo B-mode ultrasonography. Given the test sensitivity and specificity, the clinical diagnosis would be confirmed in most patients, who would then receive standard treatment for DVT. Patients with negative ultrasound findings, however, may be investigated with a second test that, if positive, also prompts treatment. If the second test is invasive, e.g. phlebography, a certain rate of complications may occur, such as post-phlebography thrombosis.

Patients under prophylaxis or treated for DVT may eventually have hemorrhagic complications, some fatal or causing major disability, e.g. cerebral hemorrhage. Patients with DVT, both diagnosed and undiagnosed, may suffer long-term morbidity, named post-thrombophlebitic syndrome, including cellulitis, venous ulceration, varicose veins, stasis dermatitis and deep vein insufficiency. Both classes of events affect quality of life and health care expenditures.

Patients who develop pulmonary embolism (PE) may die suddenly. Those who survive may receive a clinical diagnosis and therefore undergo B-mode vein ultrasonography, if not already performed, and ventilation-perfusion (VP) scan for negative ultrasound

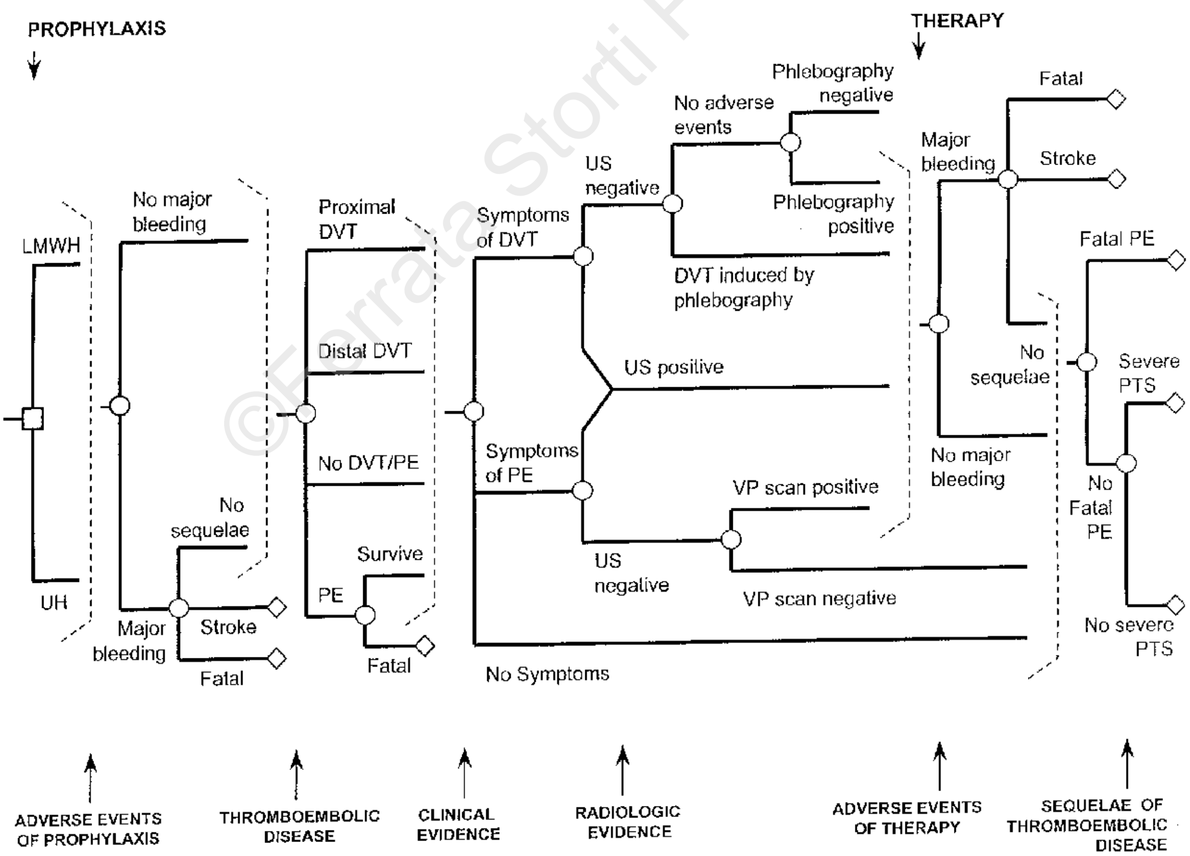

Figure 1. Decision tree. The box on the left indicates the initial decision regarding prophylaxis. Ovals denote chance events, and rhomboids outcomes.

results. Patients without PE may eventually receive a false positive clinical diagnosis of PE and receive an ultrasound or VP scan.

