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Cost Effectiveness of Fondaparinux in Non-ST-Elevation Acute Coronary Syndrome

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Abstract

Background: Fondaparinux has been shown to reduce the risk of major bleeding and 30-day mortality compared with enoxaparin, in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). However, its cost effectiveness is not well known.

Objective: To evaluate the effectiveness and economic attractiveness of fondaparinux relative to enoxaparin in patients with NSTE-ACS treated with triple antiplatelet therapy and early (non-urgent) invasive strategy.

Methods: The decision model compares two alternative strategies: subcutaneous (SC) enoxaparin (1 mg/kg 12 hourly) versus SC fondaparinux (2.5 mg/day) in NSTE-ACS patients pre-treated with triple antiplatelet therapy and early revascularization. Cost-effectiveness and cost-utility analyses were performed from a healthcare perspective, based on a Markov model with a time horizon of the patient lifespan. Univariate sensitivity analysis and probabilistic (Monte Carlo) microsimulation analysis were performed.

Results: In the base-case analysis (65 years, Thrombolysis In Myocardial Infarction [TIMI] score 4), the use of fondaparinux was associated with a significant reduction in major bleeding, a slight reduction in adverse cardiac events, and minor improvements in survival and QALYs, together with a small reduction in costs. The dominance of fondaparinux over enoxaparin remained unchanged in the univariate sensitivity analyses. According to Monte Carlo simulation, fondaparinux was cost saving in 99.9% of cases.

Conclusion: Compared with enoxaparin, the use of fondaparinux in patients with NSTE-ACS managed with an early invasive strategy appears to be cost effective, even in patients with a low risk of bleeding.

Background

Current management of patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) includes the 'upstream' administration of triple antiplatelet therapy (aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitors) jointly with anticoagulation (usually with unfractionated or low molecular weight heparin), early coronary angiography and percutaneous revascularization

if feasible.[1,2] This strategy has been shown to reduce the risk of major cardiac events, but is associated with an excess of major bleeding.[3-5] Indeed, the reported incidence of major bleeding during hospitalization in high-risk subgroups, treated with multiple antithrombotic drugs and early revascularization, is as high as 5%.[6,7]

Fondaparinux, a synthetic pentasaccharide that selectively inhibits factor Xa, was shown to reduce the risk of major bleeding and 30-day mortality compared with enoxaparin in the OASIS (Optimal Antiplatelet Strategy for InterventionS)-5 trial.[8] Subsequently, its use has been given a class I recommendation in the management (both invasive and non-invasive) of NSTE-ACS by the most influential guidelines.[1,2]

Nevertheless, the relative merits of fondaparinux and enoxaparin are controversial. Indeed, whereas the the US guidelines[1] assigned the highest grade of recommendation to both enoxaparin and fondaparinux, the European guidelines[2] assigned a lower grade of recommendation to enoxaparin, based on their different efficacy/safety profiles, and stated that enoxaparin "should be used only if the bleeding risk is low."

This disagreement calls for a formal decision analysis that unambiguously assesses the risk-benefit ratio of fondaparinux under different clinical situations (i.e. according to risk of cardiac and bleeding events) and allows the recommendations to be adjusted to individual patients.

Furthermore, when resources are limited, recommendations should consider the economic costs of new therapies and not only their risk-benefit ratios. This is particularly true in the case of a therapy that affects the risk of bleeding, an event that has a significant impact on the length of stay,[3] consumption of resources and burden of suffering.

Therefore, we constructed a decision analysis model to evaluate the efficacy and cost effectiveness of fondaparinux versus enoxaparin under current clinical conditions.

Methods

The study consisted of a cost-effectiveness and cost-utility analysis based on a Markov model[9,10] designed to compare the impact of fondaparinux relative to enoxaparin, along with aspirin, clopidogrel and upstream use (i.e. before the percutaneous procedure) of glycoprotein IIb/IIIa inhibitors as part of an early (non-urgent) invasive strategy in NSTE-ACS patients. The study was performed from the Spanish healthcare system perspective, with a lifetime horizon.

