

Fondaparinux versus enoxaparin in the management of acute coronary syndromes in Switzerland

A cost comparison analysis

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Summary

QUESTION UNDER STUDY: Anticoagulation therapy is routinely used in cases of non ST-segment elevation acute coronary syndromes (NSTEMI-ACS). The most commonly used drug in such events is enoxaparin, a low molecular weight heparin. Fondaparinux, a synthetic pentasaccharide, is as effective as enoxaparin in terms of survival or residual angina pectoris and significantly reduces bleeding complications. The purpose of this study was to assess the magnitude of cost reductions if enoxaparin were replaced by fondaparinux in Switzerland.

METHODS: Costs of hospital stay for NSTEMI-ACS with or without bleeding complications at the Geneva University Hospitals were determined for patients admitted between July 1st, 2007 and June 30th, 2008. These costs were applied to subjects recruited in the AMIS Plus registry, which gathers information on ACS in Swiss hospitals, using three scenarios. Firstly, using the baseline incidence of bleeding episodes observed in the AMIS plus registry. Secondly, using the baseline incidence of haemorrhagic episodes observed in the Geneva University Hospitals sample and thirdly, using the incidence of haemorrhagic episodes observed in the OASIS-5 study. These results and costs were then extrapolated to the national level.

RESULTS: At the Swiss national level, replacement of enoxaparin by fondaparinux would generate annual savings ranging from 854,000 Swiss Francs (scenario 1) to 3,400,000 Swiss Francs (scenario 2) and 2,845,000 Swiss Francs (scenario 3). Estimated savings accounted for 55 to 63% of total hospital costs.

CONCLUSIONS: Use of fondaparinux instead of enoxaparin in patients with NSTEMI-ACS could yield substantial savings at the local as well as the national level in Switzerland.

Key words: anticoagulation therapy; NSTEMI acute coronary events; hospital costs; cost comparison

Introduction

Antithrombotic agents are routinely used during the management of acute coronary syndromes without ST-segment elevation (NSTEMI-ACS). The OASIS-5 study [1] showed that fondaparinux, a synthetic pentasaccharide, was similarly efficient to enoxaparin in preventing ischaemic events but reduced major bleeding as well as mortality and morbidity in patients with NSTEMI-ACS regardless of their risk of persistent ischaemia [2]. Using OASIS-5 population data, a recent study showed that fondaparinux was a more cost-effective antithrombotic agent than enoxaparin in NSTEMI-ACS, both in the short and in the long term [3]. Whether the same findings and the same magnitude of savings would hold true in different populations is a matter of debate.

Fondaparinux is rarely used in Switzerland, as shown by data collected by the AMIS Plus registry (Acute Myocardial Infarcts in Switzerland), which gathers information on myocardial infarctions and ACS in Swiss hospitals [4, 5]. Several factors have been described in order to explain why the uptake of this drug in routine practice is slow [6]. The purpose of our study was to compare short-term costs related to bleeding complications and to the costs of the drugs if fondaparinux was used instead of enoxaparin during a hospital stay for a NSTEMI-ACS in Switzerland.

Methods

Patient population, clinical course and complications

We selected patients admitted between July 1st, 2007 and June 30th, 2008 to Geneva University Hospitals and who had a principal diagnosis of "Non ST-elevation myocardial infarction" or "Unstable angina". A careful reading of the discharge letters of all these patients was completed by one of us (MPK) to record adverse haemorrhagic events, i.e. major and minor bleeding, using the same criteria as

those of the OASIS-5 study [7]. A major bleeding complication was defined as a symptomatic intracranial haemorrhage, a retroperitoneal haemorrhage, an intraocular haemorrhage leading to significant loss of vision, a decrease in haemoglobin of at least 3.0 g/dl (with each blood transfusion unit equivalent to 1.0 g/dl of haemoglobin), bleeds requiring transfusion of two or more units of red blood cells or equivalents of whole blood or a clinically overt bleed that was fatal. A minor bleeding complication was considered to be any clinically significant bleeding not meeting the definition for major bleeding or leading to a surgical intervention or transfusion of one unit of blood (whole blood or packed red blood cells).

Costs

Hospital costs and costs of complications

The Geneva University Hospitals use an analytical accountability system to estimate the cost of every patient admitted to its wards. These costs represent the amount of resource actually consumed by each patient and not the tariffs reimbursed by insurance companies. The same list of patients admitted between July 1st, 2007 and June, 30th 2008 was forwarded to the accountability service which then calculated the true hospital costs per patient.