At baseline we created a model for 67 year-old patients, being the prevalent age of the patients undergoing hip replacement. The model could also be used for patients of different ages and sex. In developing the model, we made the simplifying assumptions that the incidence of heparin-induced thrombocytopenia, which may cause thrombosis in 2.5% of the treated patients, was negligible in terms of survival and resource use. Moreover, the model did not take into account the incidence of post-embolic chronic pulmonary hypertension, a very rare complication in patients with PE. Both the assumptions biased the model in favor of UH.

Scenario analysis

Scenario analysis allowed us to examine how the expected utility of the compared strategies would be affected by conceivable changes in the model's structural assumptions. This device was applied to two different durations of prophylaxis: restricted and extended prophylaxis. The former, as recommended by the *American College of Physicians*, is a 2 week regimen (as an in-patient for 7 days followed by a 7-day outpatient course) of prophylaxis. The latter is continued prophylaxis with heparin for a total of 4 weeks.[10]

Probabilities of events

To estimate the probabilities of the modeled events, we identified all English-language meta-analyses and trial reports of VTD prophylaxis published between January 1982 and January 1998 through a computerized literature search, discussion with experts and survey of citations from reviewed articles. We ordered the available evidence ranking first meta-analyses, second randomized trials, further observational studies and finally reviews and books. The best available evidence was always considered for inclusion in the analysis. The data obtained are shown in Table 1[11-25] and Table 2.[13,26-34]

The incidences of DVT and PE under prophylaxis with either LMWH or UH were derived from a meta-analysis exploring the first 2 weeks after surgery,[12] and a randomized clinical trial[11] investigating the 2-3 weeks following discharge of venographically negative patients. We extrapolated the overall incidence of venographically proven DVT and objectively documented PE, along with the effectiveness of 2 and 4 weeks prophylaxis with both LMWH and UH. In the trial investigating post-discharge prophylaxis, patients were administered 40 mg of enoxaparin once daily, while the meta-analyses providing data for in-hospital prophylaxis included studies of both enoxaparin (40 mg once daily) and other LMWHs, although the former type of studies provided 40% of the overall evaluated patients.[11,12] Since no substantial difference in effectiveness was ever documented, we considered the case-mix of patients included by the meta-analysis to be negligible. We got bleeding rates during prophylaxis from the meta-analysis[12] and extended the incidence rate associated with in-hospital prophylaxis to outpatients. The difference in bleeding rate between LMWH and UH was not significant, however, its absolute value was relevant and original figures were used for calculations. The incidence of post-thrombophlebitic syndrome was assumed to be similar between treated and untreated patients with DVT: this assumption, however, was tested by sensitivity analysis.

Table 1. Input data on clinical history of post-operative venous thromboembolic disease.

Variables	*Baseline value (%)*	*Range (%)*	*Ref.*
Overall incidence of DVT	67	47-70	11,12
Prevalence of proximal DVT	50	35-54	12
Effectiveness of LMWH prophylaxis (2 wks/4wks long)	47/66	40-54/60-70	11,12
Effectiveness of UH prophylaxis (2 wks/4wks long)	34/50	30-40/45-55	11,12
Overall incidence of PE	4	1-6	11,12
Effectiveness of LMWH prophylaxis (2 wks/4wks long)	60/90	50-70/80-95	11,12
Effectiveness of LMWH prophylaxis (2 wks/4wks long)	10/15	8-12/12-18	11,12
Fatality rate for PE:			
immediately at onset	10	8-12	13
treated	8	5-12	13
not treated	32	30-36	13
Major bleeding rate during prophylaxis with LMWH (2 week-long)	1.8	1.6-2	11,12
Major bleeding rate during prophylaxis with UH (2 week-long)	2.6	2.4-2.8	11,12
Major bleeding rate during therapy for DVT/PE	4	2-6	14,15
Fatality rate for major bleeding	20	15-30	15
Stroke rate in major bleeding	13	8-15	15
Incidence of post-phlebography DVT	3	0-5	16,17
Incidence of post-thrombophlebitis syndrome:			
proximal DVT symptomatic	41	36-48	18,19
proximal DVT asymptomatic	7.7	5-10	20,21
distal DVT symptomatic	11	5-15	18,19
distal DVT asymptomatic	0	0-5	20,21
PE (assumed to be equal to asymptomatic distal DVT)	0	0-5	
Quality adjusting factors:			
severe post-thrombophlebitis syndrome	95	90-100	23
hemorrhagic stroke	50	30-60	24,25
	(years)	(years)	
Life expectancy of a 67 year old individual	15.20	13.97-16.20	
Life expectancy of a 67 year old individual (discounted)	14.75	13.57-15.73	

Quality of life

Two issues were considered to adjust life expectancy for the quality of life: disability incurred after a

Table 2. Characteristics of diagnostic tools: physical examination and tests.

