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Research Paper

Cost-effectiveness analysis for the parenteral anticoagulants in Jordan

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Abstract

Objectives Pharmacoeconomic dimensions linking clinical effectiveness of parenteral anticoagulants for management of acute venous thromboembolism (VTE) and cost of treatment are needed to support choices by healthcare providers. The objective of the study was to conduct a cost-effectiveness analysis for 5-day treatment with parenteral anticoagulants in Jordan.

Methods Cost-effectiveness analysis was conducted based on decision analysis tree model. The perspective was the payer, considering direct medical costs. Probabilities of failure of treatment and major bleeding were derived from published clinical studies. Costs were estimated based on 2019 prices in Jordan.

Key findings The average cost of VTE hospitalization and major bleeding management in Jordan were 2324.00 US$ and 3347.40 US$, respectively. Bemiparin was associated with the highest clinical efficacy and lowest probability of major bleeding. Nadroparin had the lowest clinical efficacy, while tinzaparin was found to have the highest risk of major bleeding. Bemiparin had the lowest average cost-effectiveness ratio (101.63 US$/success) and nadroparin had the highest cost-effectiveness ratio (295.56 US$/success). Throughout the sensitivity analysis calculations, bemiparin and nadroparin had the lowest and highest cost of treatment, respectively.

Conclusions The cost of parenteral anticoagulant drugs, the same as many other drugs, does not always correlate with cost of VTE treatment. Other direct medical costs (e.g. treatment failure and management of bleeding) have a high contribution to the total cost calculation. Pharmacoeconomically, bemiparin is the dominant cost-effective parenteral anticoagulant in Jordan, while nadroparin is the dominated one.

Keywords: anticoagulants; low-molecular weight heparin; bleeding; cost-effectiveness; VTE; Jordan

Introduction

Venous thromboembolism (VTE) is a common circulatory disease that can be serious and possibly life-threatening, particularly in the elderly. In addition to being associated with significant morbidity and mortality, it has high impact on healthcare costs.[1] The reported annual incidence of VTE in Europe is estimated to range from 104 to 183 per 100 000 people each year.[2] According to the Jordanian health system profile by the World Health Organization (WHO) in 2006, circulatory diseases represent one of the significant causes of death in Jordan (38.2%).[3] However, no enough published data could be found about incidence or prevalence of VTE in Jordan.

VTE covers diseases ranging from asymptomatic vein thrombosis to symptomatic deep vein thrombosis (DVT), in which blood clots are formed in deep veins in the lower extremities. When they break

off, the clots travel through bloodstream reaching pulmonary arteries to cause pulmonary embolism (PE). PE can be fatal when the formed thrombus hinders blood supply to the lungs.[4]

Heparin-derived drugs have been considered as pivotal components for initiation of VTE treatment. Unfractionated heparin (UFH) is given parenterally and requires clinical monitoring and dose adjustment to ensure effective dose range with desirable outcomes.[4–6] Moreover, UFH may result in the occurrence of heparin-induced thrombocytopenia (HIT) as an adverse event.[7] Unlike UFH, low-molecular weight heparins (LMWHs) which are derived from UFH by chemical or enzymatic depolymerization, have more predictable pharmacokinetic properties that allow fixed-dose administration without dose adjustment based on laboratory monitoring. Yet, monitoring is still advised in cases of renal failure, obesity and upon overdosing.[4, 8] Each LMWH displays different molecular weight, molecular composition and functional properties. In fact, LMWHs have different physiochemical, biological, pharmacological and clinical properties. Since each product is developed uniquely.[4]

On the other hand, fondaparinux, a parenteral anticoagulant, neither affect platelet function nor interact with heparin platelet factor (PF-4) antibodies found in HIT patients. Consequently, it is considered as an alternative option for patients with a history of HIT.[7] A kind of uncertainty regarding which specific parenteral agent of choice for VTE acute phase treatment still exists.[9] Recently, the VTE therapeutic options underwent dramatic changes when the new direct oral anticoagulants (DOACs) have been introduced to the market.[5]