Statistical analysis and derivation of costs.

The mean and median cost of hospital stays without complication and then with minor or major bleeding complication was determined.

Since costs are known to be highly skewed (all costs were not normally distributed according to the Shapiro-Wilk test), we adjusted these costs for age and gender using a median regression analysis to estimate the adjusted median hospital costs in case of no bleeding complications or of a minor or major bleed. Interactions were also tested. (See statistical analysis below). The costs associated with each variable introduced in the model correspond to the Beta coefficient as in a usual linear regression model. They correspond to the change of cost for every one unit change of the associated independent variable.

There were no missing data since all cases were identified in the accountability service database

Costs of antithrombotic medications

On the basis of local standards, we estimated that patients admitted for an NSTEMI-ACS were treated with antithrombotic agents for three days as recommended by the European Society of Cardiology [8], except for a small number of patients with large anterior STEMIs (ST-segment elevation myocardial infarction) with apical aneurysm or apical thrombus. We therefore calculated the cost of anticoagulation therapy using the ex-factory prices of enoxaparin (173.80 Swiss francs for 10 doses of 100 mg) and fondaparinux (73.10 Swiss francs for 10 doses of 2.5 mg). Taking into consideration that patients under enoxaparin have to be treated twice a day during three days with a dose of 1 mg/kg of body weight, we calculated that the three days of treatment with enoxaparin would require six doses of 80 mg (which is the most frequently used dosage at the Geneva University Hospitals) for a cost of 83.40 Swiss Francs per patient. Fondaparinux has to be ad-

ministered daily at a dose of 2.5 mg for all patients. The three day treatment cost for fondaparinux is therefore 21.95 Swiss Francs per patient.

Total costs

For the 281 patients admitted for NSTEMI (Non ST-segment elevation myocardial infarction), we calculated total cost as the cost associated with haemorrhagic complications plus the cost of the antithrombotic medication

Main and cost comparison analyses

Main analysis

Once the hospital costs of haemorrhagic complications at the Geneva University Hospitals had been determined, we estimated the assumed reduction in hospital costs if usual anticoagulation therapy (enoxaparin) were replaced by fondaparinux, applying to the NSTEMI-ACS patients of the Geneva University Hospitals the reduction in the incidence of haemorrhagic complications observed in the OASIS-5 study (46.3% for major episodes and 65.6% for minor episodes) [1].

The baseline equation was the following:

(Cost of a major complication x incidence of major complications on enoxaparin + cost of a minor complication x incidence of minor complications on enoxaparin + cost of treatment with enoxaparin) - (Cost of a major complication x incidence of major complications on fondaparinux + cost of a minor complication x incidence of minor complications on fondaparinux + cost of treatment with fondaparinux).

Cost comparison

Using hospital costs from the University Hospitals of Geneva, we then extrapolated our findings to the AMIS plus registry population, using three scenarios:

- a reduction in haemorrhagic complications similar to the one observed in the OASIS-5 study, using the baseline incidence of bleeding episodes observed in the AMIS plus registry
- the same relative reduction using the baseline incidence of haemorrhagic episodes observed in the Geneva University Hospitals sample
- and a study using the incidence of haemorrhagic episodes observed in the OASIS-5 study.

The characteristics of the three population samples are presented in table 1. Only data available for comparison are presented in the table. In particular, clinical data and medical history were not collected in the Geneva University sample, since these were used mainly for cost calculations. Finally, since the AMIS-plus registry collects information in approximately 40% of Swiss hospitals, we extrapolated these costs to obtain national estimates.

Results

Geneva University Hospitals sample

Between July 1st, 2007 and June 30th, 2008, 281 patients were identified with a principal diagnosis of "Non ST elevation myocardial infarction" or "Unstable angina". Mean age was 68 ± 14 , and 70.5% of them were men; median length of

hospital stay (LOS) was eight days (interquartile range 5–13 days). The women in the sample were significantly older than the men (72; SD 13 vs. 66; SD14; $p < 0.001$).

Careful reading of the discharge letter and checking of laboratory results allowed us to detect 22 episodes of minor bleeds and 8 episodes of major bleeds. Haemorrhagic complications generated higher hospital costs, longer total hospital length of stay and longer stay in the intensive care unit (ICU) (table 2).

