Cost-Effectiveness of Fondaparinux in Patients with Acute Coronary Syndrome without ST-Segment Elevation

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Abstract

Background: The combined use of antithrombotic agents, antiplatelet agents and invasive strategies in acute coronary syndrome without ST-segment elevation (ACSWSTE) reduces cardiovascular events. Fondaparinux has demonstrated equivalence to enoxaparin in reducing cardiovascular events, but with a lower rate of bleeding in patients using fondaparinux.

Objective: Evaluate the cost-effectiveness of fondaparinux versus enoxaparin in patients with ACSWSTE in Brazil from the economic perspective of the Brazilian Unified Health System (SUS).

Methods: A decision analytic model was constructed to calculate the costs and consequences of the compared treatments. The model parameters were obtained from the OASIS-5 study (N = 20,078 patients with ACSWSTE randomized to fondaparinux or enoxaparin). The target outcome consisted of cardiovascular events (i.e., death, myocardial infarction, refractory ischemia and major bleeding) on days 9, 30 and 180 after ACSWSTE. We evaluated all direct costs of treatment and ACSWSTE-related events. The year of the analysis was 2010 and the costs were described in reais (R$).

Results: On day 9, the cost of treatment per patient was R$ 2,768 for fondaparinux and R$ 2,852 for enoxaparin. Approximately 80% of total costs were associated with invasive treatments. The drug costs accounted for 10% of the total cost. The combined rates of cardiovascular events and major bleeding were 7.3% and 9.0% for fondaparinux and enoxaparin, respectively. Sensitivity analyses confirmed the initial results of the model.

Conclusion: The use of fondaparinux for the treatment of patients with ACSWSTE is superior to that of enoxaparin in terms of prevention of further cardiovascular events at lower cost. (Arq Bras Cardiol 2012;99(1):613-622)

Keywords: Acute coronary syndrome; anticoagulants/therapeutic use; anticoagulants/adverse effects; cost-effectiveness analysis.

Introduction

In Brazil, as well as in developed countries, cardiovascular disease is the leading cause of death[1,2]. According to the Ministry of Health in 2005, cardiovascular diseases accounted for about one third of deaths in Brazil[3].

Acute Coronary Syndrome (ACS) comprises a set of clinical manifestations that reflect a picture of acute myocardial ischemia, including three main forms: unstable angina and acute myocardial infarction (AMI) with or without ST-segment elevation. In the United States, unstable angina is the most common cardiovascular cause of hospitalization and is also responsible for the majority of admissions to coronary care units[4].

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The physiopathological process most commonly associated with ACS involves the rupture of an inflamed atherosclerotic plaque that leads to the formation of an intravascular thrombus, with partial or complete occlusion of the coronary artery lumen[5]. For this process to occur, there is activation of the blood coagulation cascade, where the activated factor X transforms prothrombin to thrombin, which acts to convert fibrinogen to fibrin, and eventually resulting in the formation of the thrombus[6]. As a result, antithrombotic therapy is essential in the clinical management of ACS.

Drugs that interfere with the formation of thrombus, such as unfractionated heparin (UFH - for example, sodium heparin) and low molecular weight heparins (LMWH - for example, enoxaparin, dalteparin and nadroparin) have been shown to reduce mortality in the treatment of ACS, to the cost of increasing the incidence of bleeding complications[7]. In clinical trials evaluating patients with ACS without ST elevation, the results obtained with both nadroparin and dalteparin with were similar to those with UFH[8,9]. However, the use of enoxaparin evaluated in a systematic review

involving 22,000 patients showed it was more effective than UFH in preventing major events such as death or nonfatal myocardial infarction[10].

Several studies have shown an association between reduction of cardiovascular events and increased bleeding, which motivates the search for new and safer drugs regarding bleeding events[11].

Fondaparinux is a synthetic pentasaccharide that selectively inhibits activated factor X of the coagulation cascade. Initially approved for use in the prophylaxis of deep vein thrombosis in patients undergoing orthopedic surgery, fondaparinux has been widely studied as an alternative to heparin in the treatment of ACS. Among its benefits are: administration in a single daily dose, failure to induce thrombocytopenia caused by heparin and does not require anticoagulation control. Moreover, when compared to enoxaparin in the setting of acute coronary syndrome without ST elevation (ACSWSTE), fondaparinux showed a significant reduction in major bleeding (2.2% vs. 4.1%, HR = 0.52, 95% CI: 0.44 to 0 61, p <0.001) and lower cost of treatment[12].

Based on studies demonstrating a similar efficacy of fondaparinux and enoxaparin in the treatment of ACS, but with a reduction in bleeding events with fondaparinux, the objective of this study was to determine the cost-effectiveness of fondaparinux compared to enoxaparin in the treatment of patients with ACSWSTE under the economic perspective of the Ministry of Health of Brazil, manager of the Unified Health System (SUS). That is, to assess this association considering the direct costs of treatment of this condition in the setting of SUS.

