ClinicoEconomics and Outcomes Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Cost Analysis of Thromboprophylaxis in Patients at High Thromboembolic Risk with Enoxaparin, Dalteparin and Nadroparin in Colombia: A Systematic Literature Review-Based Study

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Purpose: To analyze the costs of high thromboembolic risk patients who require low molecular weight heparins (LMWHs) as a thromboprophylaxis strategy.

Methods: Cost analysis was conducted to assess LMWHs (enoxaparin versus comparators: nadroparin and dalteparin) as thromboprophylaxis for hospitalized patients with high thromboembolic risk in Oncology, General or Orthopedic Surgery, and Internal Medicine services from the healthcare provider's perspective in Colombia. A decision tree was developed, and the health outcomes considered in the analysis were deep vein thrombosis, major bleeding, pulmonary thromboembolism, and chronic pulmonary hypertension. Clinical inputs were obtained from a systematic review of the literature and the economic parameters from micro-costing. Inputs were validated by three clinical experts. Costs were expressed in 2020 US dollars (USD).

Results: In a hypothetical cohort of 10,000 patients with a thromboprophylaxis use rate of 40%, the use of enoxaparin was less costly than that of dalteparin in Oncology (difference of USD 624,669), Orthopedic Surgery (difference of USD 275,829), and Internal Medicine (difference of USD 109,119) patients. For these services, using enoxaparin was more efficient than using nadroparin (cost differences of USD 654,069, USD 416,927, and USD 92,070, respectively). Sensitivity analysis showed an important influence of the number of patients undergoing thromboprophylaxis, as well as the unit cost, and the risk of events (DVT, PTE, and CTEPH).

Conclusion: Enoxaparin is the least expensive health technology for thromboprophylaxis in most of the medical contexts analyzed in Colombia due to its efficacy and the lower risk of complications than dalteparin and nadroparin.

Keywords: thromboprophylaxis, cost-analysis, low molecular weight heparins, Colombia

Introduction

Thromboembolic disease occurs in 142–300 per 100,000 hospitalized patients per year.[1] Venous thromboembolism (VTE), a term that brings together two main clinical presentations, deep vein thrombosis (DVT) and its complication, pulmonary thromboembolism (PTE),[2] is associated with longer hospital stays and more severe complications or death in Colombia and other countries.[3,4] A worrying fact is that about 30% of patients who present a first event will experience a recurrence in the following 10 years.[1] Likewise, long-term complications, such as chronic thromboembolic pulmonary hypertension (CTEPH), generate disability and require prolonged anticoagulation management, along with its associated risks (high rates of morbidity and mortality) and costs over lifetime.[1,5] Similarly, VTE has an important impact on mortality; for example, between 60,000–300,000 people die annually in the United States because of VTE and its complications.[6]

Received: 15 June 2024
Accepted: 8 October 2024
Published: 8 November 2024

In Colombia, hospital data suggest that VTE has a high disease burden.[7,8] Guzman Sandoval et al (2021) reported a mortality rate due to VTE or its complications, and the data showed 5.83% of hospital admissions between 2014–2019.[8] Additionally, a mortality rate of 14.8% due to PTE was reported in a cohort of patients treated in different centers in the country.[7]

Pregnancy, cancer, some surgical interventions, especially Orthopedic interventions, or being bedridden for long periods[2,9] are recognized as predisposing factors for VTE. In fact, it was estimated that two-thirds of non-fatal VTE cases occur in hospitalized subjects,[1] resulting in 7.6 disability-adjusted life years (DALYs) lost per 100,000 persons annually.[5]

The use of pharmacological thromboprophylaxis in high-risk patients is indicated for the prevention of VTE and its complications,[10,11] and is a cost-effective intervention compared to no prophylaxis.[3,4] Therefore, pharmacological therapy with low molecular weight heparins (LMWHs) is approved for DVT prevention in hospitalized patients without a high risk of bleeding but with a high probability of thrombosis.[2,12] In the Colombian pharmaceutical market, there are several types of LMWHs available with different prices, effectiveness, and safety profiles,[13] so their use has differential impacts on the healthcare resource use.[14] Although the costs of thromboprophylaxis with LMWHs have been explored in Colombia in surgical and hospitalized patients,[3] the costs associated with VTE and its acute and chronic complications in patients at high risk of thrombosis have not been analyzed so far.

Considering the above, this study aimed to compare the costs of thromboprophylaxis among the three main LMWHs used (enoxaparin, dalteparin and nadroparin) in hospitalized surgical patients of Oncology, Orthopedic Surgery, and Internal Medicine in Colombia.

Material and Methods

Study Design

A cost analysis was developed from the perspective of the health system (third payer), where the costs of thromboprophylaxis using enoxaparin, dalteparin, or nadroparin in high-risk hospitalized patients (Oncology, Orthopedic Surgery, and Internal Medicine) were estimated and compared. In this cost analysis enoxaparin was used as a reference because is the LMWHs with the greatest market share in the country.[15]

Efficacy and safety inputs of the studied LMWHs were extracted from a systematic review of the literature (SLR) (Supplementary Material – Appendix 1). Subsequently, clinical experts were consulted to validate and adjust the inputs obtained, as well as those referring to the evolution of the disease and the technologies used for its management in each high-risk condition (Supplementary Material – Appendix 2). With these inputs, a bottom-up costing tool and a decision tree model was built in Microsoft® Excel to analyze and compare the costs of thromboprophylaxis with different interventions and types of patients.

Efficacy and Safety Inputs

A SLR was conducted to determine the magnitude of effect in terms of relative risk (RR) on the efficacy and safety LMWHs used for thromboprophylaxis of thrombotic events in different medical and surgical settings, such as obstetrics, oncology and orthopedics compared to placebo or non-pharmacological measures. An electronic search was carried out in MEDLINE (PubMed), Cochrane Database of Systematic Reviews, LILACS, EMBASE. The following terms were selected for the searches: "dalteparin*", "enoxaparin*", "nadroparin*", "bemiparin*", "prevention and control", "prophylaxis", "thromboembolic", "thromboembolism", "venous thrombosis". These terms were composed by Mesh and DeCS and free language considering synonyms and abbreviations. This was done in order to capture as much evidence as possible. Eligibility criteria, search strategies and data collection process are fully described in the Supplementary Material – Appendix 1. Summary measures (RR) were obtained for each technology compared to its non-use (placebo), which allowed adjustment for the probabilities of occurrence of events such as DVT, PTE, and CTEPH in the analyzed populations. Major bleeding was considered as safety outcomes (Table 1). Meta-analysis results are also shown as forest plots in the Appendix 1 (Supplementary Figures 2–11). A classical meta-analysis was applied for evidence synthesis using the *Metafor* package in R software version 4.1.1.