The age and sex adjusted total hospital costs when these two types of haemorrhagic episodes occurred are shown on table 3. This table shows the association between included variables and total hospital cost. As our purpose was not to predict costs but rather to understand which variables were associated with the cost of a hospital stay, we have listed in table 2 adjusted hospital costs for relevant variables, even though they were not statistically associated with cost differences in the cost prediction model. As anticipated, hospital care cost for a NSTEMI-ACS was increased by the occurrence of a bleeding complication.

Based on the reduction in major and minor haemorrhagic events observed in the OASIS-5 study on fondaparinux versus enoxaparin (HR (Hazard ratio) 0.52 for major episodes and 0.34 for minor episodes), use of fondaparinux at

the Geneva University Hospitals would have reduced the number of major haemorrhagic events from 8 to 4.1 (a 48% reduction) and the number of minor episodes from 22 to 7.5 (a 66% reduction). Taking into account the reduction of bleeding episodes and the costs of the drugs, replacement of enoxaparin by fondaparinux would have saved a median of 330,000 Swiss Francs for the Geneva University Hospitals during the year 2007–2008 (table 4).

Extrapolation to the AMIS plus registry sample

We examined the data collected in the AMIS plus registry for the years 2005 – 2008. During this period of time, 5,828 cases of NSTEMI-ACS were recorded. The proportion of men reached 72% and mean age was 65 years for men (SD: 13) and 73 years (SD: 12) for women. During the four years, 96 haemorrhagic events were recorded. Major haemorrhagic episodes occurred in only 27 patients (a proportion of 0.5%) whilst minor haemorrhagic episodes occurred in 69 (1.2%). The incidence of haemorrhagic events was much lower than those observed in the OASIS-5 study and in the Geneva University Hospitals sample.

Table 1: Characteristics of the patients in the three populations.

Variables	Geneva University Hospitals n = 281	AMIS plus registry n = 5,828	OASIS-5 Study n = 20,078
Age	68.1 ± 13.9	67.4 ± 13.2	66.6 ± 11.0
Male sex – n (%)	198 (70.5)	4,200 (72.1)	12,379 (61.7)
Unstable angina – n (%)	66 (23.5)	991 (18.2)	9,098 (45.3)
Heart rate – bpm		78.9 ± 20.2	73.0 ± 13.5
Systolic blood pressure – mm Hg		140.8 ± 20.1	136.4 ± 22.5
Medical History – n (%)			
Myocardial infarction		1,285 (22.3)	5,164 (25.7)
Heart failure		249 (4.3)	2,788 (13.9)
Stroke		398 (7.4)	1,244 (6.2)
Diabetes		1,148 (20.0)	5,078 (25.4)

Table 2: Unadjusted total hospital cost, total hospital length of stay and intensive care unit length of stay according to the presence or the absence of haemorrhagic complication.

Variables	No haemorrhagic complication	Minor haemorrhagic complication	Major haemorrhagic complication	P value*
Total hospital cost in Swiss francs, median (interquartile range)	22,621 (13,084–41,126)	39,653 (18,719–61,274)	48,772 (31,856–69,291)	0.002
Length of stay in days median (interquartile range)	7.5 (6.5–10.8)	10.6 (7.8–10.6)	9.2 (7.8 ± 10.6)	0.007
Length of stay in ICU in hours median (interquartile range)	24h35' (11h50' – 40h10')	42h15' (27h35' – 53h05')	41h50' (33h45' – 52h20')	0.001

Obtained through Kruskal-Wallis test

Table 3: Age and sex adjusted median hospital costs.

Independent variables associated with hospital costs	Median cost in Swiss Francs (95% CI) Standard error	p value
Major haemorrhagic episode	19,057 (3,005–35,110) 8154	0.02
Minor haemorrhagic episode	16,890 (6,763–27,019) 5144	0.001
Age (per year)	19 (–188 – 226) 105	0.86
Sex (Men vs women)	–3,768 (–10,073 – 2,538) 3,203	0.24
Constant	28,244 (8,647–47,839) 9,954	0.005

Scenario 1

When we applied the costs of the Geneva University Hospitals of haemorrhagic events to the AMIS plus registry, we used the actual proportion of major and minor haemorrhagic events observed in the registry and performed the cost calculations assuming that replacing enoxaparin by fondaparinux would reduce the incidence of haemorrhagic events in the same proportion as that observed in the OASIS-5 study (HR 0.52 for major episodes and 0.34 for minor episodes). For the four years of observation in the AMIS plus registry this would yield cost reduction of 1,365,921 Swiss Francs (341,480 Swiss Francs per year). Since only 40% of all Swiss hospitals are affiliated to the AMIS plus registry, multiplication by 2.5 would yield annual savings for the whole country of 854,000 Swiss francs (table 4).