Clinically relevant information for the available parenteral anticoagulants (i.e. UFH, LMWHs and fondaparinux) regarding their safety and efficacy in correlation with their pharmacoeconomic evaluation is needed to help healthcare providers and policy-makers to choose between these agents. The NICE guidelines for VTE prophylaxis and treatment define cost-effectiveness analysis as an economical study design that measures a single outcome for different interventions. Accordingly, these alternative interventions are compared in terms of cost per unit of effectiveness.[10] An extensive searching had been conducted, after which no comprehensive cost-effectiveness analyses for the VTE parenteral anticoagulants could be found published in the literature. However, no local cost-effectiveness studies that compared cost and assess effectiveness for the available VTE treatments in the Jordanian market were found.

In this study, cost-effectiveness analyses based on a decision analysis tree method were carried out on the available parenteral anticoagulants in Jordan, to recommend the cost-effective parenteral agent of choice for VTE acute phase treatment.

Method

Perspective of the study

The study was conducted from a payer's perspective. Only direct medical costs were included in the pharmacoeconomic analyses.

VTE treatment guideline selection

The 10th edition of CHEST guideline for VTE treatment 'Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis' was chosen as the reference guideline. It is a comprehensive guideline that was found to be compatible with the common practice for the treatment of VTE in Jordan.[11]

Cost calculation

The calculated direct medical costs were as follows:

- Average cost of 5-day treatment with the parenteral anticoagulant.
- Average cost of hospitalization for DVT/PE patients, that is, hospital stay, parenteral administration for injectable drugs and diagnostic procedures and laboratory tests.
- Average cost of management of major bleeding as the main adverse drug event (incidence depends on probabilities in the literature).
- Average cost of treatment failure, that is, the average cost of recurrent VTE treatment in hospital (incidence depends on probabilities in the literature).

All prices and calculated costs were changed from Jordanian Dinars (JOD) to US Dollars (US$). Average exchange rate in 2019 was 1 JOD = 1.4 US$.

Medication costs

Medication costs were based on wholesale prices that were calculated using the 2019 public price list on Jordan Food and Drug Administration (JFDA) website (http://www.jfda.jo/Pages/viewpage.aspx?pageID=184). Only Originator drugs were included. Medication costs were calculated for Heparin Leo (UFH), Hibor (Bemiparin), Clexane (Enoxaparin), Fraxiparine (Nadroparin), Innohep (Tinzaparin), Fragmin (Dalteparin) and Arixtra (Fondaparinux). Duration of treatment was assumed to be 5 days. Medication cost was estimated based on unit dose price. Daily dose was calculated and multiplied by the number of treatment days. The dosing regimen was derived from the most recent drug leaflet on the emc website (https://www.medicines.org.uk/emc), assuming bodyweight to be 70 kg for the purpose of daily dose determination (when needed).

Hospitalization cost for DVT, PE and bleeding cases

Cost of hospitalization was calculated retrospectively as the average of hospitalization cost for VTE patients in a private hospital in Amman, Jordan (Al-Isra'a Hospital) in the period between January and December 2019. DVT, PE and anticoagulant toxicity patients were included.

The average costs of hospitalization and management of major bleeding events were derived from VTE patients' bills. Costs of VTE medications, monitoring laboratory tests and medications related to chronic disease were all excluded from bills. Costs of hospitalization for DVT patients and PE patients were extracted from the hospital's bills. Bills of cases of surgical interventions for management of VTE were excluded. Recurrent DVT and/or PE (treatment failure) costs were considered as the average cost of all VTE patients' bills.

Safety and efficacy failure data

A systematic search for literature was conducted via PubMed and Google Scholar. Published randomized clinical trials, preferably phase 3 and/or phase 4 trials, were selected. The included population were adult patients diagnosed with VTE.