Table 1 Probabilities of Occurrence of Complications Due to Thromboprophylaxis in High-Risk Patients in Oncology, Orthopedics, and Internal Medicine

Technology	Probability			Source
	Oncologic	Orthopedic/Surgical	Internal Medicine	
	DVT			
Enoxaparin	0.18	0.32	0.08	SLR
Dalteparin	0.22	0.40	0.09	SLR
Nadroparin	0.25	0.45	0.11	SLR
No intervention	0.35	0.64	0.15	[16–19]
	PTE			
Enoxaparin	0.05	0.02	0.01	SLR
Dalteparin	0.11	0.04	0.03	SLR
Nadroparin	0.11	0.04	0.03	SLR
No intervention	0.18	0.064	0.045	[20]
	CTEPH			
Enoxaparin	0.001	0.0004	0.0003	SLR
Dalteparin	0.002	0.0008	0.0006	SLR
Nadroparin	0.002	0.0008	0.0005	SLR
No intervention	0.004	0.001	0.0009	[21]
	Major bleeding			
Enoxaparin	0.01	0.01	0.01	SLR
Dalteparin	0.02	0.02	0.02	SLR
Nadroparin	0.02	0.02	0.02	SLR
No intervention	0.01	0.01	0.01	SLR

Abbreviations: DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension.

In this study, patients at high thromboembolic risk were defined as those hospitalized with conditions or undergoing procedures known to increase the risk of VTE significantly. This includes, but is not limited to, patients with active cancer, those undergoing major orthopedic or general surgery, individuals with prolonged immobility, and patients with a history of VTE. The specific inclusion criteria for high-risk patients were aligned with established clinical guidelines and recommendations, ensuring that the population analyzed reflects those most likely to benefit from thromboprophylaxis.

Epidemiological and Clinical Inputs

To generate inputs regarding the frequency of presentation of clinical outcomes (thrombotic or bleeding events) we performed a narrative review approach of epidemiological studies reporting incidence of these events in hospitalized patients belonging to the mentioned high-risk groups. This search aimed to identify information published in Colombia. However, in the absence of local data, and also regional data from Latin America, studies from other continents were used as an information source.

The Supplementary Material – Appendix 2 details the diagnostic criteria and principles for identifying complications such as PE, DVT, and CTEPH and the definition of major bleeding in order to lately estimate the healthcare resource utilization. The study applied these criteria consistently to ensure accurate and comparable outcomes. The screening

procedures for these complications, which may influence their incidence among patients receiving different LMWHs, are also described in the Supplementary Material – Appendix 2.

Validation with Clinical Experts

By means of an interview and using a structured questionnaire, three clinical experts from different specialties (Internal Medicine and Critical Care, Vascular Medicine, and Orthopedics) were consulted to validate the different inputs obtained in the reviews performed and the estimated probabilities of progression of VTE, the technologies used for its management, as well as their probability of use and the healthcare resource utilization (HCRU).

The observations in terms of the review parameters were used to establish scenarios for each group of patients; likewise, the different elements to be cost-analyzed were validated by the experts.

Economic Inputs

Economic inputs were gathered or estimated following the methodological recommendations of the Institute for Health Technology Assessment of Colombia (IETS, in Spanish), in its manual for conducting health economic evaluations.[22] For drug prices, we used the annual weighted averages of the 2020 Drug Pricing Information System (SISMED, in Spanish),[15] corresponding to the Health Service Provider Institutions. The costs of LMWHs were sourced from commercial presentations (Clexane® for enoxaparin [USD 6.1 per syringe], Fragmin® for dalteparin [USD 3.4 per syringe], and Fraxiparine® for nadroparin [USD 2.6 per syringe]).[15] For the costs of medical procedures and inputs for the management of VTE and major bleeding outcomes, we used both national price and tariff lists for Colombia: 1) The Colombian tariff manual from the Social Security Institute (ISS, in Spanish) 2001 (multiplied by 1.3 to index prices), and 2) The tariff manual from the Compulsory Traffic Accident Insurance (SOAT, in Spanish) 2020, as recommended by IETS.[22] To analyze the costs from different medical contexts, we estimated the HCRU for the management of VTE-related outcomes and major bleeding associated with the use of LMWHs (Supplementary Material – Appendix 2 and Supplementary Tables 1–4). All costs were expressed in 2020 USD using an exchange rate of 1USD = COP$3693.[23]

Cost Analysis and Modelling

A decision tree, starting with the thromboprophylactic drug, was used to model the probabilities of potential outcomes proposed by Oliveros et al in their SLR[3] (Figure 1): DVT, major bleeding, PTE, and CTEPH. A time horizon of one year was used, and the total expected costs relevant to the complications for each alternative were considered as the outcome. Modelling was performed for a hypothetical cohort of 10,000 patients in each of the services evaluated, where 40% of them were at high risk of VTE and would require pharmacological thromboprophylaxis.

To analyze costs, a bottom-up analysis was performed using a tool built in Microsoft® Excel, where the clinical outcomes in inpatients and outpatients were simulated. The cost of thromboprophylaxis management for 14 days was assessed, assuming a daily doses of 40 mg for enoxaparin, 5000 IU for dalteparin, and 3800 IU for nadroparin. Likewise, the total costs for each complication were obtained and multiplied by the probability of occurrence of each alternative, thus obtaining the expected costs. Finally, the costs of pharmacological thromboprophylaxis and the adjusted costs of the different clinical outcomes were added and multiplied by the population undergoing prophylactic management to obtain the total cost for the cohort for each alternative, the number of complications, and the differences compared with enoxaparin.

Sensitivity Analysis

Univariate sensitivity analyses were performed to evaluate the robustness of the analysis results, which included the percentage of the population requiring thromboprophylaxis and the risk of occurrence of DVT, PTE, major bleeding, and CTEPH, using ±75% of each probability of occurrence. Variations in the relative risks of adverse events for the LMWHs using their 95% confidence intervals extracted from the SLR and their costs (highest and lowest, reported for LMWHs in SISMED) were also evaluated in the sensitivity analysis.