Methods

Study type and interventions

The type of study applied was the mathematical modeling (i.e., analytical decision tree) and Cost-Effectiveness Analysis (CEA). The following comparison was prepared for the development of the mathematical model: to treat patients with ACSWSTE with fondaparinux (2.5 mg subcutaneously once a day) *versus* enoxaparin (1 mg/kg 2 times daily). The economic perspective adopted was that used by SUS.

Target-population

Patient characteristics of the pharmacoeconomic analysis are identical to those assessed in the main clinical trial of the drugs compared here (see item "Clinical and safety data of the model"). Thus, the population studied consisted of patients hospitalized with symptoms of ACSWSTE (i.e., NSTEMI and unstable angina), aged 60 years and older and of both sexes.

Model design

To estimate the cost-effectiveness of treatments, we designed a computer model that simulates the expected number of events and the resulting costs for each therapeutic option in the comparison. In this model, the time period analyzed was 9, 30 or 180 days after treatment administration. We did not apply discount rates, as the time period is less than one year.

All patients start at the model at a single moment: hospitalized patients who are diagnosed with ACSWSTE. After that, the patient follows the standard treatment for ACSWSTE, which is either fondaparinux or enoxaparin and at the end of the time period, one estimates how many patients had each of the outcomes of interest: death, AMI, refractory ischemia and major bleeding.

The diagram depicting the decision tree used to evaluate treatment cost and consequences after the diagnosis of ACSWSTE is shown in figure 1. The treatment flow chart is the one recommended by clinical guidelines of the American College of Cardiology[13].

Patients diagnosed with ACSWSTE are therefore treated initially with acetylsalicylic acid (ASA), clopidogrel, and anticoagulant therapy (fondaparinux or enoxaparin). The patient could be submitted to early invasive strategy, undergoing coronary angiography, or through the conservative strategy. The use of glycoprotein IIbIIIa inhibitors is considered in both treatment strategies (conservative and invasive). In the absence of an event that indicates coronary angiography, a functional test is performed as a means of risk stratification. If the result is low coronary risk, the patient will only undergo medical treatment. Otherwise, the patient will be submitted to coronary angiography.

After coronary angiography, patients can undergo Coronary Artery Bypass Surgery (CABG), target vessel angioplasty or medical treatment. When patients undergo CABG, clopidogrel and anticoagulant are withdrawn and ASA is maintained. In case of angioplasty, ASA and clopidogrel are maintained, and the treatment with glycoprotein and LMWH is initiated. Moreover, the anticoagulant treatment is withdrawn. In case of medical treatment, the patient maintains ASA and clopidogrel, and anticoagulation therapy continues for 48 hours. The transition probabilities for every moment of the mathematical model were obtained from Mehta et al[14] and are described in Table 1.

Clinical and safety data used in the model

The mathematical model accurately reflects the results of the randomized clinical trial OASIS-5[12].

The OASIS-5 study had as primary objective demonstrate the noninferiority of fondaparinux when compared to enoxaparin in patients with ACSWSTE regarding the decrease in the combined outcome of death, AMI or refractory ischemia on day nine. Another primary objective was safety-related, i.e., decrease in major bleeding. The treatment regimen consisted of fondaparinux 2.5 mg once daily or enoxaparin 1 mg/ kg/ dose, twice daily for a mean of five days of treatment, both subcutaneously.

The primary outcome of decrease of death, AMI or refractory ischemia on day nine was similar between groups (5.8% fondaparinux *vs*. enoxaparin 5.7%, HR = 1.01, 95% CI: 0.90 to 1.13), demonstrating the noninferiority