Data Sources

The source of data on the use of procedures (i.e. percutaneous coronary intervention, coronary artery bypass graft) and baseline risk of events (bleeding, death, myocardial infarction [MI]) was a personal database of one of the authors (JLP) on the use of antithrombotics in acute coronary syndrome, periodically updated with a PubMed search, and manual review of citations of the retrieved articles. The PubMed search strategy used the following descriptors: ('Angioplasty, transluminal, percutaneous coronary' [MeSH] OR 'myocardial ischemia/therapy' [MeSH]) AND (ticlopidine OR clopidogrel OR prasugrel OR thienopyridine OR fondaparinux) AND (IIb? IIIa OR tirofiban OR eptifibatide* OR abciximab) AND (mortality OR survival OR death OR myocardial infarct* OR bleeding OR haemorrhage OR thrombocytopen* OR thrombopen*).

The selection of studies finally included in the decision tree was performed in a non-systematic way, and conditioned on the adequacy of the data to the decision problem[4-8,11-19] (table I). Data from systematic reviews were preferred when available; however, these were scarce.[5,12]

The 30-day baseline risk for further events of NSTE-ACS patients was defined according to the Thrombolysis In Myocardial Infarction (TIMI) score,[11] and adjusted for the effectiveness of triple antiplatelet therapy.[5] Most data inputs on the comparative effectiveness and safety of fondaparinux versus enoxaparin in NSTE-ACS patients at high risk of further events were obtained from the results of the OASIS-5 trial.[8] In this study, 20 078 patients with NSTE-ACS were randomized to receive either fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg bodyweight twice daily) for a mean of 6 days. The incidence of

Table I. Estimated probabilities and effect measures

Variable	Baseline value	Range	References
Probability of percutaneous revascularization after coronary angiography	0.55	0.4–0.8	4
Probability of coronary artery bypass graft after coronary angiography	0.27	0.10–0.40	4
Baseline risk of major bleeding after coronary artery bypass graft	0.05	0.01–0.1	14
Baseline risk of major bleeding after coronary angiography (without clopidogrel or glycoprotein IIb/IIIa antagonists)	0.02	0.01–0.04	8,5,7
RR of major cardiac events after bleeding	5.53	3.97–7.26	6
RR of major bleeding with fondaparinux[a]	0.72	0.64–1.2	8
Proportion of adverse cardiac events with death	0.186	0.09–0.28	12
Annual mortality of old uncomplicated coronary syndrome	0.0765	0.05–0.09	17
Mortality of old MI	0.0734	0.05–0.09	17
Late mortality due to coronary artery disease	0.009	0.005–0.018	20
Annual risk of non-fatal infarction in old previously uncomplicated coronary syndrome	0.02	0.01–0.04	17
Risk of events during the first month			11,13,18
TIMI score 0–1	0.034		
TIMI score 2	0.043		
TIMI score 3	0.077		
TIMI score 4	0.119		
TIMI score 5	0.152		
TIMI score 6–7	0.191		
RR of major bleeding with clopidogrel	1.5	1–2	16,19
RR of major bleeding with triple vs double antiplatelet therapy	1.4	1–2	5
RR of major bleeding with upstream vs selective administration of GPIIb/IIIa inhibitors	1.10	1.03–1.16	4
RR of death with acute MI vs old uncomplicated coronary syndrome	1.33	1–2	15
RR of adverse cardiac events with clopidogrel	0.83	0.70–0.99	16
RR of adverse cardiac events with glycoprotein IIb/IIIa inhibitors in patients treated with clopidogrel	0.67	0.56–0.80	5

a RR at 180 days; conservatively, the upper limit of the 95% CI reported in the OASIS-5 trial[8] was used as baseline estimation.