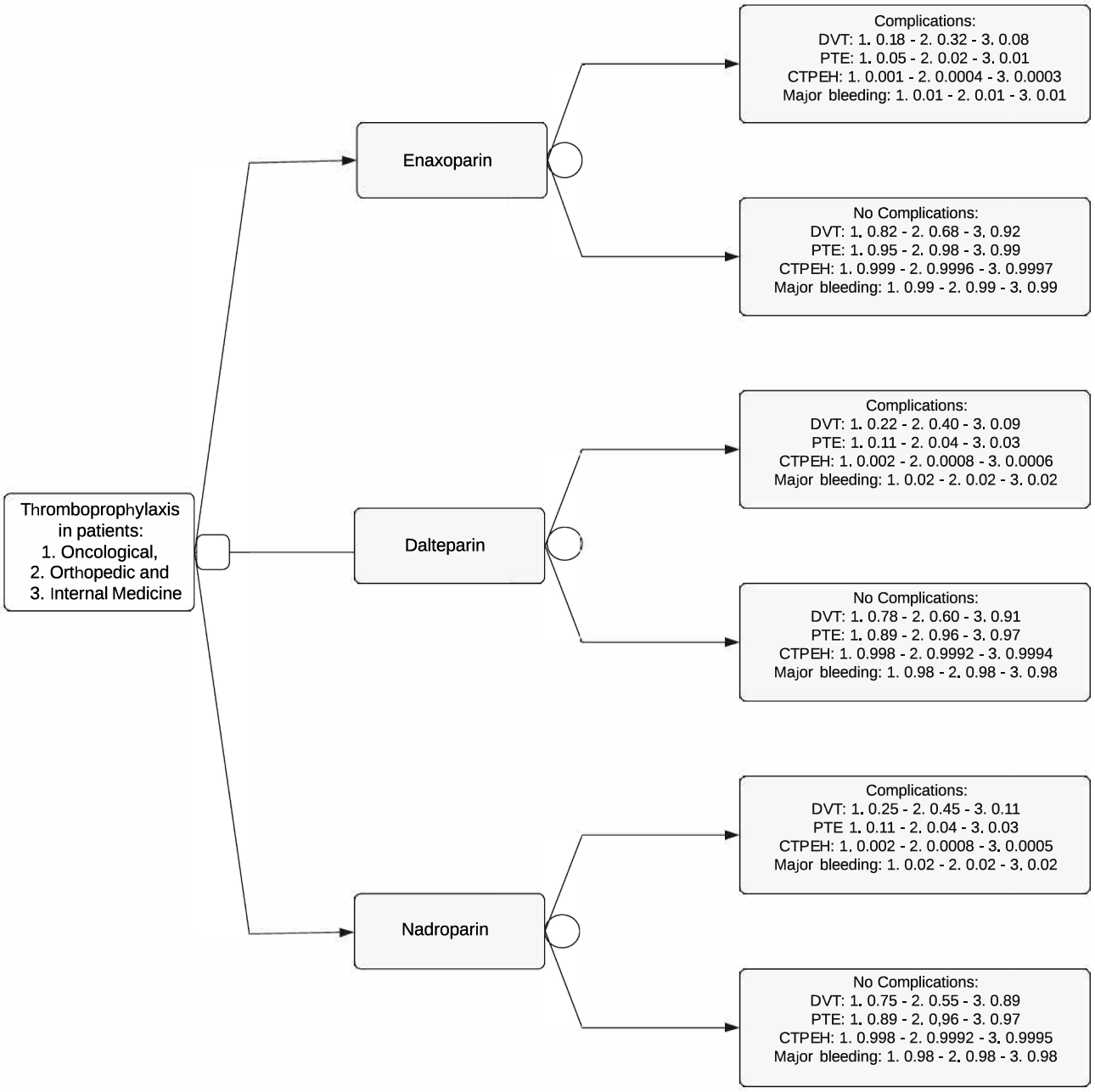

Figure 1 Decision tree to model the use of enoxaparin, dalteparin, and nadroparin for thromboprophylaxis in Oncological, Orthopedic, and Internal Medicine patients in Colombia.

Results

A total of 24 RCTs were used as input to generate summary measures for efficacy and safety. Thirteen (n=13) RCTs evaluated the efficacy and safety of enoxaparin, seven of dalteparin, two of nadroparin and two of bemiparin. Studies were considered of moderate to high quality. Bemiparin was not included in the cost analysis section because it is not commercially available in Colombia. The PRISMA flowchart of this SLR, the included RCTs and forest plots of metanalyses are presented in the Supplementary Material – Appendix 1 (Supplementary Tables 1, 2 and Supplementary Figures 1–11).

Based on the incidence of outcomes in not treated patients, RRs for each technology to prevent the selected outcomes were used to calculate the probabilities of presentation in treated patients. The probabilities of the occurrence of complications due to thromboprophylaxis in high-risk patients in Oncology, Orthopedics, and Internal Medicine are

reported in Table 1. Enoxaparin demonstrated a lower likelihood of complications, including thrombotic or bleeding events, than the other options (Table 1 and Supplementary Table 1 in the Supplementary Material – Appendix 3). The Intensive Care Unit (ICU) and general ward for Oncology patients exclusively utilized LMWH for thromboprophylaxis. Additionally, there was a high rate of ICU admission among Orthopedic patients with PTE (Supplementary Material – Appendix 2 and Supplementary Table 3).

In a theoretical cohort of 10,000 individuals, 40% of whom were receiving thromboprophylaxis, our analysis revealed that the costs (excluding clinical outcomes) were higher for enoxaparin at USD 342,229 than for dalteparin at USD 188,455. This resulted in a cost difference of USD 153,774 in favor of dalteparin over enoxaparin. Notably, for nadroparin, the cost amounted to USD 143,296, which represents a difference of USD 198,933 when compared with enoxaparin (see Table 2 for details).