Variables	*Baseline value (%)*	*Range (%)*	*Ref.*
Sensitivity of venous US for:			
symptomatic proximal DVT	90	82-95	26
asymptomatic proximal DVT	62	38-80	26,27
symptomatic distal DVT	79	69-85	26
asymptomatic distal DVT	48	30-60	26
symptomatic PE	61	40-70	26,28
Sensitivity of venography	100	80-100	29,30
Sensitivity of VP scan for PE	92	70-100	31
Specificity of venous US	78	69-85	26
Specificity of venography	100	80-100	ass.
Specificity of VP scan	87	70-95	31
Incidence of clinically false positive PE:			
without DVT	1.2	1-1.4	32
with DVT	18	16-20	33
Incidence of clinically false positive DVT	13	10-20	32
Sensitivity of clinical symptoms for:			
proximal DVT	40	32-48	34
distal DVT	5	4-6	34
PE	27	23-35	13
Rate of phlebography performance	25	0-100	ass.

ass.= assumed.

hemorrhagic stroke and discomfort of the post-thrombophlebitis syndrome (Table 1). Mild and moderate post-thrombophlebitic syndrome were assumed not to affect quality of life, according to a standard gamble interview of patients having incurred thromboembolism.[22] The influence of warfarin treatment on patients' perception of quality of life was assumed to be negligible.[23]

Resource use and costs

Drug acquisition costs were estimated from market price, given a 50% discount rate for hospital purchase. The whole price was calculated for outpatient administration of the drugs. At baseline, patients were assumed to receive enoxaparin 40 mg once daily or subcutaneous standard heparin 5,000 IU thrice daily. The cost variations due to different marketed products were considered in the sensitivity analysis.[35] The cost of nursing time was estimated using payment rates derived from local billings, and assuming a work time of 10 minutes per dose. Subcutaneous injections were assumed to be self-administered after hospital discharge. The additional costs incurred because of home administration by a nurse were explored by sensitivity analysis. The costs of treatments were based on local prices and are reported in Table 3.

The costs of laboratory and diagnostic tests were estimated using relative value scales developed by the *Italian Laboratory Society* and the *French Society of Radiologists*, respectively. Costs of work units for these services as well as daily general ward care were estimated using local administrative data.

Table 3. Costs.

Costs	*Baseline (US $)*	*Range (US $)*	*Ref.*
Prophylaxis with LMWH (2 weeks)	63	20-110	Local
Prophylaxis with UH (2 weeks)	61	20-110	Local
Vein ultrasonography	28	20-34	Local
Phlebography	178	800-1,700	Local
Ventilation/perfusion scan	157	120-180	Local
Cost of treating DVT	2,208	2,000-2,400	Local
Cost of treating PE	3,150	2,900-3,300	Local
Cost of stroke	10,981	8,000-16,000	36
Cost of treating major bleeding	3,117	3,000-3,500	37
Cost of treating post-thrombotic syndrome	3,486	4,200-4,600	38

ass.= assumed.

We used data from a local survey to estimate the duration of stay in an internal medicine ward for an episode of confirmed DVT, assuming similar courses for patients experiencing DVT both during the hospital stay for hip replacement and after discharge. Resources used for an episode of PE were assumed to be those for an episode of DVT plus an additional short stay at the intensive care unit.

Other than these direct costs, we also considered indirect costs, represented by absence from work. Indirect costs were assumed to make a minimal contribution in the patients over 65 years old because of no loss of productivity, provided that the majority of these patients were retired. The annual income of patients younger than 65 was assumed to be $25,000 and, on the basis of the experts' panel judgment, it was assumed that only late complications of the DVT would affect indirect cost.