Scenario 2

Extrapolation of the proportion of major (2.9%) and minor (7.9%) haemorrhagic episodes observed in the Geneva University Hospitals sample to the AMIS plus registry sample, led to an estimate of 169 cases of major and 460 cases of minor haemorrhagic events. Assuming that replacing enoxaparin by fondaparinux would reduce the incidence of haemorrhagic events in the same proportion as that observed in the OASIS-5, this scenario would yield annual savings for the whole country of 3,400,000 Swiss Francs (table 4).

Scenario 3

Finally, we created a final scenario applying the incidence of haemorrhagic episodes observed in the OASIS-5 study to the AMIS plus registry sample, (4.1 to 2.2% for major haemorrhagic episodes and 3.2 to 1.1 for minor haemorrhagic episodes). The net saving per year extrapolated to the national level using this scenario would be 2,845,000 Swiss Francs (table 4).

Discussion

Our different scenarios confirm that fondaparinux can offer substantial economical savings in patients with low or

moderate risk NSTEMI-ACS when compared to enoxaparin. This favourable effect is not only due to the lower price of fondaparinux, but also to the decrease of costly haemorrhagic complications during hospitalisation. Our different scenarios showed that mean savings reached between 51% and 61% of total hospital costs.

Compared with the cost-effectiveness analysis using the OASIS-5 study population, [3] we could not analyse the cost-effectiveness of actually replacing enoxaparin by fondaparinux but tried to model and estimate the savings offered by this strategy on the scale of one hospital (the Geneva University Hospitals), of hospitals participating in a national registry and at a national scale. Thus, our results depend on the assumptions used for our calculations. In the Geneva University Hospitals sample, the incidence of haemorrhagic episodes was closer to that observed in the OASIS-5 study than to that reported in the AMIS plus sample. This could be explained by two phenomena. Firstly, it could be postulated that there was an under-reporting of haemorrhagic events in the AMIS plus registry. Missing data were frequent in entry fields related to haemorrhagic complications and, of the 96 haemorrhagic events reported, only 57 were precisely localised. Secondly, the local practice in Geneva may reflect more invasiveness in terms of interventional procedures in NSTEMI-ACS patients. This could also account for the fact that minor haemorrhagic episodes were more frequent in the Geneva University Hospitals sample than in the OASIS-5 study. These discrepancies in the incidences of haemorrhagic events during hospitalisation led us to elaborate several scenarios in our analysis. Nevertheless, in all cases, our calculations showed substantial savings for strategies using fondaparinux rather than enoxaparin.

Cost considerations should not be the only concerns when recommending the use of one or another therapy. Fondaparinux has been shown to be non-inferior to subcutaneous enoxaparin in terms of mortality and NSTEMI-ACS relapse in the large and well designed OASIS-5 trial [1]. In NSTEMI-ACS patients, the use of other anticoagulant agents, such as GP IIb/IIIa inhibitors, often have to be considered. Fondaparinux in association with GPIIb/IIIa inhibitors reduces the risk of bleeding when compared to enoxaparin [9]. Im-

Table 4: Cost comparison between Enoxaparin and Fondaparinux according to the different scenarios.

	Treatment with enoxaparin				Treatment with fondaparinux				Net saving/year Cost reduction (%) CI95
	Drugs	Major haemorrhagic events	Minor haemorrhagic events	Total	Drugs	Major haemorrhagic events	Minor haemorrhagic events	Total	
Baseline estimate: the Geneva University Hospitals n = 281	23,435	152,456 n = 8	371,580 n = 22	547,471	6,168	76,228 n = 4	135,120 n = 8	217,516	330,000 (60%) 124,000 – 536,000
Scenario 1.* Proportion of haemorrhagic events observed in the AMIS plus registry n = 5,828	486,055	514,539 n = 27	1,165,410 n = 69	2,166,004	127,925	266,798 n = 14	405,360 n = 24	800,083	854,000 (63%)** 427,200 – 1,269,000
Scenario 2.* Proportion of haemorrhagic events observed in the Geneva University Hospitals n = 5,828	486,055	3,220,633 n = 169	7,769,400 n = 460	11,476,088	127,925	1,677,016 n = 88	2,634,840 n = 156	4,439,781	3,400,000 (61%)** 1,824,000 – 7,135,000
Scenario 3.* Proportion of haemorrhagic events observed in the OASIS-5 study n = 5,828	486,055	4,554,623 n = 239	3,158,430 n = 187	8,199,108	127,925	2,439,296 n = 128	1,080,960 n = 64	3,648,181	2,845,000 (55%)** 952,000–4,737,000