Table 2 Costs Derived from Thromboprophylaxis in Different High-Risk Medical Contexts

Management and Setting	Enoxaparin	Dalteparin	Nadroparin
Oncology			
Thromboprophylaxis	$ 342,229	$ 188,455	$ 143,296
DVT	$ 909,191	$ 951,115	$1,066,993
Inpatient	$ 586,066	$ 630,568	$ 710,000
Outpatient	$ 323,126	$ 320,548	$ 356,994
PTE	$ 516,555	$ 1,022,698	$ 1,001,353
Inpatient	$ 457,707	$ 903,080	$ 883,881
Outpatient	$ 58,849	$ 119,617	$ 117,471
Major bleeding	$ 92,548	$ 215,628	$ 199,408
Inpatient	$ 92,495	$ 215,504	$ 199,294
Outpatient	$ 53	$ 124	$ 115
CTEPH	$ 103,637	$ 210,933	$ 207,179
Inpatient	$ 4239	$ 8760	$ 8619
Outpatient	$ 99,398	$ 202,173	$ 198,560
Total cost	$ 1,964,161	$ 2,588,829	$ 2,618,229
Orthopedics			
Thromboprophylaxis	$ 342,229	$ 188,455	$ 143,296
DVT	$ 1,662,521	$ 1,739,182	$ 1,951,073
Inpatient	$ 1,071,663	$ 1,153,038	$ 1,298,285
Outpatient	$ 590,858	$ 586,144	$ 652,788
PTE	$ 195,390	$ 386,892	$ 378,822
Inpatient	$ 178,386	$ 352,483	$ 345,048
Outpatient	$ 17,004	$ 34,409	$ 33,774

(*Continued*)

Table 2 (Continued).

Management and Setting	Enoxaparin	Dalteparin	Nadroparin
Major bleeding	$ 92,548	$ 215,630	$ 199,408
Inpatient	$ 92,495	$ 215,504	$ 199,294
Outpatient	$ 53	$ 124	$ 115
CTEPH	$ 37,078	$ 75,439	$ 74,094
Inpatient	$ 1317	$ 2721	$ 2678
Outpatient	$ 35,761	$ 72,718	$ 71,416
Total cost	$ 2,329,767	$ 2,605,597	$ 2,746,694
Internal Medicine			
Thromboprophylaxis	$ 342,229	$ 188,455	$ 143,296
DVT	$ 389,653	$ 407,621	$ 457,283
Inpatient	$ 251,171	$ 270,243	$ 304,286
Outpatient	$ 138,482	$ 137,378	$ 152,997
PTE	$ 99,755	$ 194,628	$ 190,242
Inpatient	$ 88,932	$ 172,775	$ 168,797
Outpatient	$ 10,823	$ 21,853	$ 21,445
Major bleeding	$ 92,548	$ 215,628	$ 199,408
Inpatient	$ 92,495	$ 215,504	$ 199,294
Outpatient	$ 53	$ 124	$ 115
CTEPH	$ 26,070	$ 53,043	$ 52,097
Inpatient	$ 926	$ 1913	$ 1883
Outpatient	$ 25,145	$ 51,130	$ 50,215
Total cost	$ 950,257	$ 1,059,376	$ 1,042,326

Abbreviations: DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension.

Costs and Scenario Analysis of Enoxaparin in Oncology

Across all Oncology settings, utilizing enoxaparin for management consistently led to lower costs compared to dalteparin and nadroparin, with the exception being the outpatient management of DVT, where had higher costs than dalteparin (enoxaparin = 323,126 vs dalteparin = 320,548). Managing PTE with dalteparin and nadroparin was ~2 times more costly than with enoxaparin; this ratio was 2.3 and 2.1 times in the management of major bleedings, respectively. For DVT, dalteparin and nadroparin were 5 and 17% more costly than enoxaparin, respectively. The total cost (of all inpatient and outpatient events) of thromboprophylaxis and its complications was lower with enoxaparin than with dalteparin (difference: USD 624,669; 32% more expensive) and nadroparin (difference: USD 654,069; 33% more expensive) (Table 2).

For dalteparin versus enoxaparin, the probability of DVT was the key driver of the analysis, ranging from USD 133,146 to USD 1,116,191 for adverse event costs. For nadroparin versus enoxaparin, the greatest impact was the relative risk of PTE of nadroparin (RR NADRO PTE), with adverse events costs varying between USD 112,353 and USD 1,786,746 (Figure 2a). In both comparisons, the results always favored enoxaparin.