MI = myocardial infarction; **RR** = relative risk; **TIMI** = Thrombolysis in Myocardial Infarction.

the primary outcome (a composite of death, MI or refractory ischaemia at 9 days) was similar in the two groups (hazard ratio [HR] 1.01; 95% CI 0.90, 1.13). The upper limit of the CI was well below the pre-specified boundary of 1.183 for non-inferiority ($p = 0.007$). At the same point, major bleeds were almost halved with fondaparinux (HR 0.52; 95% CI 0.44, 0.61). Major bleeding was an independent predictor of long-term mortality, which was significantly reduced with fondaparinux at 30 days (HR 0.83; 95% CI 0.71, 0.97) but not at 6 months (HR 0.89; 95% CI 0.80, 1.0).

Regarding the impact of bleeding on the risk of major cardiac events, the main source of data was an observational study[6] involving more than 30 000 patients. The effect of age on late mortality was estimated from the 2005 age-specific mortality rate of the Spanish population,[21] and adjusted for disease-specific mortality rate using the Declining Exponential Approximation of Life Expectancy (DEALE).[22,23]

Data on the healthcare costs were obtained from Spanish studies[1,3,24-30] (table II). All costs (€) were updated to the year 2006 using the Spanish medical inflation index.[31] According to the perspective of the economic evaluation, we considered only direct medical healthcare costs.[27,32,33]

The utilities data sources[34-36] are summarized in table III. None of them provided separate utility estimates for all the relevant states based on consistent evaluation methods. Therefore, consensus among the authors was used when appropriate.

Table II. Estimated costs (€, year 2006 values)

Variable	Base case	Range	References
Daily cost of fondaparinux	14.5	7.25–14.5	26
Daily costs of enoxaparin	13.722	6.861–13.722	26
Duration of treatment with fondaparinux (days)	8	0–8	1
Duration of treatment with enoxaparin (days)	8	0–8	1
Daily cost of clopidogrel	2.06	1.37–2.06	26
Cost of upstream glycoprotein IIb/IIIa therapy (1 day)	312	312–374	26
Cost of downstream abciximab	781	781	25
Daily cost of hospitalization in the cardiology ward	403	300–500	25
Daily cost of hospitalization in the intensive care unit	1 238	600–1700	24
Additional length of stay in cardiology ward due to bleeding	4	0–4	3,28,27
Cost of percutaneous revascularization	1 710	1 000–2 000	29,30
Cost of coronary artery bypass graft	14 617	12 000–16 000	30
Cost of an episode of major bleeding	1 394	1 000–1 500	25
Annual medical costs of patient with old myocardial infarction	753	600–1 200	24
Cost of an adverse cardiac event	8 840	3 000–10 000	24

Decision Model

The study is based on a previously reported decision tree,[20] validated in several external cohorts[8,15,37-40] and tailored to the purpose and available data. The model compares two alternative strategies in patients experiencing a first episode of NSTE-ACS pretreated with aspirin, clopidogrel and a glycoprotein IIb/IIIa antagonist and undergoing early coronary catheterization. Under strategy A (baseline comparator) enoxaparin (1 mg/kg subcutaneously every 12 hours) was added to the initial treatment. Under strategy B, enoxaparin was replaced by fondaparinux (2.5 mg/day subcutaneously), with a similar duration of treatment.[1]

Each of these strategies was included in the decision-tree model as a Markov node, with monthly cycles and four possible mutually exclusive states (figures 1 and 2). The monthly length of the cycles was chosen due to the higher incidence of bleeding, more frequent adverse cardiac events and greater resource consumption during the first 30 days ('early acute coronary syndrome state').[6] Appropriate calculations were made, when necessary, to turn annual into monthly probability rates.[41]

The model is analysed recursively, as transitions between states, according to the associated transition probabilities. During the first cycle, the patient can undergo some therapeutic procedures (percutaneous revascularization, coronary bypass graft) and experience adverse events (major bleeding, fatal or non-fatal MI) with the corresponding costs: i.e. hospitalization costs (drugs, intensive care unit and cardiology ward stay),

Table III. Estimated utilities and disutilities

Variable	Base-case value	Range	Source
Utility of an old uncomplicated coronary syndrome	0.817	0.6–0.94	[15,17,36][a] and expert opinion
Utility of an old myocardial infarction	0.80	0.6–0.94	[15,17,36][a] and expert opinion
Utility of experiencing an adverse cardiac event	–0.1	–0.1–0	[35][a]
Utility of experiencing an episode of major bleeding	–0.05	–0.1–0	[34] and expert opinion
Utility of experiencing a coronary artery bypass graft	–0.1	–0.2–0	[36][a] and expert opinion
Utility of experiencing percutaneous coronary revascularization	–0.05	–0.1–0	[36][a] and expert opinion

a Time trade-off method.