* Costs for 4 years calculated from the AMIS plus registry data ** Extrapolation to the national level for 1 year

portantly, GPIIb/IIIa inhibitors are clearly recommended in high risk NSTEMI-ACS and this is in accordance with an early invasive strategy. However concerns have been noted with the invasive strategy of patients treated by fondaparinux because of catheter-related thrombus formation. As a result of these adverse events for fondaparinux reported during PCI (percutaneous coronary intervention), the safety committee of the OASIS-5 trial recommended an adjunctive use of 200 IU (International Units) of unfractionated heparin (UFH) to flush the catheters, however despite a persistent significant increase of catheter-related thrombosis. So far, no specific data are available on the efficacy and safety of fondaparinux in high-risk ACS applicable to an early-invasive strategy. Taking into account the higher benefit of an early invasive strategy in high-risk ACS with a subsequent shorter duration of anticoagulation therapy, the risk of bleeding is certainly lower compared to a longer duration of anticoagulation. Moreover, the higher risk of guiding-catheter thrombosis should favour the use of UFH in those settings where early PCI is routinely performed for high risk ACS patients. In addition, because of the favourable results of many randomised trials, the use of the trans-radial access for PCI should be encouraged in settings where high-risk ACS benefit from an early invasive approach.

Special consideration should always be given to frail patients (patients with impaired renal function) [10]. Unfortunately, patients with creatinine levels ≥ 265 $\mu\text{mol/l}$ were excluded from the OASIS-5 trial. Therefore, only limited conclusions on the use of fondaparinux in case of renal impairment can be drawn. Age is related to a significant increase in the risk of major bleeding during ACS therapy [11] and evidence is often lacking as to how anticoagulation should be managed in these patients. Since elderly patients are the fastest growing segment of the population and are frequently subject to ACS, it can be postulated that adaptation of anticoagulant therapy in elderly subjects would modify the incidence of bleeding events and therefore reduce the overall costs of the complications of anticoagulation. It is of note that recent guidelines have highlighted the higher benefit in terms of bleeding risk of fondaparinux in case of NSTEMI-ACS among the elderly than among younger patients [12].

Limitations of the current study include the possible and probable low report rate of haemorrhagic events in the AMIS database or in the discharge reports of the Geneva University Hospitals. We were not able to verify the quality of the data entered in the AMIS plus registry. For the Geneva University Hospitals database, in addition to reading the discharge reports, we examined laboratory data in order to detect a drop in haemoglobin concentration that would have been associated with a serious haemorrhagic event. Unfortunately we were not able to perform the same verification for minor haemorrhagic events and, thus, we had to rely on reports only. Nevertheless, the fact that, in the Geneva University Hospitals sample, the incidence of haemorrhagic episodes was close to that observed in the OASIS-5 study, and that minor haemorrhagic episodes were more frequent than in the OASIS-5 study, makes us think that the incidences we used in our modelling were not grossly inaccurate. One way of avoiding

such problems would have been to perform a prospective study with observed data collected in the case report forms. Due to limited resources this option could not be followed. A further study limitation was the proportion of hospitals participating in the data collection of the AMIS plus registry. Only about 40% of Swiss hospitals participate in the project. They are listed in the following internet link (<http://www.amis-plus.ch/participants.htm>). It can be seen that three out of the five university hospitals collect data, and that most of cantonal hospitals are enlisted in the participating centres. We cannot ensure that the AMIS database constitutes a representative sample of the hospitals in our country but, to date, it is the largest database available. Our only purpose was to estimate the magnitude of the cost savings that could be expected by replacing enoxaparin by fondaparinux. Even though the data that we used may suffer from some biases, our findings provide some hints on the issue.

In conclusion, the use of fondaparinux instead of enoxaparin in patients with NSTEMI-ACS and without an early invasive approach could yield substantial savings at the local as well as at the national level in Switzerland, mainly by reducing the incidence of costly haemorrhagic complications.

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