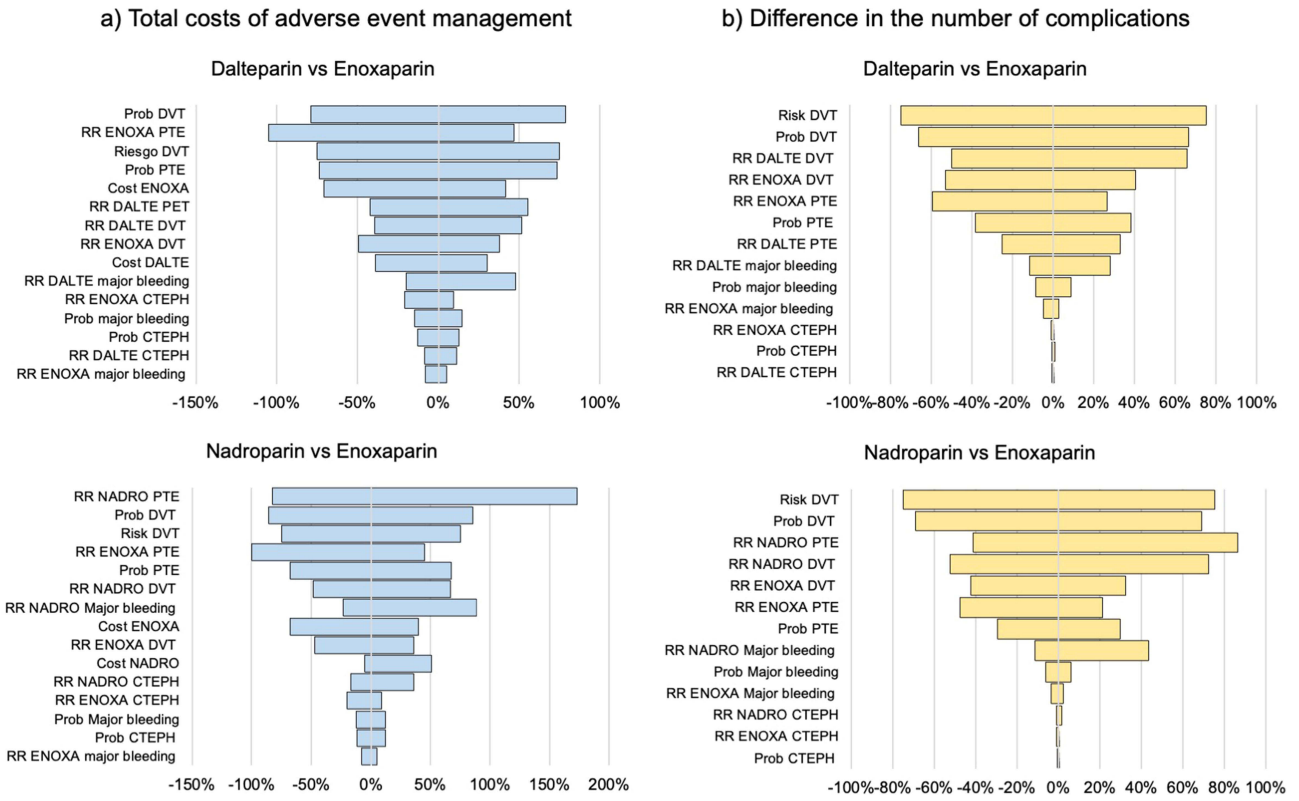

Figure 2 Sensitivity analysis of the difference in total management costs and number of complications due to thromboprophylaxis in Oncology patients. Dalteparin vs enoxaparin and nadroparin vs enoxaparin*. (**a**) Total costs of adverse event management. (**b**) Difference in the number of complications.
Notes: *Sensitivity analysis performed with the following minimum and maximum LMWH prices (enoxaparin: USD 0.09017/mg-$0.25860/mg; dalteparin: USD 0.00022/UI-$0.00102/UI; nadroparin: USD 0.00060/UI- $0.00514/UI).

For the difference in the number of complications in the dalteparin versus enoxaparin analysis, the variable with the greatest impact was the percentage of patients to be managed with thromboprophylaxis (Risk DVT), varying between 112 and 785 events. This same variable had the greatest influence in nadroparin versus enoxaparin, with the results varying from 140 to 841 complications (Figure 2b). The ranges presented here were always in favor of enoxaparin.

Cost and Scenario Analysis of Enoxaparin in Orthopedics

The total cost in Orthopedics was lower for enoxaparin followed by dalteparin (difference USD 275,829; 12% higher), with nadroparin being the most expensive at USD 2,746,694 (difference USD 416,927; 18% higher) (Table 2). For PTE, major bleeding, and HTPC, management with enoxaparin was ~2 times cheaper than that with nadroparin and dalteparin. The largest difference occurred in the outpatient setting of major bleedings management, where dalteparin was 2.3 times more expensive than enoxaparin, and nadroparin was 2.2 times more.

For the cost differences between dalteparin and enoxaparin, the relative risk of dalteparin for DVT (RR DALTE DVT) was the variable with the greatest impact in adverse event costs, varying the results from USD 172,992 in favor of dalteparin to USD 864,907 in favor of enoxaparin. In the nadroparin versus enoxaparin setting, the greatest impact was on the risk of DVT with nadroparin (RR NADRO DVT), with the result varying between USD 160,151 in favor of nadroparin and USD 1,213,844 in favor of enoxaparin (Figure 3a).

Comparing the number of complications of dalteparin versus enoxaparin, the variable with the greatest impact was the relative risk of DVT with dalteparin (RR DALTE DVT), making the results varied between 34 and 981. The relative risk of PTE with nadroparin (RR NADRO DVT) had the greatest influence on nadroparin versus enoxaparin, with results ranging from 127 to 1,407 (Figure 3b). Both the ranges presented here were in favor of enoxaparin.