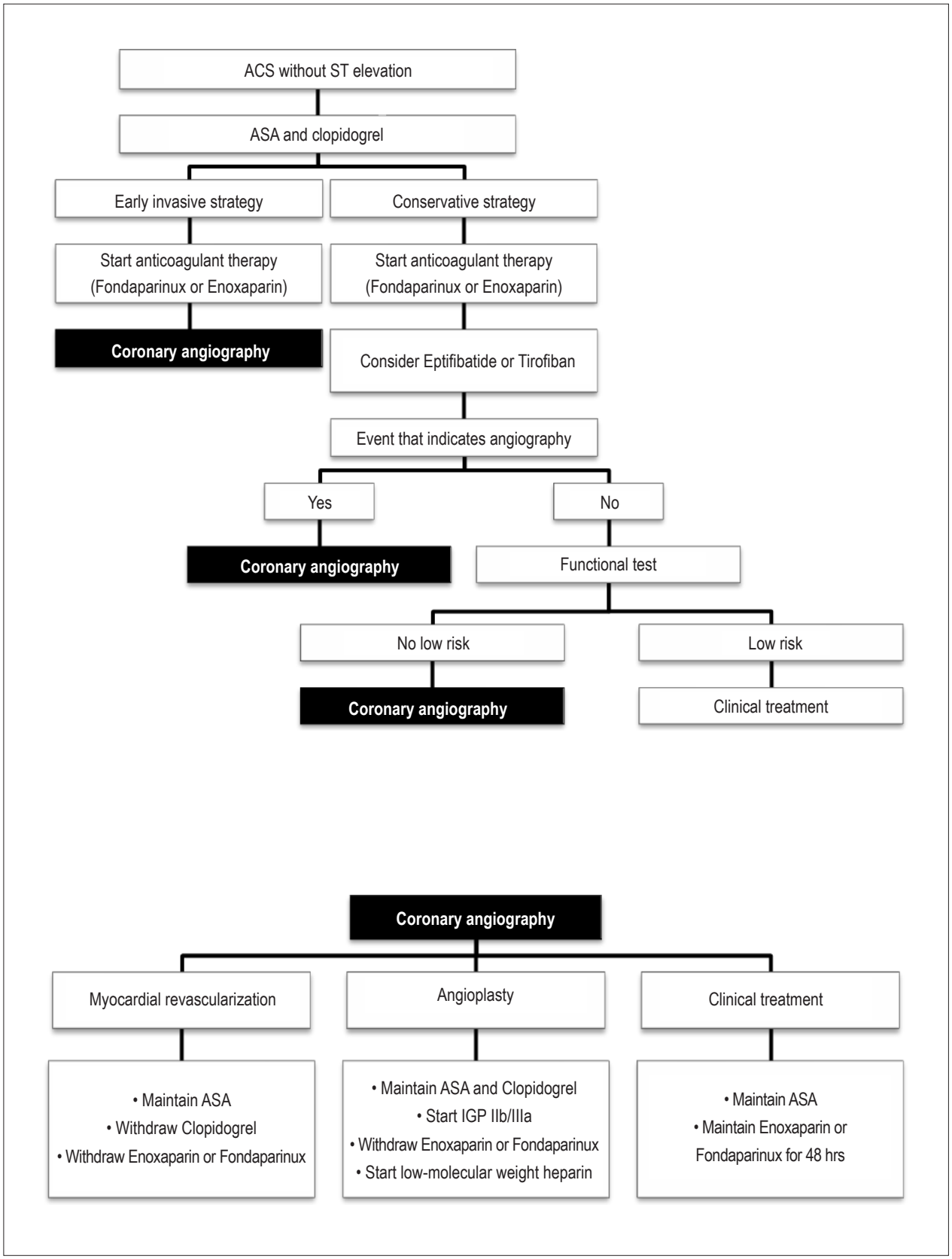

Figure 1 – *Diagram representing the decision tree used to measure the costs and consequences of treatment based on a diagnosis of Acute Coronary Syndrome without ST-segment elevation.*

Table 1 – Transition probabilities between stages of the treatment of acute coronary syndrome without ST-segment elevation

Transition	Probability	Source
Diagnosis - early invasive strategy - Angiography	14.11%[1]	Mehta et al.[14], 2007
Diagnosis - conservative strategy	85.89%[2]	
Conservative strategy - Event indicating angiography - Angiography	22.89%[3]	Mehta et al.[14], 2007
Conservative strategy - Event not indicating angiography (Functional Testing)	77.11%[2]	
Functional testing - not low risk - Angiography	55.84%[4]	Mehta et al.[14], 2007
Functional Testing - Medical Treatment	44.16%[2]	
Coronary angiography - Coronary artery bypass grafting	13.81%[5]	Mehta et al.[14], 2007
Coronary angiography - angioplasty	43.91%[6]	
Coronary angiography - Medical Treatment	42.28%[2]	

[1] Proportion of patients in both groups that underwent angiography within 24 hours. [(1.414+1.420)/20.078]; [2] Patients that did not go to other arm (s); [3] Proportion of the number of patients who underwent angiography in up to 48 hours compared to total angiograms weighted by the ratio of individuals who were not referred to angiography before. [(1.976+1.972/20.078) / 85,89%]; [4] Total number of patients who underwent angiography less those who underwent in up to 48 hours in relation to the total number of patients weighted by the ratio of individuals who were not referred to angiography before. [(14.206 - 2.834 - 3.948)/20.078) / (85,89% * 77,11%)]; [5] Proportion of number of patients who underwent CABG in relation to those who were referred to angiography. [1.862 / 14.206]; [6] Proportion of number of patients who underwent angioplasty in relation to those who were referred to angiography. [6.238 / 14.206]

of fondaparinux when compared with enoxaparin. When assessing the primary safety endpoint, the results favored the use of fondaparinux, due to the lower incidence of major bleeding (2.2% *versus* 4.1%, HR = 0.52, 95% CI: 0.44 to 0.61, p <0.001).

