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Using Triple Antiplatelet Therapy in Patients with Non-ST Elevation Acute Coronary Syndrome Managed Invasively: A Cost-Effectiveness Analysis

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ABSTRACT

Objectives: To assess the incremental cost-effectiveness ratio (ICER) of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors in patients with non-ST elevation acute coronary syndrome (NSTE-ACS) pretreated with aspirin and clopidogrel undergoing an early invasive treatment strategy.

Methods: Cost-effectiveness analysis and cost-utility analysis were performed from a health-care system perspective, based on a Markov model with a time horizon of the patient life span. The risk of death and ischemic events was assessed using the Thrombolysis in Myocardial Infarction (TIMI) risk score. We compared three strategies: 1) routine upstream use of a GPIIb/IIIa inhibitor to all patients before angiography, 2) deferred selective use of abciximab in the catheterization laboratory just before angioplasty, and 3) double antiplatelet therapy without GPIIb/IIIa inhibitors. Both univariate sensitivity analysis and second-order probabilistic microsimulation were performed.

Results: In the base case (65 years old, TIMI score 3), strategy A was the most effective, with an ICER of €15,150 per quality-adjusted life-year gained. Strategy B was dominated by a combination of strategies A and C. The ICER was very sensitive to the age and baseline risk of the patient. According to the widely accepted cost-effectiveness thresholds, strategy A would be cost-effective only in patients with an intermediate to high TIMI score, especially within the younger age groups. The probability that strategy A was cost-effective under the base case was 91.2%.

Conclusions: The use of GPIIb/IIIa inhibitors upstream in high-risk NSTE-ACS patients (TIMI score ≥3) pretreated with aspirin and clopidogrel is cost-effective, particularly in the younger age groups.

Keywords: acute coronary syndrome, clopidogrel, cost-effectiveness, glycoprotein IIb/IIIa inhibitors.

Introduction

The use of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors reduce the risk of adverse cardiac events in high-risk patients with non-ST elevation acute coronary syndrome (NSTE-ACS) managed with an early invasive strategy [1,2]. Therefore, the current guidelines recommend the use of GPIIb/IIIa inhibitors in these patients, either upstream to all patients or selectively in the catheterization laboratory just before angioplasty in patients with suitable coronary lesions [3–6].

GIIb/IIIa inhibitors are currently given along with clopidogrel and aspirin (*triple antiplatelet therapy*) [3–5]. Nevertheless, the available economic evaluations are based on randomized clinical trial studies that compare the efficacy of double antiplatelet therapy (a GPIIb/IIIa inhibitor plus aspirin) versus aspirin. Because clopidogrel has not been routinely used in these trials, they do not inform about the incremental efficacy and safety of GPIIb/IIIa inhibitors in patients pretreated with clopidogrel. Consequently, most of the available economic evaluations do not represent the current clinical practice [7].

Recently, several studies have provided new evidence on the benefits and risks of using GPIIb/IIIa inhibitors in patients pretreated with clopidogrel [8,9], whereas other studies have added important information on the comparative advantages of selective and upstream strategies [10,11]. Therefore, a new economic evaluation of the use of GPIIb/IIIa inhibitors under current clinical conditions, which combines the most recent clinical and economic studies, is justified.

Methods

The aim of this study was to assess the effectiveness and economic efficiency of GPIIb/IIIa inhibitors (either upstream or selectively) added to aspirin and clopidogrel, compared with aspirin and clopidogrel alone, in NSTE-ACS patients who undergo an early invasive treatment strategy. The study was performed from the

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Spanish public health care system perspective, with a time horizon of the patient life span.

Data Inputs (Tables 1–3)

The main source of evidence about the comparative effectiveness and safety of triple versus double antiplatelet therapy was a recent systematic review and meta-analysis [9] based on nine randomized controlled trials. According to this review, the addition of GPIIb/IIIa inhibitors reduced the risk of death or myocardial infarction at 30 days in those trials that included patients with NSTE-ACS (relative risk [RR] 0.67; 95% confidence interval [CI] 0.56–0.80) but not in studies that excluded NSTE-ACS patients (RR 1.07; 95% CI 0.75–1.53) (*P*-test of interaction 0.0175).