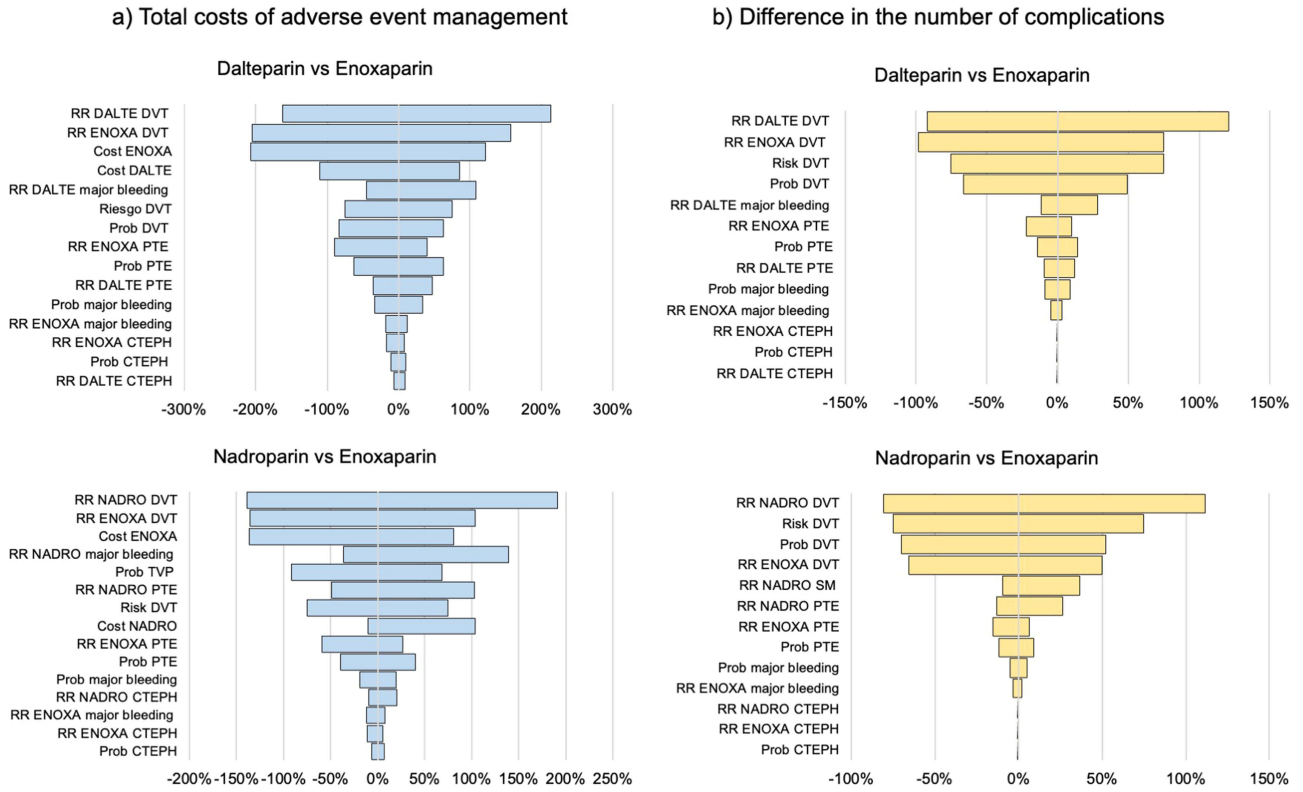

Figure 3 Sensitivity analysis of the difference in total management costs and number of complications due to thromboprophylaxis in Orthopedic patients. Dalteparin vs enoxaparin and nadroparin vs enoxaparin*. (**a**) Total costs of adverse event management. (**b**) Difference in the number of complications.
Notes: *Sensitivity analysis performed with the following minimum and maximum LMWH prices (enoxaparin: USD 0.09017/mg-$0.25860/mg; dalteparin: USD 0.00022/UI-$0.00102/UI; nadroparin: USD 0.00060/UI- $0.00514/UI).

Costs and Scenario Analysis of Enoxaparin in Internal Medicine

In the Internal Medicine scenario, enoxaparin was the most economical LWMHs (Table 2), followed by nadroparin (difference USD 92,070; 10% higher), with dalteparin having the highest total cost (difference USD 109,119; 11% higher).

In the adverse event cost comparison of dalteparin versus enoxaparin, the cost of the latter (Cost ENOXA) had the greatest impact, with results varying from USD 210,772 in favor of dalteparin to USD 298,122 in favor of enoxaparin. The relative risk of nadroparin in major bleeding (RR NADRO major bleeding) had the greatest impact on the comparison of nadroparin versus enoxaparin, varying the adverse event costs between USD 59,633 in favor of nadroparin and USD 671,212 in favor of enoxaparin (Figure 4a).

In the number of complications of dalteparin versus enoxaparin, the variable with the greatest impact was the percentage of the population with thromboprophylaxis (Risk DVT), producing a result that varied between 45 and 320. These two ranges favored enoxaparin (Figure 4b).

Discussion

This study presents an updated estimate of the costs of thromboprophylaxis in Colombia. To our knowledge, this is one of the first studies on the continent that differentiates costs for medical and surgical care services. Based on the SLR (Supplementary Material – Appendix 1), representative data were obtained on the evidence of the efficacy and safety of the three LMWHs authorized for thromboprophylaxis in Colombia. Enoxaparin, the most extensively evaluated LMWH, stands out as the one with the most robust evidence supporting its efficacy in preventing thrombotic events and associated complications. Our findings indicate that, in different medical settings including Oncology, Internal Medicine, and Orthopedics, enoxaparin consistently incurs lower costs than dalteparin and nadroparin. Our findings show that, in

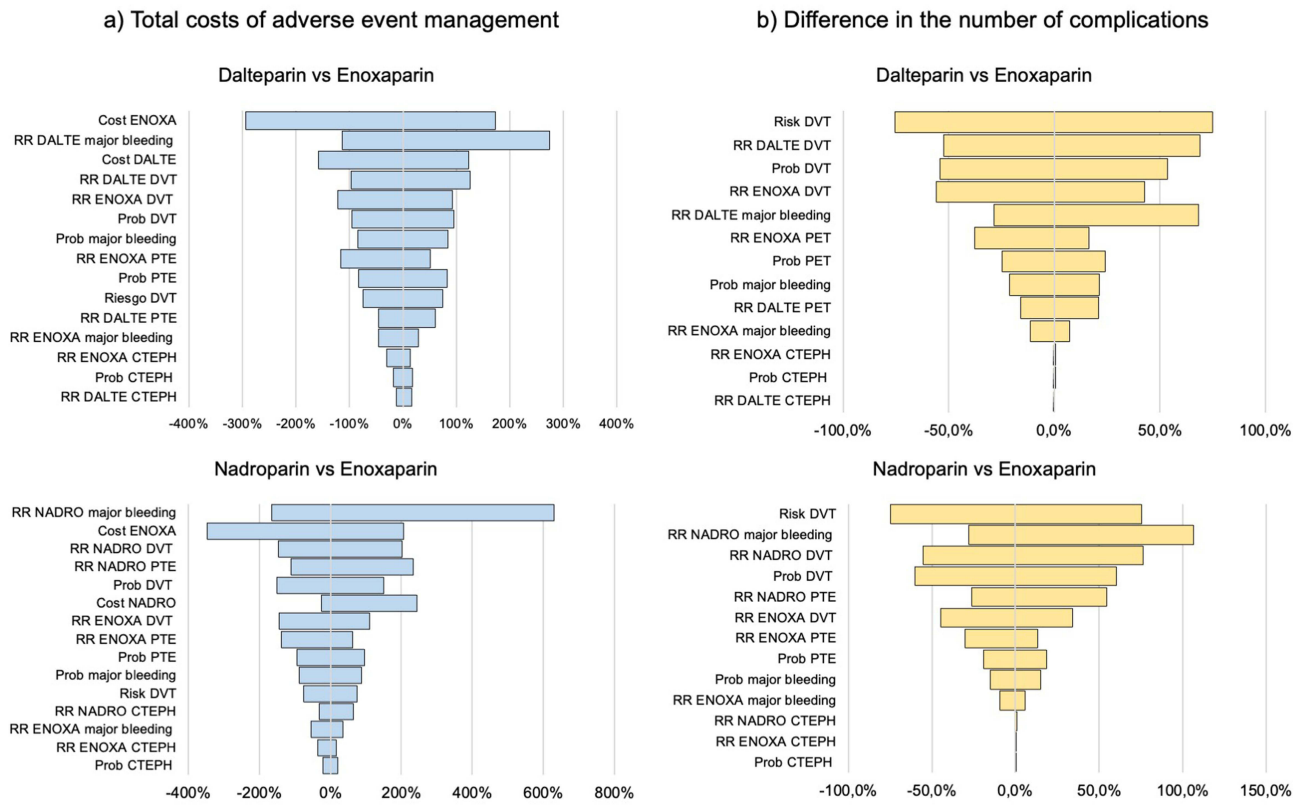

Figure 4 Sensitivity analysis of the difference in total management costs and number of complications due to thromboprophylaxis in Internal Medicine patients. Dalteparin vs enoxaparin and nadroparin vs enoxaparin*. (**a**) Total cost of adverse event management. (**b**) Difference in the number of complications.
Notes: *Sensitivity analysis performed with the following minimum and maximum LMWH prices (enoxaparin: USD 0.09017/mg-$0.25860/mg; dalteparin: USD 0.00022/UI-$0.00102/UI; nadroparin: USD 0.00060/UI- $0.00514/UI).