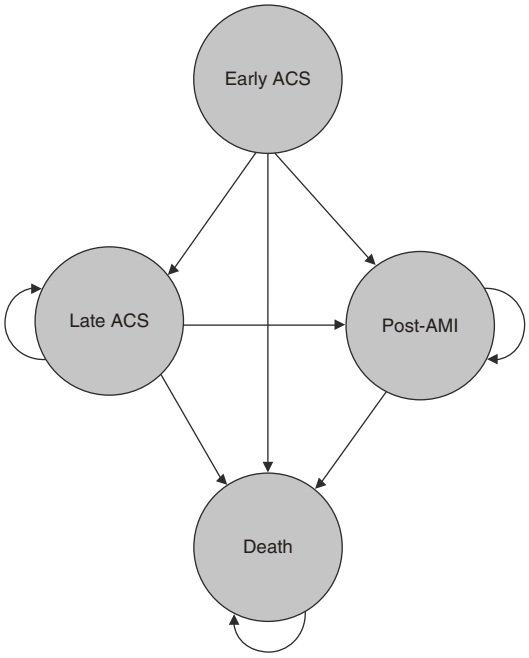

Fig. 1. Markov states diagram. **ACS** = acute coronary syndrome; **AMI** = acute myocardial infarction.

costs of invasive procedures and bleeding-related costs (including additional length of stay). Costs related to the detection and treatment of heparin-induced thrombocytopenia were not considered.

After the first cycle, the patient moves to one of three possible states: 'late acute coronary syndrome' (if no complications occur), 'post-myocardial infarction' (if the patient experiences a non-fatal cardiac event) or 'death'. During each cycle, utilities and costs are accumulated, depending on the specific status or the occurrence of a particular event (transition costs/utilities). The model considers both the possibility of age-related death (according to the age-specific mortality rate of the Spanish population during the year 2005)[21] and the possibility of cardiac events (either fatal or non-fatal).

The model assumes that the effect of the drugs under evaluation is restricted to the first month and that the ultimate effect of fondaparinux on the 30-day risk of cardiac events (death and non-fatal MI) is entirely due to its effect on the risk of bleeding.[8] Prognosis after the first month depends entirely on the specific Markov state (Markovian assumption). In the same way, the model also assumes that anticoagulation is given for 1 day if a successful percutaneous procedure is performed, 5 days in the case of surgical revascularization and 7 days otherwise. Likewise, the model assumes that each episode of bleeding is associated with 4 additional days of stay in the cardiology ward.[3,6,27,28]

Data Analysis

The expected costs and outputs (risk of major bleeding, adverse cardiac events, length of life and QALYs) under the base case (a 65-year-old patient with a TIMI score of 4, and the rest of the variables at the basal value in tables I–III) were estimated using second-order Monte Carlo simulation.[9,10,23,41] A discount rate (with a basal annual rate of 3%)[33,41] was applied to costs, years of life, utilities and number of bleeding and cardiac events.

The costs and outcomes of the two strategies (enoxaparin versus fondaparinux) were compared throughout the calculation of the incremental cost-effectiveness ratio and the net health benefit (NHB).[41,42] The NHB can be interpreted as the effectiveness adjusted for the associated costs after taking into consideration society's threshold willingness to pay (WTP) [€30 000 per year of life gained in the Spanish society].[43] Values of incremental NHB exceeding zero indicate that the intervention is cost effective given the threshold WTP.