The data that evaluated the secondary outcomes of single events in 180 days, showed a lower incidence of mortality (5.8% versus 6.5%, HR = 0.89, 95%CI: 0.80 to 1.00, p = 0.05) and lower incidence of death and AMI (10.5% *versus* 11.4%, HR = 0.92, 95%CI: 0.84 to 1.00, p = 0.05) in the fondaparinux group. Clinical and safety data used in the study are shown in Table 2.

Use of resources and treatment costs

This pharmacoeconomic analysis includes only direct medical costs, which are of interest to SUS. The non-medical and indirect costs were not included in the analysis. The cost categories analyzed were: a) cost of medicines, b) costs of tests and events, and c) costs of hospital services.

Drug costs were obtained from the Price List of the Ministry of Health[15], except for fondaparinux, where we used the cost of manufacturing plus 17% tax (ICMS)[16]. The price adjustment coefficient (PAC, 22.5%) was applied to the cost of treatment with fondaparinux for sales in public health area. All costs resulting from laboratory and imaging tests, as well as costs related to bleeding and stroke events were selected from the Procedure, Medication and OPM Management System of SUS (SIGTAP)[17] regarding procedures performed in 2009. Table 3 shows the medical resources assessed in the pharmacoeconomic analysis and their monetary values.

It was considered that patients treated with fondaparinux use 2.5 mg daily. Those treated with enoxaparin received doses of 1 mg/kg 2 times a day. The duration of anticoagulant treatment in the model was five days for patients that followed medical treatment, and two and a half days for those referred to angioplasty or coronary artery bypass surgery. Additionally, the patient uses 100 mg of aspirin a day, 300 mg of clopidogrel on the first day and 75 mg on the other days of treatment until the final analysis of the time period.

The cost of glycoprotein inhibitors (IIbIIIa GPI) was calculated based on their loading and maintenance doses. The loading dose of tirofiban was 0.4 mcg/kg/min for 30 minutes and maintenance dose was 0.1 mcg/kg/min for 48-96 hours. Abciximab was used at a dose of 0.25 mg/kg, with a maintenance dose of 0.125 mcg/kg/min for 12 hours. The time of treatment was set at 72 hours for tirofiban (mean between 48 and 96 hours) and 12 hours and abciximab. The proportion of individuals who used each GPI was calculated from the study by Jolly et al[18], where 18% of patients used GPI, of which 73% used tirofiban and 27% abciximab.

The cost related to the occurrence of major bleeding was associated with ICU stay duration of seven days, totaling R$ 3,320.46. In addition, costs were computed regarding three units of packed red blood cells, totaling R$ 159.27. The cost of acute CVA was estimated at R$ 2,604.33, taking into account 4.5 daily hospital fees, three days in the ICU, laboratory and imaging tests required for diagnosis and monitoring. Costs related to AMI were obtained by the study of Ribeiro et al.[19] and adjusted to current values (total of R$ 7,960.06).

Cost-effectiveness analyses and budgetary impact

The economic evaluation of the use of fondaparinux *versus* enoxaparin was calculated using the Incremental cost-effectiveness ratio (ICER), given by the ratio between the difference of costs and benefits obtained from the use of each medication.

We also calculated the budgetary impact for SUS regarding the use of fondaparinux or enoxaparin in the treatment of ACSWSTE. For this purpose, we obtained the total number of hospital treatments in SUS for angina pectoris (ICD10 I20) or acute myocardial infarction (ICD10 I21) during the year 2009[20]. In this case, the use of fondaparinux or enoxaparin

Table 2 – Effectiveness and safety of fondaparinux and enoxaparin in the treatment of acute coronary syndrome without ST-segment elevation

	Enoxaparin		Fondaparinux	
	N	%	N	%
Total	10,021	100%	10,057	100%
9 days				
Death	186	1.9%	177	1.8%
Myocardial infarction	264	2.6%	263	2.6%
Cerebrovascular Accident	45	0.4%	37	0.4%
Major bleeding	412	4.1%	217	2.2%
Death, myocardial infarction, refractory ischemia , or major bleeding (combined outcome)	905	9.0%	737	7.3%
30 days				
Death	352	3.5%	295	2.9%
Myocardial infarction	411	4.1%	387	3.8%
Cerebrovascular Accident	95	0.9%	74	0.7%
Major bleeding	494	4.9%	313	3.1%
Death, myocardial infarction, refractory ischemia , or major bleeding (combined outcome)	1.238	12.4%	1.025	10.2%
180 days				
Death	638	6.4%	574	5.7%
Myocardial infarction	635	6.3%	606	6.0%
Cerebrovascular Accident	161	1.6%	127	1.3%
Major bleeding	569	5.7%	417	4.1%
Death, myocardial infarction, refractory ischemia , or major bleeding (combined outcome)	1.698	16.9%	1.493	14.8%

OASIS-5[12] Study

was simulated in the aforementioned hospital treatments and budgetary impact was calculated for each comparator.