oncology, the management of PTE with dalteparin and nadroparin resulted in ~2 times higher costs than with enoxaparin. In major bleeding management, it was more than twice, and in DVT, the cost was slightly lower for enoxaparin. In the simulation of Orthopedic patients, the ratios found were similar, and in Internal Medicine, in terms of total direct medical costs, enoxaparin was 10% and 11% cheaper than nadroparin and dalteparin, respectively. The results showed that for the three LMWHs, the number of complications and their associated direct medical costs depended on the type of high-risk patient, being lower in Internal Medicine than in Oncology and Orthopedics. This is because the risk of DVT in Internal Medicine patients was 15%, while for Oncology and Orthopedics patients, it was 35% and 64%, respectively. Although a study found similar costs for enoxaparin, nadroparin, and dalteparin,[24] and other suggest the use of dalteparin over other LMWHs for preventing recurrent venous because of its cost-effectiveness,[25] in our study among all the services analyzed, enoxaparin produced the lowest number of complications and costs when compared to dalteparin and nadroparin, since their relative risks obtained in the meta-analysis were lower for all the complications studied.

The occurrence of complications in our models was primarily influenced by the risk of DVT, which directly affected the percentage of occurrence and number of patients developing PTE and CTEPH. Lower DVT risk values, as observed in the Internal Medicine setting, corresponded to fewer patients experiencing these two additional complications. This influence of risk was consistently evident across various sensitivity analyses, where the probability of DVT occurrence emerged as the variable with the most significant impact on cost differences and the occurrence of complications in several of the evaluated scenarios. DVT and its associated complications are relevant in terms of morbidity and mortality and have a direct impact on increasing direct medical costs and healthcare spending.[26] In the United States (2014), after the first year of occurrence, treating a single case of these complications ranged between USD 13,232 and USD 16,540 (2020 dollars); moreover, annual management of complications varied between USD 19,848–25,361.[14] Between 2019 and 2021, in Brazil, DVT and major bleeding associated with enoxaparin thromboprophylaxis also produced a high

hospital direct medical cost burden in a cohort of 61 patients, with an average per patient of USD 1443 for 2020.[27] This is consistent with our findings, where, depending on the specialty and LMWH used, the management of DVT in 4,000 patients in the hypothetical cohort ranged from USD 389,653 to USD 1,951,073. Although in most complications the costs were mainly hospital costs, the management of CTEPH is mostly ambulatory due to its chronicity, highlighting the health and economic consequences of the sequelae of this type of event, which in the case of CTEPH has a direct impact on the quality of life and long-term survival of patients.[16,28]

This study has several limitations. Given the absence of sufficient studies to perform separate meta-analyses for each medical context, evidence was globally synthesized. In this sense, although event probabilities were tailored for each at-risk patient type, the same relative risk estimates for each treatment option were applied in all medical settings. In addition, the same probabilities were assumed for PTE and CTEPH, as well as for DVT with dalteparin due to lack of evidence. No head-to-head comparative studies among LMWHs are available; then, the relative comparisons were interpreted based on the presence or absence of each LMWH. The study did not include other at-risk populations, such as the gynecobstetric population, primarily owing to the limited availability of relevant data regarding the efficacy and safety of LMWHs in this context. Thromboprophylaxis is indicated in high-risk pregnant women in several clinical practice guidelines in different countries, including Colombia;[17] however, these recommendations are based on the efficacy demonstrated in Internal Medicine patients. There is still a need to generate clinical evidence for LMWH in this population.

Finally, the potential impact of unmeasured patient characteristics on the outcomes of thromboprophylaxis with different LMWHs may influence our analysis. Factors such as a history of VTE, thrombophilia, active autoimmune diseases, varicose veins, and prior major bleeding[29,30] were not consistently reported across the studies included in our SLR. The heterogeneity of these clinical characteristics among patients receiving the three LMWHs could influence the observed efficacy and safety outcomes. Although we used a systematic review to gather the most reliable data available, the inability to control for these factors may limit the generalizability of our findings. Future research with more granular patient-level data must assess these characteristics' impact on thromboprophylaxis outcomes.

Despite the above, the findings here describe the economic burden associated with direct medical costs of VTE and its complications in the Colombian setting, as well as the influence of the type of high-risk patients receiving thromboprophylaxis and the efficacy and costs of the different LMWHs available in the Colombian market. Future analyses are needed that include the indirect costs associated with the loss of productivity due to the events and complications studied, which simulate the costs due to premature mortality and disability of persons with thromboembolic disease in Colombia. This would provide a complete picture of the real economic burden from a societal perspective.

Conclusion

This cost analysis adapted to the Colombian context indicates that, due to the differences on efficacy of enoxaparin over dalteparin and nadroparin, this is the least expensive technology in all the medical contexts analyzed (Oncology, Orthopedic and Internal Medicine). It is important to bear in mind that the type of high-risk patient substantially influences the estimates of costs associated with thromboprophylaxis. This influence extends to factors such as the chosen treatment regimens, and the probabilities associated with adverse events and treatment effectiveness.

Funding

Sanofi of Colombia.

Disclosure

JRS serve as a speaker for Sanofi on an occasional basis, participating in events and presentations related to the company's interests in the healthcare sector. JCGC, JZ, JFL, and NJAZ received fees from ALZAK for developing this project. SLG and LSG are full-time employees of Sanofi and may own stock or stock options. The authors report no other conflicts of interest in this work.