The uncertainty around the true value of the variables included in the decision tree was analysed with one-way sensitivity analyses[20,23-36,37-41] using the range of all values in tables I–III, and the results were robust for all of them. The most influential variables (age, baseline risk of bleeding, relative risk of major bleeding and TIMI score) were selected for further sensitivity analyses (figure 3).

Furthermore, the simultaneous effect of all the variables included in the model (multivariate sensitivity analysis) was assessed using Monte Carlo probabilistic sensitivity analysis.[41] In this

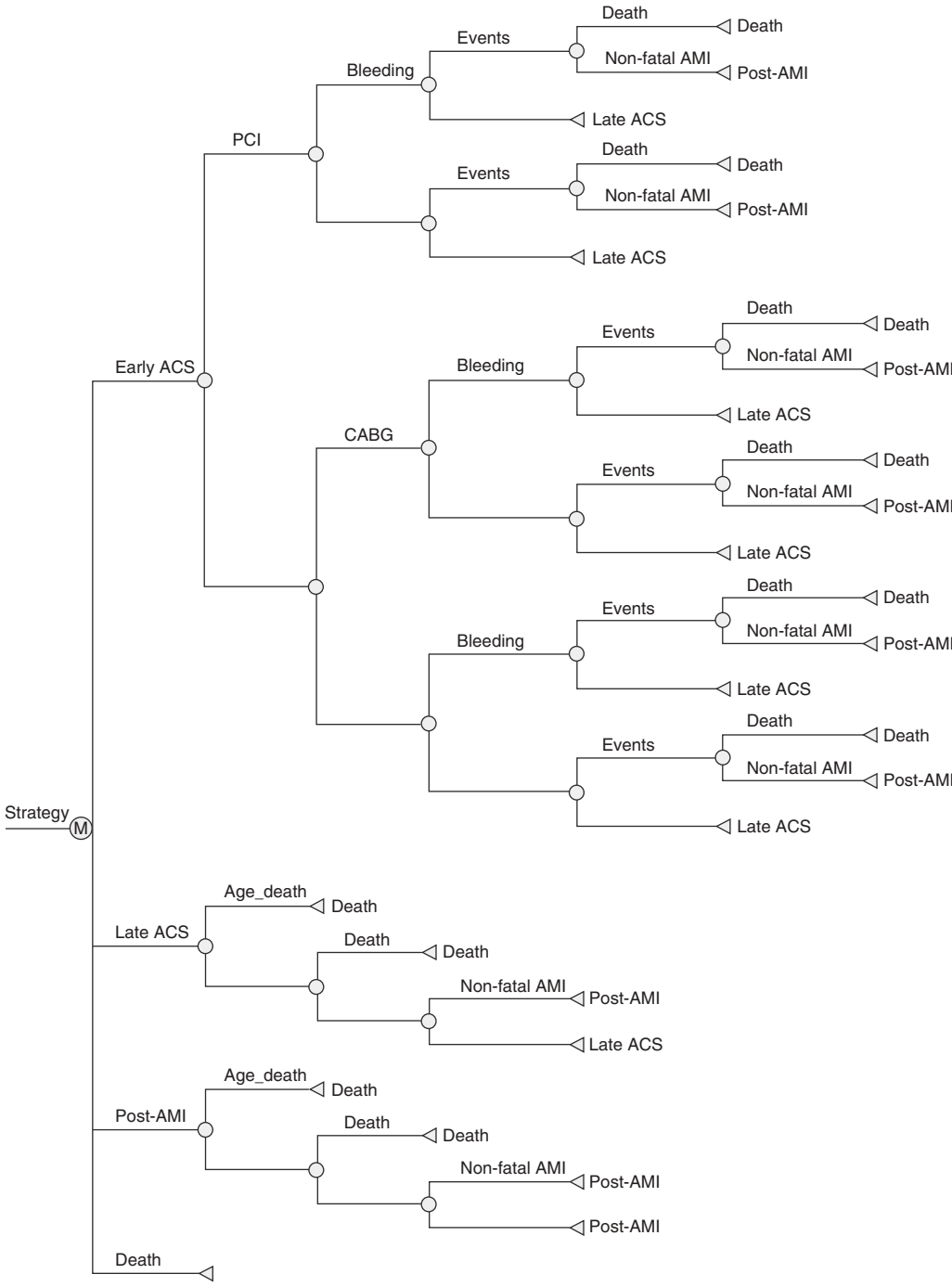