Sensitivity analysis

Univariate sensitivity analyses were performed to determine the impact of the uncertainty of each parameter included in pharmacoeconomic studies. A probabilistic sensitivity analysis was also applied by using distributions to substitute specific point parameters of the mathematical model.

All costs included in the analysis were varied by ±20% by using a gamma distribution. Beta distributions were used for the probabilities of transition, as well as effectiveness and safety of the comparators. A thousand simultaneous and random Monte Carlo (2nd order) simulations were used in the probabilistic analysis. The results were evaluated and classified as follows: Quadrant 1 (incremental effectiveness > 0 and incremental cost > 0); Quadrant 2 (incremental effectiveness < 0 and incremental cost > 0); Quadrant 3 (incremental effectiveness < 0 and incremental cost < 0) and Quadrant 4 (incremental effectiveness > 0 and incremental cost < 0).

Results

The cost analysis showed that ACSWSTE treatment with fondaparinux generates less cost when compared to enoxaparin. Table 4 describes the results of cost analysis for each time period of the study.

Approximately 80% of the total cost was associated with invasive treatments (i.e., PCI and CABG). The drug costs accounted for approximately 10% of the total cost. For each patient treated with fondaparinux, there was a savings of R$ 85.00 on average. Of these, most (77%) of the costs was related to the treatment of bleeding complications. The difference in drug costs alone accounted for 16% of the total cost. The other costs (i.e., transfusions, AMI and CVA events) accounted for the remaining 7% of the difference in the total cost of treatment among the comparators. The difference in treatment costs between fondaparinux and enoxaparin remained virtually unchanged on days 30 and 180 after the diagnosis of ACSWSTE.

The combined rates of cardiovascular events and major bleeding (i.e., net benefit) were 7.3% and 9.0% for fondaparinux and enoxaparin, respectively. The results remained virtually unchanged on days 30 and 180 post-ACSWSTE. Considering the efficacy data of the OASIS-5 study (Table 2), we assessed the ICER between fondaparinux and enoxaparin. ACSWSTE treatment with fondaparinux was superior (i.e., lower cost and greater benefit in terms of reduction of combined events of death, AMI, refractory ischemia and major bleeding).

Table 3 – Medical resources used in the mathematical model and their respective monetary values

Medical resources	Unit	Unit value	Source
Medications			
Fondaparinux (syringe)	2,5 mg	R$ 10.46	CMED
Enoxaparin (ampoule)	60 mg	R$ 5.19	BPS
Clopidogrel (tablet)	75 mg	R$ 0.91	BPS
Acetylsalicylic acid (tablet)	100 mg	R$ 0.01	BPS
Tirofiban (ampoule)	50 mg	R$ 596.00	BPS
Abciximab (ampoule)	10 mg	R$ 1.471.87	CMED
Unfractionated heparin (ampoule)	5 mg	R$ 4.41	BPS
Exams and procedures*			
0211020060 exercise test / ergometric test	1 un	R$ 31.26	SIGTAP
0205010032 transthoracic echocardiography	1 un	R$ 42.38	SIGTAP
0210010029 aortic arch angiography	1 un	R$ 137.01	SIGTAP
0406030014 coronary angioplasty	1 un	R$ 3.585.76	SIGTAP
0406010927 On-pump myocardial revascularization	1 un	R$ 10.216.32	SIGTAP
Events*			
Cerebrovascular Accident			
0206010079 skull computed tomography	1 un	R$ 98.79	SIGTAP
0205010040 Color Doppler ultrasound of vessels	1 un	R$ 40.17	SIGTAP
0211020036 Electrocardiogram	1 un	R$ 5.15	SIGTAP
0204030170 Chest X-ray (pa)	1 un	R$ 6.92	SIGTAP
0205010032 transthoracic echocardiography	1 un	R$ 42.38	SIGTAP
0202020380 complete blood count	1 un	R$ 4.11	SIGTAP
0202010473 glucose measurement	1 un	R$ 1.85	SIGTAP
0202010317 creatinine measurement	1 un	R$ 1.85	SIGTAP
0202010694 urea measurement	1 un	R$ 1.85	SIGTAP
0202010635 sodium measurement	1 un	R$ 1.86	SIGTAP
0202010600 potassium measurement	1 un	R$ 1.86	SIGTAP
0211080020 gasometry	1 un	R$ 2.99	SIGTAP
0202020134 activated partial thromboplastin time	1 un	R$ 5.77	SIGTAP
0202020142 prothrombin time and activity	1 un	R$ 2.73	SIGTAP
0202120023 direct and reverse ABO determination	1 un	R$ 1.37	SIGTAP
0202010295 total cholesterol measurement	1 un	R$ 1.85	SIGTAP
0202010678 measurement of triglycerides	1 un	R$ 3.51	SIGTAP
0202020290 fibrinogen measurement	1 un	R$ 4.60	SIGTAP
0303080094 daily cost of hospitalization	1 un	R$ 182.27	SIGTAP
0303040149 treatment of CVA (ICU)	1 un	R$ 485.23	SIGTAP
Acute Myocardial Infarction			
Hospitalization and pharmacological treatment	Est.	R$ 1,957.36	Ribeiro et al.19, 2005
Medical consultation	Est.	R$ 242.55	Ribeiro et al.19, 2005
Laboratory assessment	Est.	R$ 220.50	Ribeiro et al.19, 2005
Image tracing assessment	Est.	R$ 525.81	Ribeiro et al.19, 2005
Ambulatory catheterism	Est.	R$ 605.53	Ribeiro et al.19, 2005
Bleeding			
0303040076 conservative treatment of hemorrhage (ICU)	1 un	R$ 474.35	SIGTAP
0212020013 leukocyte-reduced packed blood cells	1 un	R$ 45.00	SIGTAP
0306020068 packed blood cell transfusion	1 un	R$ 8.09	SIGTAP