Conversely, the evidence about the effectiveness of routine upstream versus selective use of GPIIb/IIIa inhibitors is less straightforward [10,11]. In the ACUITY timing trial [11], the selective deferred strategy was associated with a nonsignificant relative increase of ischemic complications at 30 days (7.9% vs. 7.1%; RR 1.12; 95% CI 0.97–1.29) and a statistically significant reduction in major bleeding (6.1% vs. 4.9%; RR 0.80; 95% CI 0.67–0.95; $P = 0.009$). Unfortunately, the ACUITY study did not inform about long-term clinical outcomes; therefore, the long-term effect of bleeding on future adverse cardiac events was obtained from other sources [12].

Data of the health-care costs were obtained from Spanish studies. The costs were adjusted for inflation using the Spanish consumer price index and were actualized to the year 2006 [13]. According to the perspective of the economic evaluation, the study only considered direct health-care costs, and ignored indirect costs (as the time of the patient and their attendants), while intangible costs (related to the pain and suffering of the patient) were included in the denominator of the cost-effectiveness, as part of the quality-adjusted life-years (QALYs) [14].

The utilities associated with the different events and health states were obtained from a nonsystematic review of the literature. A number of data sources provided useful estimated utilities associated with coronary disease and bleeding complications. Nevertheless, none of these sources provided separate estimates for all the relevant states based on consistent valuation methods. Therefore, consensus among the authors was used when appropriate. The sources of data about the effectiveness, costs and utilities are summarized in Tables 1–3 [1,7,9–12,15–26].

Decision Model

The study was based on a Markov model [27] that compared three strategies for high-risk patients with NSTE-ACS treated with aspirin and clopidogrel as part of an early invasive strategy. Strategy A consisted of the early administration ("upstream") of a GPIIb/IIIa inhibitor (tirofiban or epitifibatide) to all the patients before coronary angiography. Under strategy B ("selective" strategy), the GPIIb/IIIa inhibitor (in this case abciximab) was deferred for those patients in which, after the performance of a coronary angio-

Table 1 Estimated probabilities and effect measures

Variable	Basal value	Rank	Source
Mortality of old uncomplicated coronary syndrome	0.0765	0.05–0.09	Robinson et al. 2005 [7]
Mortality of old myocardial infarction	0.0734	0.05–0.09	Robinson et al. 2005 [7]
Late mortality caused by coronary artery disease	0.009	0.005–0.018	This article
Annual risk of nonfatal infarction in old previously uncomplicated coronary syndrome	0.02	0.01–0.04	Robinson et al. 2005 [7]
Absolute risk of events increase after an episode of major bleeding	0.2	0.05–0.3	Stone et al. 2007 [11]
Proportion of adverse cardiac events with death	0.186	0.09–0.28	Bosch and Marrugat 2001 [1]
Probability of percutaneous revascularization alters coronary angiography	0.55	0.4–0.8	Stone et al. 2007 [11]
Probability of coronary artery bypass graft after coronary angiography	0.27	0.10–0.40	Stone et al. 2007 [11]
Basal risk of major bleeding	0.015	0.01–0.03	Glaser et al. 2006 [10]
Basal risk of major bleeding after coronary artery bypass graft	0.05	0.01–0.1	Glaser et al. 2006 [10]
Basal risk of major bleeding after coronary angiography	0.02	0.01–0.04	Yusuf et al. 2006 [12], Latour-Pérez et al. 2007 [9]
Relative risk (RR) of adverse cardiac events with clopidogrel	0.83	0.70–0.99	Mehta et al. 2001 [16]
RR of adverse cardiac events with GPIIb/IIIa inhibitors in patients treated with clopidogrel	0.67	0.56–0.80	Latour-Pérez et al. 2007 [9]
RR of major bleeding with clopidogrel	1.5	1–2	Mehta et al. 2001 [16], Steinhubl et al. 2002 [17]
RR of major bleeding with triple vs. double antiplatelet therapy	1.4	1–2	Latour-Pérez et al. 2007 [9]
RR of major bleeding with upstream vs. selective administration of GPIIb/IIIa inhibitors	1.10	1.03–1.16	Stone et al. 2007 [11]
RR of death with acute myocardial infarction vs. old uncomplicated coronary syndrome	1.33	1–2	Mark et al. 2000 [19]
Risk of events during the first year:		—	Antman et al. 2000 [15] and projection of authors
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		