Fig. 2. Decision-tree model (reproduced from Latour-Perez et al.,[20] with permission). In the real model, there is one decision node with two alternative strategies (enoxaparin and fondaparinux). **ACS** = acute coronary syndrome; **AMI** = acute myocardial infarction; **CABG** = coronary artery bypass graft; **M** = Markov node; **PCI** = percutaneous coronary intervention.

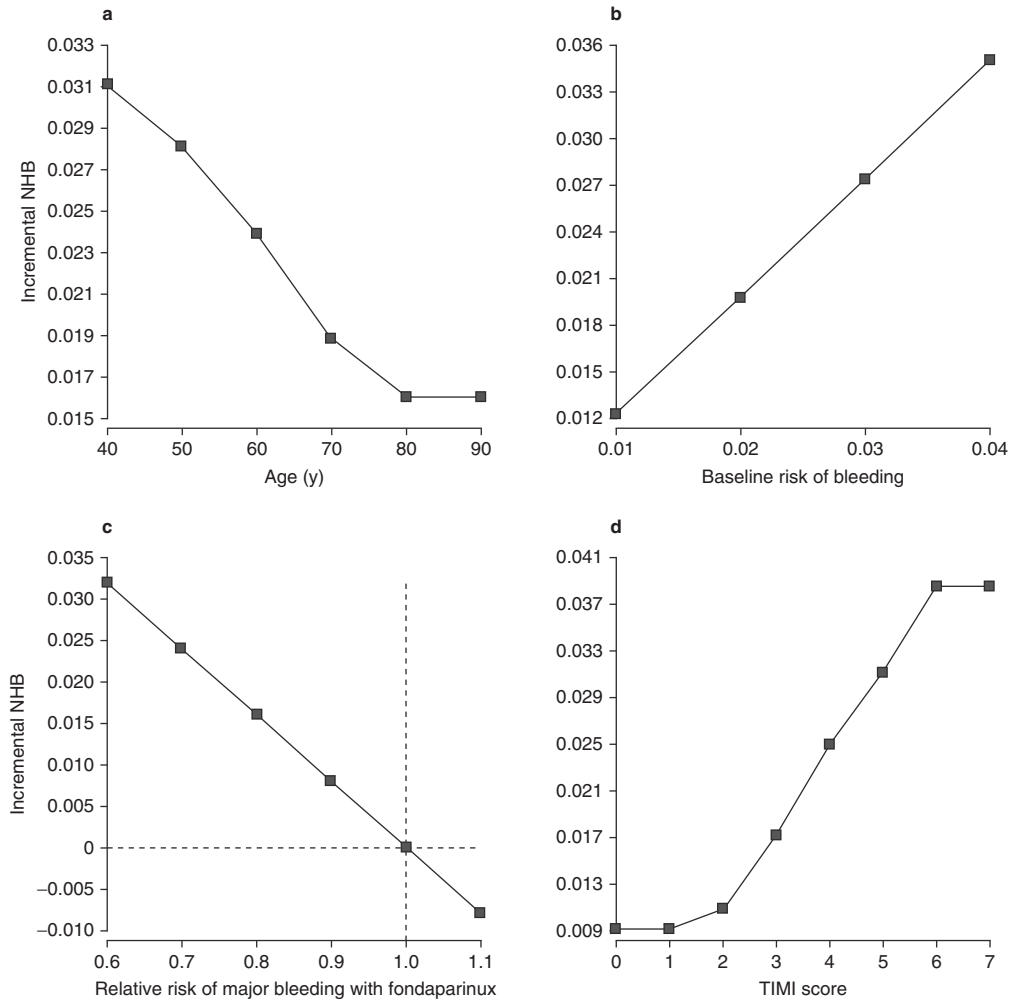

Fig. 3. One-way sensitivity analyses showing the effect of (**a**) age; (**b**) baseline bleeding risk; (**c**) relative risk of major bleeding (fondaparinux vs enoxaparin); and (**d**) baseline Thrombolysis in Myocardial Infarction (TIMI) risk score on the incremental net health benefit (NHB).