** The numbers refer to SIGTAP codes for each item listed; BPS - Healthcare Price Bank; CMED - Medication Regulation Chamber ; Qt - Quantity; Est - Estimate; SIGTAP - SUS Price Lists and Procedure Management System; Un - Unit; ICU - Intensive Care Unit.*

Table 4 – Results of the cost analysis of fondaparinux and enoxaparin in the treatment of acute coronary syndrome without ST-segment elevation

Horizonte	Cost composition	Fondaparinux	Enoxaparin	Difference
9 days	**Medications**			
	Antithrombotic agent	R$ 41.46	R$ 55.24	R$ 13.48
	Clopidogrel	R$ 10.34	R$ 10.34	R$ -
	Acetylsalicylic Acid	R$ 0.06	R$ 0.06	R$ -
	Glycoprotein inhibitors	R$ 216.41	R$ 216.41	R$ -
	Exams			
	Functional test	R$ 48.76	R$ 48.76	R$ -
	Coronary angiography	R$ 96.94	R$ 96.94	R$ -
	Myocardial revascularization	R$ 947.44	R$ 947.44	R$ -
	Angioplasty	R$ 1,114.05	R$ 1,114.05	R$ -
	Events			
	Myocardial infarction	R$ 208.16	R$ 209.71	R$ 1.54
	CVA	R$ 9.58	R$ 11.69	R$ 2.11
	Major bleedings	R$ 71.65	R$ 136.52	R$ 64.87
	Transfusion	R$ 2.80	R$ 4.99	R$ 2.19
	TOTAL	**R$ 2,767.98**	**R$ 2,852.17**	**R$ 84.19**
30 days	**TOTAL**	**R$ 2.925.15**	**R$ 3,026.77**	**R$ 01.62**
180 days	**TOTAL**	**R$ 3,273.32**	**R$ 3,372.87**	**R$ 99.55**

After modifying each parameter of the study in ± 20% of its original value, univariate sensitivity analyses did not reveal variables that could change the results obtained. Probabilistic analyses were also performed and showed that approximately 99.9% of the simulations confirmed that fondaparinux was better than enoxaparin in relation to the incremental cost-effectiveness. Figure 2 shows the cloud-point diagram resulting from the probabilistic sensitivity analysis.

The total number of admissions in SUS in 2009 was 99,642 for angina pectoris (ICD10 I20) and 66,994 for acute myocardial infarction (ICD10 I21). The budgetary impact analysis estimated that the use of fondaparinux, rather than enoxaparin, for the treatment of patients with ACSWSTE results in savings of approximately U.S. $ 16.7 million annually for SUS. The decrease in the SUS budgetary impact after five years of drug replacement (constant at 20% per year), can reach R$ 85 million, and the isolated drug component also generates cost savings for SUS of $ 2.3 million a year.

Discussion

The CEA and budgetary impact were created for critical evaluation of fondaparinux *versus* enoxaparin in patients with ACSWSTE, concerning the noninferiority of the decrease in the combined outcome of death, AMI and refractory ischemia and superiority in the reduction of major bleeding. The objective was to estimate the potential clinical and economic benefits in the direct comparison between the two drugs, to aid the decision making by physicians and managers in the setting of SUS.