Costs incurred because of post-thrombophlebitic syndrome were taken from a recent economic analysis.[36] Costs due to major bleeding and stroke were taken from the literature.[37,38] Health expenditures for post-thrombophlebitic syndrome and stroke were both discounted at a 3% annual rate up to the third year after the occurrence of VTD, since this is the median time for the development of a severe thrombophlebitic syndrome;[18] all the expenditures were assumed to be sustained punctually and only once. All calculations were made in 1998 dollars (given that 1,700 Italian Liras equal 1 US dollar).

Analysis

Both discounted (at a 3% yearly rate) and undiscounted expected costs and quality-adjusted life expectancy were calculated for each strategy. The marginal effectiveness was rated for the marginal costs. A sensitivity analysis was conducted to identify the parameters that had the greatest impact on cost-effectiveness results. This analysis explored the input variables over their entire range, which corresponded to the confidence interval of meta-analyses, the observed range of published data or a 20% interval around the point value when no range was available.

Model calculations were performed by DATA 3.0 (TreeAge Software Inc. Boston, MA, USA).

Results

Baseline analysis

According to our model, prophylaxis with LMWH in 67 year-old patients undergoing hip replacement saved 2 more lives in 1,000 treated patients than prophylaxis with UH, that is LMWH saved 25 quality-adjusted discounted days of life over UH. The expected cost of prophylaxis with LMWH was $75 lower than prophylaxis with UH. Prophylaxis with LMWH, therefore, saved both life and money, i.e. dominated prophylaxis with UH in the hip replacement setting.

The overall cost incurred by patients undergoing prophylaxis was more than $2,000 for both LMWH and UH. A large part (81%) of the expected costs was incurred because of adverse effects of the anticoagulant therapy for both prophylaxis and therapy of the unprevented thromboses, such as cerebral bleeding. As a matter of fact, despite the low frequency of cerebral bleeding during prophylaxis (0.2-0.3%) and during therapy (0.6%), the high costs incurred by a single event caused a substantial economic burden on the average patient. Further, 13% of the overall costs were due to VTD prophylaxis (3%) and treatment (10%), while 5% were incurred because of post-thrombophlebitic syndrome. The residual 1% was for diagnostic procedures.

Sensitivity and scenario analyses

We examined the sensitivity of our results to changes in some of our key assumptions and parameters. Baseline results changed according to age-adjusted population life expectancy: marginal effectiveness linearly decreased from 58 to 14 quality-adjusted days when age was varied from 80 to 50 years, respectively. Wide variations in all the other parameters did not significantly alter the incremental outcomes, therefore proving the robustness of the model.

When confidence intervals of LMWH and UH effectiveness reported by literature were explored, no overlapping was observed between the two drugs either for expected effectiveness or for costs. When bleeding complications of prophylaxis and therapy for unprevented thromboses were set as null, the expected marginal effectiveness decreased by 10 days, yet LMNH use resulted in a net increase of cost savings. When post-thrombophlebitis syndrome was assumed to occur in all patients after a clinically asymptomatic and untreated DVT, but was completely prevented in patients with a diagnosed and treated DVT, the cost saving of the use of LMWH instead of UH became more than thrice the baseline. Wide variations of the purchase cost of LMWH did not significantly alter the incremental outcomes. The cost saving associated with the use of LMWH was abolished when the cost of the prophylaxis reached $140, i.e. more than double the current market price. Finally, when a repeated ultrasound examination was included instead of phlebography as the second test in patients with the clinical suspect of DVT, no substantial changes were observed in the results.

Table 4. Results of baseline analysis. Quality-adjusted life expectancy (QALE) is measured in years, while marginal QALE is measured in days. Costs are measured in 1998 US dollars.

Strategy	*QALE (yrs)*	*Marginal QALE (days)*	*Cost ($)*	*Marginal Cost ($)*
LMWH	13.40	+25	2,208	-78
UH	13.33		2,283	

Longer courses of prophylaxis were tested by a separate analysis. Both LMWH and UH were assumed to be continued for 4 weeks overall, with an additional effectiveness of 20% for LMWH and 16% for UH,[11] along with an increased rate of major bleeding of 0.2% for LMWH[11] and 0.3% for UF (Table 1). Overall costs incurred for the extended prophylaxis were lower than for the restricted one, and marginal cost savings obtained by prophylaxis with LMWH instead of UH were $89, while marginal life gained was 33 quality-adjusted days (Table 4). As a result, extended prophylaxis with a LMWH dominated extended prophylaxis with UH, and also dominated restricted prophylaxis.