Data from published trials about use of parenteral anticoagulants were pooled to determine the probabilities of major bleeding events and treatment failure within 3 up to 6 months of therapy. Probability of major bleeding was chosen as the safety concern because it is a clinically overt event. Recurrent VTE events (DVT,

fatal and non-fatal PE) throughout the study duration were considered the efficacy failure endpoint for all parenteral anticoagulants. The exclusion criteria for the reference clinical studies were: 1 – clinical trials on drugs that were not registered in Jordan in 2019 and 2 – studies on patients belonging to other age groups (elderly and paediatrics), pregnant women and patients with chronic comorbidities (e.g. cancer patients, obese and patients with impaired renal function).

Pharmacoeconomic analysis

Cost-effectiveness analyses were conducted on Heparin Leo, Clexane, Hibor, Fraxiparine, Innohep, Fragmin and Arixtra when they are used as initial treatment for VTE (first 5 days) before switching to dabigatran or while overlapping with warfarin. The aim was to determine the cost-effective parenteral anticoagulant – by calculating average cost-effectiveness ratio – to be used initially in switching and overlapping treatment strategies. The first outcome on the decision analysis tree was treatment success. For [yes], two branches were added expressing the adverse event (major bleeding) probabilities. In case of treatment failure, re-hospitalization due to PE and/or DVT events was assumed.

For the compared parenteral agents, total costs obtained from the decision analysis tree were listed along with their treatment success probabilities. Accordingly, the cost-effective drug of choice can be decided.

Sensitivity analysis

Sensitivity analyses were conducted for the cost of treatment that was calculated by using the decision analysis tree. The tested parameters were one-way sensitivity analysis assuming reduction in unit dose prices down to 50%, since according to the drug pricing law in Jordan, prices of drugs are in favour not to increase with each drug re-pricing episode, and two-way sensitivity analysis assuming ±30% changes in VTE re-hospitalization cost and major bleeding management cost.

Results

Cost calculation

Medication cost

The cost of medications and the approved dosing regimens for VTE treatments are listed in Table 1. Medication costs for 5-day therapy with Heparin Leo, Clexane, Hibor, Fragmin, Innohep, Fraxiparine and Arixtra were (34.02 US$), (90.30 US$), (84.65 US$), (78.75 US$), (69.15 US$), (80.40 US$) and (75.25 US$), respectively.

Hospitalization cost

Thirty-two bills for DVT, PE and anticoagulant toxicity admissions were reviewed. According to primary diagnosis, number of admissions was 20, 5 and 7 for PE, DVT and major bleeding, respectively. The average cost of DVT hospitalization was 2018.18 US$ (SD = 1489.35 US$) with an average length of stay (LOS) of 3.5 days (SD = 3.0 days). The average cost of PE hospitalization was 3386.67 US$ (SD = 1439.10 US$) with an average LOS of 4.8 days (SD = 2.6 days). Collectively, the average cost of hospitalization for all VTE events was 2324.00 US$ (SD = 1517.05 US$) with an average LOS of 3.8 days (SD = 3.0 days). The average cost of major bleeding management was 3347.40 US$ (SD = 2881.26 US$) with an average LOS of 4.1 days (SD = 3.0 days).

Table 1 Total cost for 5-day treatment with parenteral anticoagulants

Anticoagulant	Strength	Pack size	Pack price (US$)	Unit dose price (US$)	VTE treatment dose	5-day treatment cost (US$)
Heparin Leo 5000 IU/ml vial (UFH)	5000 IU/ml	50 Vial × 5 ml	243.42	4.86	Loading dose: 5000 units intravenouslyMaintenance dose: 10 000–20 000 units twice daily (15 000 units twice daily were assumed)	34.02
Clexane PFS (enoxaparin)	8000 IU/0.8 ml	2 PFS	18.06	9.03	1 mg/kg twice daily	90.30
Hibor PFS (bemiparin)	7500 IU/0.3 ml	2 PFS	33.85	16.93	115 IU/kg once daily or 7500 IU once daily if body weight ≥70 kg	84.65
Fraxiparine PFS (nadroparin)	7600 IU/0.8 ml	2 PFS	16.07	8.04	85 IU/kg twice daily	80.40
Innohep PFS (tinzaparin)	14 000 IU/0.7 ml	2 PFS	27.65	13.83	175 IU/kg once daily	69.15
Fragmin PFS (dalteparin)	5000 IU/0.2 ml	10 PFS	52.5	5.25	200 IU/kg once daily or 15 000 IU once daily if body weight (69–82 kg)	78.75
Arixtra PFS (fondaparinux)	7.5 mg/0.6 ml	10 PFS	150.50	15.05	7.5 mg once daily, when patient's body weight is 50–100 kg	75.25