The OASIS-5 study, in which the present model of cost-effectiveness was based, is characterized as a multicenter clinical trial with more than 20,000 patients, with a total of 576 participating centers from 41 countries, including Brazil and comprised 831 patients from different ethnic groups. It also had a longer follow-up (180 days after the diagnosis of ACSWSTE) among the studies carried out so far, met all methodological quality criteria for direct comparison between fondaparinux and enoxaparin in patients with ACSWSTE in relation to reducing the combined outcome of death, AMI or refractory ischemia and superiority in the reduction of major bleeding[12]. These characteristics give the OASIS-5 study internal/external validity and statistical strength for generalization and application of results in the setting of SUS.

The CEA showed that the use of fondaparinux is an attractive strategy (i.e., showed a lower cost and greater benefit) in all scenarios, when compared with enoxaparin. Fondaparinux was able to not only reduce the total cost of treatment of ACSWSTE (influenced by the reduction in severe bleeding events), but also the cost of antithrombin therapy itself. The substitution of enoxaparin by fondaparinux in the treatment of ACSWSTE is simple, safe, effective, uses the same route of administration and requires no additional medical or hospital resources.

The budgetary impact of such substitution may reach R$ 85,000,000.00 in savings for SUS in five years. Therefore, the data described here can result in better allocation of resources within the public health system and generate, to the beneficiaries of SUS, direct access to drugs of proven effectiveness and lower cost to the Brazilian public health sector.

In accordance with the results shown here, other economic evaluations around the world also demonstrated the best cost-effectiveness ratio of fondaparinux compared to enoxaparin in hospitalized patients with ACSWSTE[21-23].

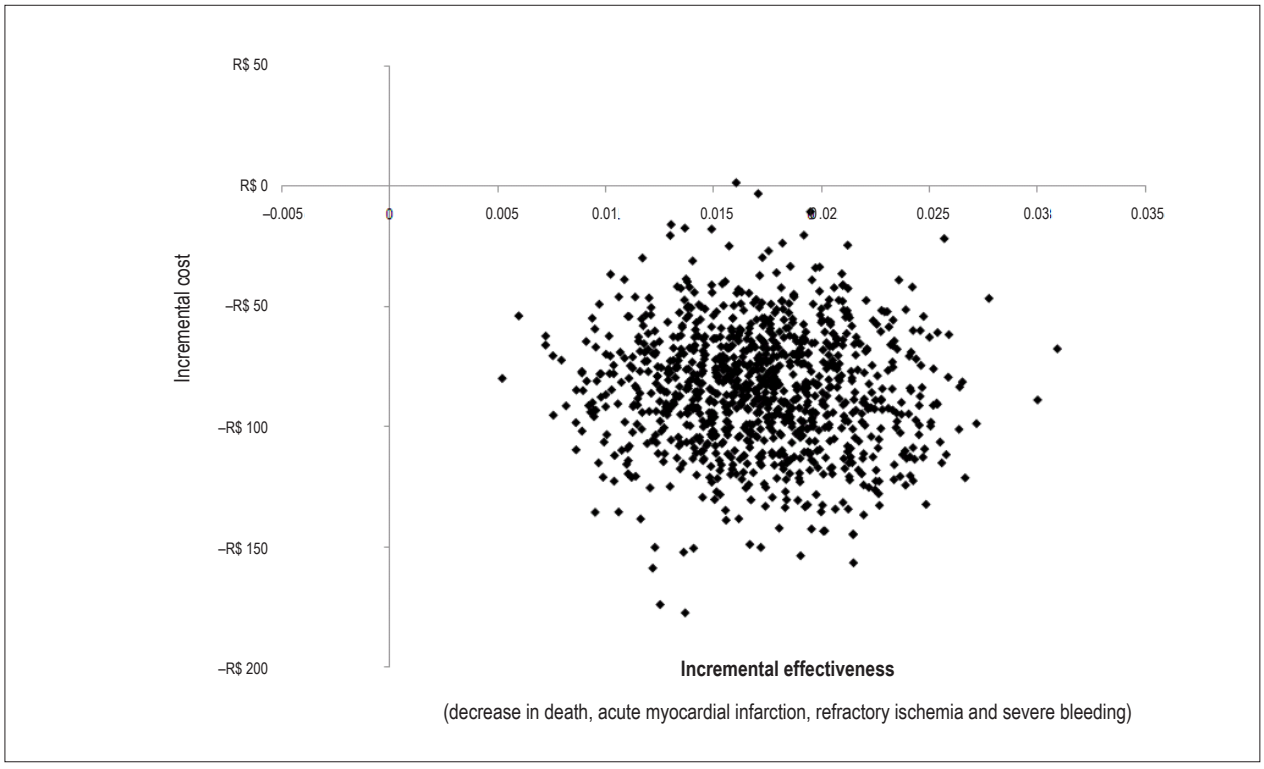

Figure 2 – *Cloud-point diagram resulting from the probabilistic sensitivity analysis.*

Univariate and multivariate sensitivity analyses confirmed the favorable economic result of the substitution of enoxaparin by fondaparinux. In other words, even if we consider possible variations in the parameters analyzed in the mathematical model, there is almost 100% probability of fondaparinux reducing costs with fewer adverse events than enoxaparin.