analysis, empirical cost variables (except hospitalization days and pharmaceutical prices) were assigned log-Normal distributions, and variables without a known distributional form (that is, those with assumed values or those with values based on a range of published reports) were assigned triangular distributions. For each run of the model, a value of each input variable is picked at random from its distribution. Performing a large number of iterations yields a distribution of effectiveness and cost values that permits the estimation of the probability that the intervention is cost effective for various threshold values of the cost-effectiveness ratio.

All the analyses were performed using the commercial software DATA-Pro version 11 (TreeAge Software Inc., Williamstown, MA, US).

Results

Reference Case Analysis: Costs and Effects

Under the reference case, the use of fondaparinux was associated with a lower expected cost

Table IV. Estimated costs (€, year 2006 values) and effects for the reference case[a]

Strategy	Cost	Bleeding events	Cardiac events	Survival (y)	QALYs
Enoxaparin	21 378	0.064	0.503	11.942	9.627
Fondaparinux	21 326	0.050	0.499	11.961	9.649
Number needed to treat		71	250	53	46

a A 3% discount rate is applied to all variables. All estimations have been calculated using Monte Carlo simulation.

per patient, a lower rate of bleeding, a lower rate of major cardiac events, a higher expected survival and more QALYs than enoxaparin (table IV). Under the base-case assumptions, we need to treat 71 patients to prevent an episode of major bleeding, 250 patients to prevent an adverse cardiac event, 53 patients to gain 1 year of life and 46 patients to gain one QALY. Therefore, the use of fondaparinux under the base-case scenario was cost saving (cost per QALY negative, incremental NHB 0.023).

Sensitivity Analysis

The dominance of fondaparinux over enoxaparin persisted in the one-way cost-effectiveness sensitivity analyses for all the variables considered, except in those hypothetical scenarios of relative risk of bleeding with fondaparinux ≥1, as expected. It should be remarked that the use of fondaparinux was economically attractive even in patients at low risk of bleeding. Indeed, the incremental effectiveness of fondaparinux in a patient with a basal risk of bleeding of 1% (rest of variables as in the reference case) would be of 0.012 QALYs with a cost saving of €28.

Figure 3 shows the one-way cost-effectiveness sensitivity analysis for the four most influential variables, demonstrating that the incremental NHB of fondaparinux was higher with the lower age of the patient, higher basal risk of bleeding, lower relative risk of bleeding with fondaparinux and higher risk of events (TIMI score).

According to the Monte Carlo simulation, the use of fondaparinux was cost saving in 99.9% of the cases (figure 4) and cost effective in the remaining 0.1%. The incremental NHB varied slightly with the threshold WTP (from 0.025 to 0.021 for a threshold of €10 000 and €70 000 per QALY, respectively).

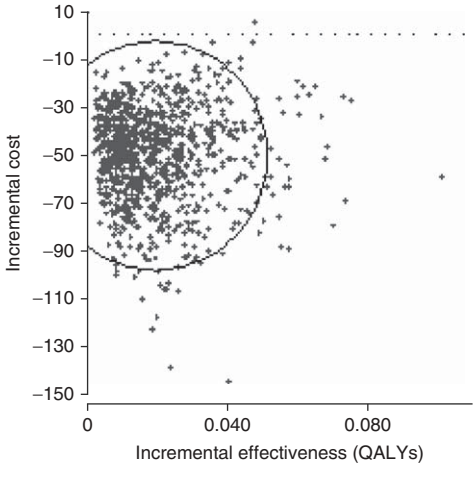

Fig. 4. Cost-effectiveness plane (€, year 2006 values) for fondaparinux vs enoxaparin in acute coronary syndrome.