Table 2 Published RCTs of parenteral anticoagulants as initial therapy for VTE

Study	Number of participants	Duration	Group 1	Group 2	Patients who had major bleeding events		Patients who had recurrent VTE	
					Group 1	Group 2	Group 1	Group 2
Büller *et al.*[12]	2205	3 months	Fondaparinux (*n* = 1098)	Enoxaparin (*n* = 1107)	12	13	43	45
Suchkov *et al.*[13]	312	3 months	Bemiparin (*n* = 162)	Enoxaparin (*n* = 150)	0	0	1	1
Kakkar *et al.*[14]	222	3 months	Bemiparin (*n* = 111)	UFH (*n* = 111)	0	1	1	4
Koopman *et al.*[15]	400	6 months	Nadroparin (*n* = 202)	UFH (*n* = 198)	1	4	14	17
Prandoni *et al.*[16]	170	6 months	Nadroparin (*n* = 85)	UFH (*n* = 85)	1	3	6	12
Wells *et al.*[17]	505	3 months	Tinzaparin (*n* = 254)	Dalteparin (*n* = 251)	5	2	10	9
Hull *et al.*[18]	200	3 months	Tinzaparin (*n* = 97)	UFH (*n* = 103)	1	2	0	7
Merli *et al.*[19]	900	6 months	Enoxaparin (*n* = 610)	UFH (*n* = 290)	9	6	22	12
Luomanmäki *et al.*[20]	248	6 months	Dalteparin (*n* = 117)	UFH (*n* = 131)	0	1	3	2
Dager *et al.*[21]	140	6 months	Tinzaparin followed by warfarin		5		1	

Table 3 Pooled analysis of the RCTs safety and efficacy failure of the parental anticoagulants

Anticoagulant	Total number of patients	Recurrent VTE, % (*n*)	Major bleeding, % (*n*)
UFH	918	5.88 (54)	1.85 (17)
Enoxaparin	1867	3.64 (68)	1.18 (22)
Bemiparin	273	0.73 (2)	0.00 (0)
Nadroparin	287	6.97 (20)	0.70 (2)
Tinzaparin	491	2.24 (11)	2.24 (11)
Dalteparin	368	3.26 (12)	0.54 (2)
Fondaparinux	1098	3.92 (43)	1.09 (12)

Efficacy failure and safety

A total number of 10 published randomized controlled trials (RCTs) representing 5302 patients were found after conducting an extensive PubMed and Google Scholar searching on phase III and phase VI studies about safety and efficacy of parenteral anticoagulants upon use as an initial therapy for VTE (Tables 2 and 3). In all studies, warfarin was the oral anticoagulant that was used for the following long-term therapy.

Of the 1098 patients who received fondaparinux, 43 patients had recurrent thrombotic events (3.92%), and 12 (1.09%) of them had major bleeding. Out of 1867 patients who received enoxaparin, 68 patients (3.64%) had recurrent VTE events, while only 22 of them (1.18%) had major bleeding events. Notably, no major bleeding events were reported for patients who received bemiparin, and only two patients had recurrent VTE (0.73%). The highest percentage of recurrent VTE was found in patients who received nadroparin (6.79%). On the other hand, only 2 of 287 patients on nadroparin (0.7%) had major bleeding. When tinzaparin was tested, an equal number of major bleeding and recurrent thrombotic events were reported, representing 2.24% for both safety and efficacy failure. Of those who received UFH, 5.88% had recurrent VTE, and the second highest rate of major bleeding (1.85%).