GPIIb/IIIa, glycoprotein IIb/IIIa.

Table 2 Estimated costs

Variable	Basal value	Rank	Source
Daily cost of clopidogrel	2.06	1.37–2.06	Sale prices (public/hospital)
Cost of upstream GPIIb/IIIa therapy	312	312–374	Sale prices (public/hospital)
Cost of downstream abciximab	781	781	Cequier et al. 2006 [20]
Daily cost of hospitalization in the cardiology ward	403	300–500	Cequier et al. 2006 [20]
Daily cost of hospitalization in the intensive care unit	1,238	600–1,700	Badia et al. 2005 [21]
Cost of percutaneous revascularization	1,710	1,000–2,000	Oliva et al. 2004 [22], Russell et al. 2006 [23]
Cost of coronary artery bypass graft	14,617	12,000–16,000	Russell et al. 2006 [23]
Cost of an episode of major bleeding	1,394	1,000–1,500	Cequier et al. 2006 [20]
Yearly medical costs of patient with old myocardial infarction	753	600–1,200	Badia et al. 2005 [21]
Cost of an adverse cardiac event	8,840	3,000–10,000	Badia et al. 2005 [21]

All the costs are in euros and are actualized to June of 2006.
GPIIb/IIIa, glycoprotein IIb/IIIa.

graphy, it was decided to carry out an immediate percutaneous revascularization procedure. In strategy C ("reference comparison group"), the patients were assumed to receive standard antiplatelet therapy (aspirin + clopidogrel) without systematic administration of a GPIIb/IIIa inhibitor (bailout use is permitted).

Each one of these three strategies was included in a decision tree as a Markov node, with annual cycles and four possible states (Figs. 1 and 2): early acute coronary syndrome (the first year after the admission), late coronary syndrome (patients without adverse cardiac events after the first year), postmyocardial infarction (patients with myocardial infarction or reinfarction after the admission), and death (the absorbent state). Initially, all the patients begin the process with the early acute coronary syndrome state. During the first year, the model considered the possibility of undergoing some procedures (percutaneous revascularization, aorto-coronary bypass graft) and adverse events (major bleeding, recurrent ischemia, myocardial infarction, or cardiac death). From beginning of the second year on, the model considered simply the possibility of age-related death (according to the age-specific mortality rate of the Spanish population during the year 2005 [28]) and the possibility of suffering cardiac events (either fatal or nonfatal).

The model was analyzed in a recursive way, as transitions between states. Each Markov state was associated with different costs and utilities. During each cycle, the patients stayed in a single state and accumulated costs and utilities, depending on the specific Markov state. In addition to the costs and utilities related to the permanence in a state, certain procedures and events were "penalized" with extra costs ("transition costs") and disutilities. Because a long time horizon was considered, a discount rate was applied for both costs and utilities (with a basal annual rate of 3%) [14].

The decision model presented certain peculiarities and structural assumptions that should be highlighted. First, the model assumed that the effect of the GPIIbIIIa inhibitors was restricted to the first year; from the second year on, the prognosis was entirely determined by the Markov state in which the patient was located. It was also assumed that the short-term efficacy (RR) of small molecule GPIIb/IIIa inhibitors (tirofiban or eptifibatide) upstream was equivalent to that of abciximab administered downstream, while the upstream strategy was associated with a higher rate of major bleeding [11]. Additionally, the model assumed that the previous use of a GPIIb/IIIa inhibitor did not modify the revascularization rates and that the relative proportion of coronary events (death and nonfatal myocardial infarction) remained constant in time and independent of the applied therapeutic strategy.