References

1. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol*. 2015;12:464–474. doi:10.1038/nrcardio.2015.83
2. Witt D, Clark N, Vazquez S. Venous Thromboembolism. Eleventh. In: DiPiro J, Yee G, Posey M, Haines S, Nolin T, Ellingrot V, editors. *Pharmacotherapy: A Pathophysiologic Approach. Eleventh*. New York: McGraw Hill; 2020:732–821.
3. Oliveros H, Lobelo R, Martínez F, et al. Análisis costo-efectividad de las heparinas de bajo peso molecular en tromboprofilaxis temprana en pacientes médicos y quirúrgicos. *Acta Medica Colombiana*. 2006;31:71–82.
4. Pineo GF, Hull RD. Economic and practical aspects of thromboprophylaxis with unfractionated and low-molecular weight heparins in hospitalized medical patients. *Clin App Thrombosis/Hemostasis*. 2009;15(5):489–500. doi:10.1177/1076029609335910
5. Martin KA, Cuttica MJ. Chronic thromboembolic pulmonary hypertension: anticoagulation and beyond. *Hematology*. 2021;2021(1):478. doi:10.1182/HEMATOLOGY.2021000282
6. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res*. 2016;118(9):1340–1347. doi:10.1161/CIRCRESAHA.115.306841
7. Dennis R, Rodríguez MN. Estudio nacional sobre tromboembolismo venoso en población hospitalaria en Colombia. *Acta Med Colomb*. 1996;21:55–63.
8. Sandoval JDG, Cerón DKR, Sánchez BEB, Arcila HFL. Comportamiento de la enfermedad tromboembólica venosa en un centro hospitalario de la ciudad de Popayán, Colombia. *Revista Salud Bosque*. 2021;11:1–18.
9. Scheres LJJ, Lijfering WM, Cannegieter SC. Current and future burden of venous thrombosis: not simply predictable. *Res Pract Thromb Haemost*. 2018;2(2):199–208. doi:10.1002/rth2.12101
10. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198–3225. doi:10.1182/bloodadvances.2018022954
11. Villani M, Ageno W, Grandone E, Dentali F. The prevention and treatment of venous thromboembolism in pregnancy. *Expert Rev Cardiovasc Ther*. 2017;15(5):397–402. doi:10.1080/14779072.2017.1319279
12. Routhier N, Tagalakis V. *Venous Thromboembolism (VTE) Prophylaxis: Straight to the Point of Care*. London; 2021.
13. Hao C, Sun M, Wang H, Zhang L, Wang W. Low molecular weight heparins and their clinical applications. *Prog Mol Biol Transl Sci*. 2019;163:21–39. doi:10.1016/bs.pmbts.2019.02.003
14. Grosse SD, Nelson RE, Nyarko KA, Richardson LC, Raskob GE. The economic burden of incident venous thromboembolism in the United States: a review of estimated attributable healthcare costs. *Thromb Res*. 2016;137:3–10. doi:10.1016/j.thromres.2015.11.033
15. Ministerio de Salud y Protección Social. SISMED - Sistema de Información de Precios de Medicamentos. In: Portal SISMED. Available from: https://www.sispro.gov.co/central-prestadores-de-servicios/Pages/SISMED-Sistema-de-Informacion-de-Precios-de-Medicamentos.aspx.2022 Accessed February 09, 2022.
16. Salisbury JP, Curbelo P, Arcaus M, Cáneva J. Hipertensión pulmonar tromboembólica crónica. *Rev Med Urug*. 2011;27:166–174.
17. Grillo-Ardila CF, Mogollón-Mariño AC, Amaya-Guío J, Molano-Franco D, Correa-Pérez LP, Martínez MF. Guía de práctica clínica para la prevención de eventos tromboembólicos venosos durante la gestación, el parto o el puerperio. *Rev Colomb Obstet Ginecol*. 2017;68(4):286–304. doi:10.18597/RCOG.3084
18. Brose KMJ, Lee AYY. Cancer-associated thrombosis: prevention and treatment. *Curr Oncol*. 2008;15(11):S58–67. doi:10.3747/co.2008.177
19. de Stefano V, Martinelli I, Rossi E, et al. The risk of recurrent venous thromboembolism in pregnancy and puerperium without antithrombotic prophylaxis. *Br J Haematol*. 2006;135(3):386–391. doi:10.1111/j.1365-2141.2006.06317.x
20. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(3 Suppl):338S–400S. doi:10.1378/chest.126.3_suppl.338S
21. Agnelli G. Prevention of Venous Thromboembolism in Surgical Patients. *Circulation*. 2004;110:IV–4–IV–12. doi:10.1161/01.CIR.0000150639.98514.6c
22. Instituto de Evaluación Tecnológica en Salud. Manual para la elaboración de evaluaciones económicas en salud. Bogotá D.C; 2014. Available from: www.iets.org.co. Accessed October 16, 2024.
23. Banco de la República de Colombia. Tasa Representativa del Mercado (TRM - Peso por dólar) | banco de la República. 2020, Available from: https://www.banrep.gov.co/es/estadisticas/trm. Accessed February 14, 2024.
24. Shafiq N, Malhotra S, Pandhi P, Sharma N, Bhalla A, Grover A. A Randomized Controlled Clinical Trial to Evaluate the Efficacy, Safety, Cost-Effectiveness and Effect on PAI-1 Levels of the Three Low-Molecular-Weight Heparins–Enoxaparin, Nadroparin and Dalteparin: the ESCAPe-END Study. *Pharmacology*. 2006;78(3):136–143. doi:10.1159/000096484
25. Dranitsaris G, Shane LG, Woodruff S. Low-molecular-weight heparins for the prevention of recurrent venous thromboembolism in patients with cancer: a systematic literature review of efficacy and cost-effectiveness. *J Oncol Pharm Pract*. 2019;25(1):68–75. doi:10.1177/1078155217727140
26. Dobesh P. Economic burden of venous thromboembolism in hospitalized patients. *Pharmacotherapy*. 2009;29(8):943–953. doi:10.1592/phco.29.8.943
27. Lenci Marques G, de Franca AC, Saito AC, et al. Clinical Outcomes and Costs of Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Inpatients: a Cross-Sectional Study. *Cureus*. 2021;13:1–6. doi:10.7759/cureus.15497
28. Roman A, Barbera JA, Castillo MJ, Muñoz R, Escribano P. Calidad de vida relacionada con la salud en una cohorte nacional de pacientes con hipertensión arterial pulmonar o hipertensión pulmonar tromboembólica crónica. *Arch Bronconeumol*. 2013;49(5):181–188. doi:10.1016/j.arbres.2012.12.007
29. Schafer AI. Thrombotic disorders: hypercoagulable states. In: *Goldman's Cecil Medicine*. Elsevier; 2012:1148–1154.
30. Beltrán-Gámez ME, Sandoval-Zárate J, Pulido T. De la tromboembolia pulmonar aguda a la hipertensión pulmonar tromboembólica crónica: implicaciones en la patobiología y fisiopatología. *Arch Cardiol Mex*. 2017;87(1):26–34. doi:10.1016/j.acmx.2016.10.003