Pharmacoeconomic analysis

Cost-effectiveness analysis

Parenteral anticoagulants are ideally used for the first 5 days immediately after diagnosis with VTE. Cost-effectiveness calculations based on decision analysis tree (Figure 1) were conducted to compare the parenteral anticoagulants under pharmacoeconomic investigation (Tables 4 and 5). It was found that Bemiparin (Hibor) had the highest efficacy (99.3%) and the lowest treatment cost (100.92 US$) when compared with other parenteral anticoagulants in Jordan. At the same time, Nadroparin (Fraxiparin) was found to be the parenteral anticoagulant with the lowest efficacy (93.0%) and the highest treatment cost (274.87 US$). Average cost-effectiveness ratio for parenteral anticoagulants in Jordan was ranging from 101.63 to 295.56 US$/treatment efficacy.

Sensitivity analysis

Figure 2 represents the decrease in cost of VTE treatment with each of the anticoagulants under investigation, according to the decrease in their unit dose prices.

Figure 3 represents the change in cost of VTE treatment with each of the anticoagulants under investigation, according to the change in cost of VTE re-hospitalization, while Figure 4 represents the change in cost of VTE treatment according to the change in cost of major bleeding management. In all scenarios tested in sensitivity analysis, no major changes in ranking of the parenteral anticoagulants could be anticipated. Treatment with bemiparin had the lowest cost among other parenteral anticoagulants even when their unit dose prices become 50% lower, and when cost of VTE or major bleeding hospitalizations changes by 30%. Within the same ranges in sensitivity analyses, nadroparin continued to be associated with the highest treatment costs.

Discussion

To our knowledge, this is the first study that evaluates the cost-effectiveness of the available VTE therapeutic alternatives in Jordan. Outcomes of this study are expected to influence decisions taken by practitioners, decision makers in public and private health sectors, health policymakers, and the JFDA to consider prescribing and purchasing the cost-effective parenteral anticoagulants for treatment of VTE.

In this piece of research, costs of DVT, PE and anticoagulants-associated major bleeding treatment per indexed admission were estimated according to hospital public prices based on real data extracted from inpatients records of a private hospital in Amman.

In Jordan, one study dated in 2016 had estimated the united cost of hospital services. Average cost per admission was 674.2 US$; 149.3 US$ per inpatient day, and 88.3 US$ per bed day.[22] These findings were less than the calculated average VTE inpatient day, where the average cost of DVT inpatient day was 576.8 US$ and for PE was 705.6 US$.

The costs of medications were calculated based on 2019 JFDA medication price list. The JFDA pricing process follows specific pricing policy based on drug's country of origin price, median

Figure 1 Cost-effectiveness decision analysis tree.

price in a basket of reference countries and price in Saudi Arabia. Medication prices may vary and change over time based on changing in their prices in the country of origin. Yet, they generally tend not to increase.[23]

The results demonstrated that Bemiparin (Hibor) was the dominant parenteral anticoagulant all the way. With the relatively highest efficacy and lowest cost of treatment, it can be considered as the injectable anticoagulant drug of choice for the included category of VTE patients. On the other hand, Nadroparin (Fraxiparin) was the dominated parenteral anticoagulant according to the drugs' pricing system in Jordan. It had the relatively lowest efficacy accompanied with the highest cost of treatment among other choices. Pooled data from parenteral anticoagulant studies show that bemiparin has not been associated with major bleeding events. At the same time, it is associated with the highest efficacy rate compared with other parenteral anticoagulants regarding protection against recurrent VTE. Meanwhile, nadroparin has the highest rate of VTE reoccurrence followed by UFH which has also the highest rate of major bleeding.