Discussion

In this paper we examined the cost-effectiveness of administering LMWH instead of UH for prophylaxis of VTD after elective hip replacement, taking a societal perspective of analysis and considering the long term outcomes of the prophylaxis. By a decision analysis model we assessed the clinical and economic burden of prophylaxis itself and of short and long term effects of unprevented VTD. The expected economic outcome of the analysis was a cost saving with LMWH of about $75 per treated patient. The expected health outcome of prophylaxis was 25 quality-adjusted days of life saved by LMWH for the population of 65 year-old patients, and more for younger patients. Our results, therefore, prove that prophylaxis with LMWH was a dominant choice relative to UH, since it both saves lives and money. This result confirmed previous analyses that took a more limited perspective. In two studies[4,39] LMWH generated cost savings of $20 to $50 for each patient receiving prophylaxis. The authors interpreted the results as a consequence of a favorable market, although they did not include long-term costs in the analysis.

This long-term, society perspective, however, produced an expected cost for prophylaxis of $2,200 per patient, that is about $2,000 higher than the expected costs reported by cost-effectiveness analyses with a limited perspective.[2,4,37,40-43] Breakdown of the expected costs demonstrated that the major component of this cost was due to hemorrhagic complications of prophylaxis and therapy for unprevented DVT, and most importantly cerebral hemorrhages. This should focus the attention of researchers on investigatation of new strategies to improve the monitoring of therapy for DVT, or safer treatments.

The results of our analysis proved to be stable despite conceivable variations of the parameters used in the baseline analysis. Cost saving resulted to be null only at a value of LMWH effectiveness that was outside the range reported in the literature, or by doubling the overall costs of prophylaxis with LMWH.

The results of our baseline analysis, which simulated a prophylaxis restricted to 2 week duration, were stable with a longer course of prophylaxis: 4 weeks extended prophylaxis with LMWH was dominant over short course prophylaxis with either LMWH or UH. This is in accordance with results obtained by comparing 6 weeks of prophylaxis with warfarin with short courses.[39,43]

The current study is unique for several reasons. First, it carefully modeled diagnostic pathways according to clinical practice: thus, ultrasound vein screening was not included, since it is ineffective[45] and not routinely performed. Second, it quantified all the relevant health consequences of VTD, without disregarding the side effects of either prophylaxis or therapy. Third, the model was designed for a prolonged period which thus included late consequences, in particular two long-term sequelae of VTD that are both disabling and resource consuming: the post-thrombophlebitic syndrome and cerebral bleeding due to anticoagulant therapy. Finally, it undertook an assessment of long term effects of prophylaxis on quality of life, so as to allow comparison of the proposed procedure with other medical interventions.

We should also emphasize some peculiarities and limitations of this study. First, the model was based on a strategy of care that did not include any instrumental surveillance of post-surgical patients, which may not be regarded as standard care in some hospitals. The duration of hospital stay after surgery may vary, thus modifying the hospital cost of the drugs. Second, the results of the current economic evaluation are somewhat dependent on the Italian health care system, and on our Institution, since most of the costs were calculated from local billing and national market data. Generalization of the results should be valid in alternative settings provided that the relative prices of resources are not too different. Finally, our study is also limited by the constraints of any decision analysis, which must simplify the complex process of clinical medical practice. Accordingly, we have not taken into account the use of pulmonary angiography or surgical interventions for post-embolic chronic pulmonary hypertension, a very rare complication in patients with PE, or the clinical and economic effects of heparin-induced thrombocytopenia. Both assumptions however biased the model against LMWH.

On the basis of our study we strengthen the recommendations of the European Consensus Statement to use LMWH prophylaxis in elective hip replacement. Several other medical interventions proved to be dominant strategies in comparison to common practice, yet not all of them have been introduced into clinical practice, i.e. vaccination for hepatitis B virus,[46] screening for hemochromatosis,[47] antimicrobial prophylaxis before shock wave lithotripsy,[48] sotalol therapy for life-threatening ventricular arrhythmias.[49] 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.

Contributions and Acknowledgments

All the four authors gave substantial contributions to the conception and design of the study, drafting of the article and final approval of the version to be published. Moreover, MM built and analyzed the model of the data and interpreted the results, while GB critically revised the article.

The order of authorship was a joint decision by the coauthors and reflects the overall effort employed for the study and the article.

Disclosures

Conflict of interest: none.

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