The probabilistic certainty of the cost-effectiveness of fondaparinux over enoxaparin is given mainly by the large statistical power of the OASIS-5 study. As mentioned before, in addition to reducing costs and events associated with severe bleeding, fondaparinux shows a lower cost for ACSWSTE treatment when compared to enoxaparin, which also confirms the strength of the economic results observed.

Regardless of the PAC (i.e., discount for sales to the government), the cost of treatment with fondaparinux still remains lower to that with enoxaparin (R$ 53.88 *versus* R$ 55.24, respectively). It is noteworthy that the price of enoxaparin is derived from the Price Lists of the Ministry of Health, i.e., it is the government price of purchase that contains commercial discounts and PAC (when applicable).

Additionally, the mean cost of hospital services provided by SUS in 2009 (i.e., real-life data) was R$ 3,090.83 for the ICD10 I20 (angina pectoris) and R$ 2,707.84 for I21 (acute myocardial infarction)[20]. The values are very close to the cost of ACSWSTE treatments estimated in this pharmacoeconomic analysis, which also refer to the accuracy of the analysis and quality of data assessed here.

Limitations

This present analysis has some technical and methodological limitations. As it is a mathematical simulation of a clinical trial, the results presented herein may vary in actual clinical practice, where the characteristics of hospitalized patients can vary significantly. Therefore, it is correct to affirm that the prescription of fondaparinux has a positive economic impact when compared to enoxaparin only in patients such as those in the OASIS-5 study (i.e., the population of interest in the economic analysis). Any transference of economic outcomes to patients with different characteristics (i.e., greater disease severity, comorbidities, age younger than 50 years, or with a picture of recent CVA) should be performed with caution. Future studies will determine the cost-effectiveness of fondaparinux in patients with different clinical and demographic characteristics.

Similarly, the analysis also has limitations regarding its economic estimate. The values used in the calculations refer to values of reimbursement of the SUS / SIGTAP price list, which in many cases have other values added to it when a procedure is performed (e.g., coronary angioplasty), such as ICU daily cost, high-cost medications, special materials, etc. Likewise, it is usually observed in clinical practice that reimbursement values are mostly insufficient to cover the actual costs of a specific procedure. Therefore, the treatment costs of ACSWSTE calculated in the present analysis may be underestimated from the economic perspective of hospital management. However, this limitation does not interfere with the presented choice or cost-effectiveness results.

Another important point concerns the use of fondaparinux during Percutaneous Coronary Intervention (PCI). According to the OASIS-5 study, the use of fondaparinux during coronary intervention requires further study. Specifically, there was a possibility that adjunctive unfractionated heparin per-procedure would be necessary, which could increase the risk of bleeding at the access site.

The recent THE FUTURA/OASIS-8 study, however, evaluated the safety of two UFH regimens during PCI in high-risk patients with ACSWSTE, initially treated with fondaparinux[24]. The main assessed outcomes were the incidence of major or minor bleeding and vascular complications at the access site 48 hours after PCI. The primary outcome occurred in 4.7% of the randomized patients in the low-dose UFH group (50 U/kg) *versus* 5.8% in the standard UFH dose group (85 U/kg and 60 U/kg when they used IGP IIb/IIIa), and therefore, there was no difference between the groups (odds ratio [OR] = 0.80, 95% confidence interval [CI]: 0.54 to 1.19 p = 0.27). The rate of major bleeding was not different between groups, either. The rate of thrombus catheter was very low (0.5% in the low-dose group and 0.1% in the standard-dose group, p = 0.15) and did not reach statistical significance.

Conclusion

Considering that severe bleeding is associated with increased mortality in patients with ACSWSTE, it is therefore necessary to find new anticoagulants that act selectively in the coagulation cascade. Fondaparinux, a selective inhibitor of factor Xa is associated with a lower rate of bleeding. Furthermore, it is prescribed as a single daily dose, regardless of patient weight, and provides a lower cost of treatment. Due to these characteristics, it must be considered as a cost-effective option for the treatment of patients with ACSWSTE.

In conclusion, treatment with fondaparinux is at least as effective as treatment with enoxaparin, combined with a lower direct cost, generating a positive impact on the finances of the Brazilian Public Health System - SUS.

Potential Conflict of Interest

Dr. Alexandre Olimpio and Dr. Márcio Machado, both GSK employees, and Mrs. Camila Pepe and Dr. Rui Ramos, who are paid for delivering lectures, declare to have conflicts of interests.

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