Although UFH (Heparin Leo 5000 IU/ml vial) had the lowest unit dose price among all parenteral anticoagulants, and dalteparin (Fragmin PFS) had the lowest unit dose price among other LMWHs, this did not count significantly in making their total cost of treatment lower than other choices of parenteral anticoagulants. Considering the sensitivity analyses that were conducted on costs of medications, recurrent VTE hospitalization and major bleeding, bemiparin and nadroparin reserved their positions being the pharmacoeconomically

Table 4 Costs and probabilities for parenteral anticoagulants clinical outcomes

Clinical outcomes	Average cost (US$)	Probabilities	Cost × probabilities (US$)
UFH			
Success with no adverse events	34.02	0.941 × 0.981	31.40
Success with adverse events (major bleeding)	(34.02 + 3347.40)	0.941 × 0.019	60.46
Treatment failure (re-hospitalization DVT and/or PE)	(34.02 + 2324.00)	0.059	139.12
Total		1	230.98
Enoxaparin			
Success with no adverse events	90.30	0.964 × 0.988	86.00
Success with adverse events (major bleeding)	(90.30 + 3347.40)	0.964 × 0.012	39.77
Treatment failure (re-hospitalization DVT and/or PE)	(90.30 + 2324.00)	0.036	86.91
Total		1	212.68
Bemiparin			
Success with no adverse events	84.65	0.993 × 1	84.06
Success with adverse events (major bleeding)	(84.65 + 3347.40)	0.993 × 0	0.00
Treatment failure (re-hospitalization DVT and/or PE)	(84.65 + 2324.00)	0.007	16.86
Total		1	100.92
Nadroparin			
Success with no adverse events	80.40	0.930 × 0.993	74.25
Success with adverse events (major bleeding)	(80.40 + 3347.40)	0.930 × 0.007	22.31
Treatment failure (re-hospitalization DVT and/or PE)	(80.40 + 2324.00)	0.070	168.31
Total		1	264.87
Tinzaparin			
Success with no adverse events	69.15	0.978 × 0.978	66.14
Success with adverse events (major bleeding)	(69.15 + 3347.40)	0.978 × 0.022	73.51
Treatment failure (re-hospitalization DVT and/or PE)	(69.15 + 2324.00)	0.022	52.65
Total		1	192.30
Dalteparin			
Success with no adverse events	78.75	0.967 × 0.995	75.77
Success with adverse events (major bleeding)	(78.75 + 3347.40)	0.967 × 0.005	16.57
Treatment failure (re-hospitalization DVT and/or PE)	(78.75 + 2324.00)	0.033	79.29
Total		1	171.63
Fondaparinux			
Success with no adverse events	75.25	0.961 × 0.989	71.52
Success with adverse events (major bleeding)	(75.25 + 3347.40)	0.961 × 0.011	36.18
Treatment failure (re-hospitalization DVT and/or PE)	(75.25 + 2324.00)	0.039	93.57
Total		1	201.27

Table 5 Final total cost versus clinical outcome (as treatment success)

Drug name	Average total cost (US$)	Clinical outcome (treatment success)	Average cost-effectiveness ratio (US$/success)
UFH	230.98	0.941	245.46
Enoxaparin	212.68	0.964	220.62
Bemiparin	*100.92* (lowest)	*0.993* (highest)	101.63
Nadroparin	*264.87* (highest)	*0.930* (lowest)	295.56
Tinzaparin	192.30	0.977	196.83
Dalteparin	171.63	0.967	177.49
Fondaparinux	201.27	0.961	209.44

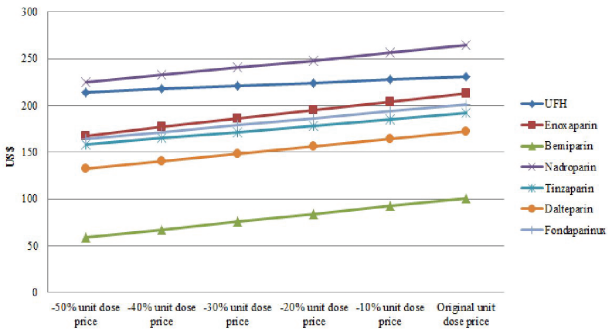

Figure 2 One-way sensitivity analysis for unit dose prices.

dominant and dominated parenteral anticoagulant drugs of choice, respectively.