Discussion

Our results suggest that the use of fondaparinux together with triple antiplatelet therapy in NSTE-ACS patients submitted to early (non-urgent) invasive therapy is cost saving. The strategy of fondaparinux was found to be dominant in almost all the scenarios considered, and the highest cost effectiveness of fondaparinux was found in younger patients, patients at high risk of a cardiac event (high TIMI score) and patients at the highest risk of bleeding. The economic attractiveness of fondaparinux over enoxaparin persisted as long as the relative risk of bleeding with fondaparinux was <1.

These findings favour the European guidelines[2] recommendations over the US guidelines.[1] Conversely, our results do not support the European guidelines, which suggest that

enoxaparin should be used only if the bleeding risk is low. Indeed, according to our model, treating with fondaparinux 1000 patients with a basal risk of bleeding as low as 1% (rest of variables as in the reference case), we would obtain an overall gain of 12 QALYs while saving €28 000.

Our study has some limitations. The study is based on a model that, by definition, is a simplification of the reality, where some real-life situations cannot fit accurately. Moreover, the long-term horizon, otherwise necessary to reflect the whole spectrum of consequences of therapy, requires making a series of difficult-to-demonstrate assumptions. Nevertheless, it is reassuring that the predicted survival of our model has been shown to fit reasonably well with the real experience of various external cohorts.[20] Furthermore, in some aspects (such as the unawareness of the heparin-induced thrombocytopenia), the model is conservatively biased in favour of enoxaparin, which reinforces the conclusions of the study.

Of course, data on costs and utilities values are measured in our study with some degree of error. However, despite the uncertainty on the measured probabilities, utilities and costs, the sensitivity analysis suggests that our conclusions are robust and stable over a range of parameter estimates and assumptions.

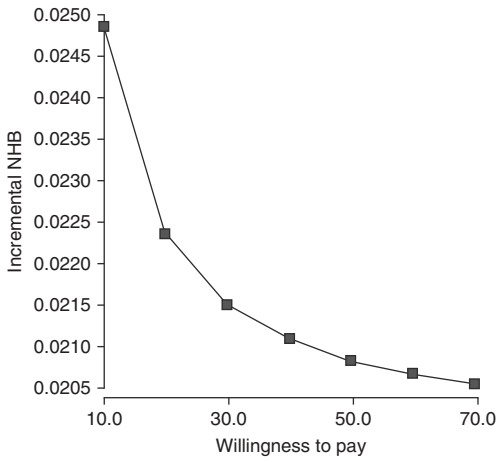

Fig. 5. Incremental net health benefit (NHB) as a function of the willingness-to-pay ratio (€, year 2006 values, per QALY).

It could be argued that our study, based on data from Spain, cannot be extrapolated to other countries. However, although the external validity of economic evaluations is always debatable, the economic evaluations on clopidogrel[44,45] and GPIIb/IIIa inhibitors[17,46] in NSTE-ACS patients conducted in different countries provide results that are remarkably consistent. On the other hand, the estimated NHB over a wide range of WTP thresholds suggests that the results of our study can be extrapolated to other Western countries (figure 5). Moreover, the long-term cost-effectiveness estimated in our study is closely similar to results reported by Sculpher et al in a US population.[47]

Conversely, our study has some strengths that should be emphasized. In particular, the study integrates recent evidence on the risks and benefits of triple antiplatelet therapy[5] and the impact of bleeding on outcomes[6] that could not be included in previous economic evaluations. Moreover, our study reflects contemporary practice on the management of patients with NSTE-ACS, and provides relevant information to formulate evidence-based recommendations tailored to the individual characteristics of the patient. These recommendations should become sounder as new refinements in the risk stratification (and especially in the risk of bleeding)[2,7,48,49] are developed.

Conclusions

This analysis suggests that the use of fondaparinux in the treatment of NSTE-ACS patients may be a cost-effective choice over enoxaparin from the Spanish healthcare payer perspective.

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