No comprehensive pharmacoeconomic analyses could be found in the literature for parenteral anticoagulants. Gomez-Outes *et al.* demonstrated that bemiparin was dominant over enoxaparin in post-operative prophylaxis by giving better outcomes accompanied with higher cost-saving. Nevertheless, bemiparin alone or with oral vitamin-K inhibitor were pharmacoeconomically dominant regimens over UFH in DVT treatment from the perspective of the Spanish National Health System.[24] Post-operative bemiparin administration was not only as effective as, but safer than the pre-operative start of prophylactic administration. Consequently, at-risk patients can be admitted to hospital on the same day of surgery, thus lower LOS and cost when compared with enoxaparin.[25] The pharmacoeconomic analysis study that was conducted by the ESFERA Study Team, supports our finding as they explore that bemiparin administration for VTE treatment was associated with mean of 3 days hospitalization reduction, less frequent monitoring and low risk of bleeding.[26]

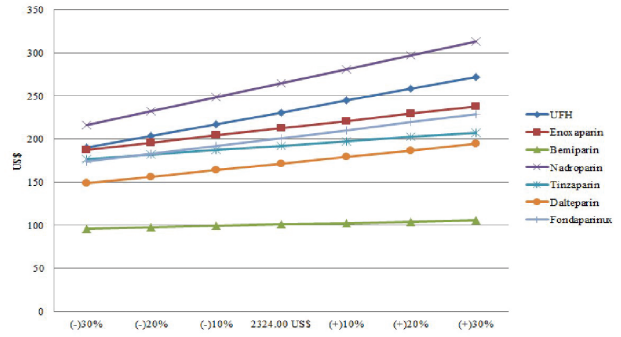

Figure 3 Two-way sensitivity analysis for cost of VTE re-hospitalization.

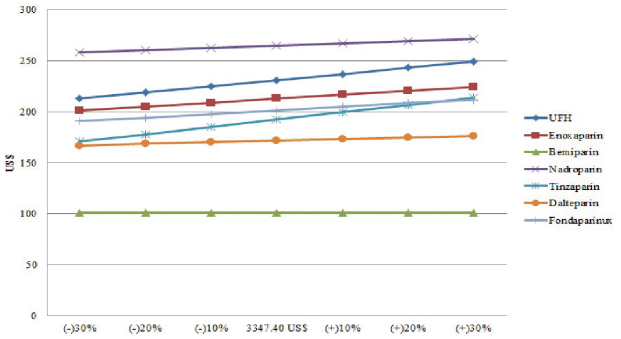

Figure 4 Two-way sensitivity analysis for cost of management of major bleeding.

The limitation of this study is that it had outsourced data from only one private hospital in Jordan, which can limit the generalization to all medical centres in the country.

Conclusions

In conclusion, the cost of medication of anticoagulants, the same as many other drugs, does not always reflect the cost of treatment of VTE. Other direct medical costs can have a considerably high contribution to the total cost calculation. Although the difference in efficacy and safety between most of the parenteral anticoagulants seems to be not clinically significant, it can have a significant impact on cost-effectiveness analyses and making decisions on treatment choices. Pharmacoeconomically, the LMWH bemiparin (Hibor) is the dominant cost-effective injectable anticoagulant in Jordan, while Nadroparin (Fraxiparin) is the dominated choice.

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Author Contributions

Shatha Alquraan collected data and conducted cost-effectiveness analysis, and Feras Darwish El-Hajji conducated sentitivity analysis.

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Conflict of Interest

The researchers confirm that there are no relevant financial or non-financial competing interests or any conflict of interest with any of the companies, marketing authorization holders, producers or pharmaceutical bodies.

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