The risk of adverse cardiac events during the first year depended on the baseline risk of the patient (as measured by its TIMI risk score [15]) and the effec-

Table 3 Estimated utilities

Variable	Basal value	Rank	Source
Utility of and old uncomplicated coronary syndrome	0.817	0.6–0.94	Robinson et al. 2005* [7] Mark et al. 1995* [18] Kuntz et al. 1996* [26], and this article†
Utility of an old myocardial infarction	0.80	0.6–0.94	Robinson et al. 2005 [7] Mark et al. 1995* [18] Kuntz et al. 1996* [26], and this article†
Utility of suffering an adverse cardiac event	−0.1	−0.1–0	Kalish et al. 1995* [24]
Utility of suffering an episode of major bleeding	−0.05	−0.1–0	Eckman et al. 1998† [25], and this article†
Utility of suffering a coronary artery bypass graft	−0.1	−0.2–0	Kuntz et al. 1996* [26], and this article†
Utility of suffering percutaneous coronary revascularization	−0.05	−0.1–0	Kuntz et al. 1996* [26], and this article†

*Time trade-off method.
†Expert criteria.

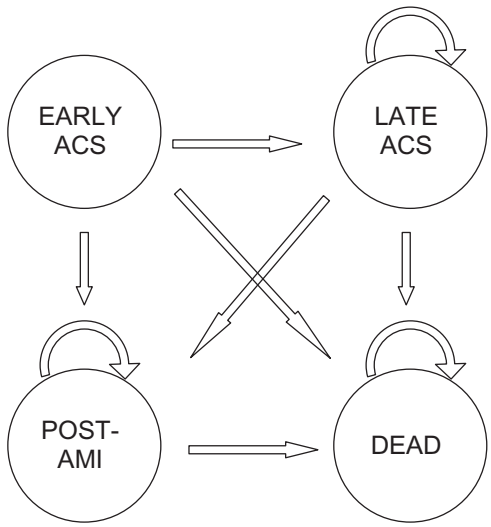

Figure 1 Markov states diagram. ACS, acute coronary syndrome; AMI, acute myocardial infarction.

tiveness (RR) of the therapeutic intervention considered. Because the original score [15] dealt with the short-term prognosis, the risk of death or nonfatal infarction during the first year was estimated by graphical extrapolation [19]. For example, if a patient has a baseline risk of events in the first year of 0.047 (corresponding approximately to a TIMI score of 3) treated with clopidogrel (RR 0.83), the probability of suffering a cardiac event during the first year will be of 0.039 (0.047×0.83). The model took into account the increase of coronary events after one episode of bleeding, probably related to the withdrawal of the antiplatelet therapy and/or the development of a pro-trombotic state [12,29].

The impact of the patient's age was recognized in the model by using two strategies. On the one hand, the higher incidence of events during the first year in elderly patients was incorporated in the TIMI score (age was one of the items). On the other hand, the model analyzed separately the late mortality attributable to age according to the age-specific mortality rate for the Spanish population [28] and the late mortality because of coronary artery disease [30].

Data Analysis

To validate the model, the survival observed in several external cohorts [12,19,31–34] was compared with the survival predicted by the model for similar levels of age and baseline risk.

The analysis began with the estimation of the incremental cost-effectiveness ratio (ICER) for a base case (a 65-year-old patient with a TIMI score of 3, and the remainder of the variables at the basal levels [Tables 1–3]). This base case represented approximately the average patient included in the published cohort studies [12,19,31–34]. The incremental cost per QALY gained, cost per year of life gained, and cost per event prevented were calculated. A basal discount rate was applied to all the estimations.

To assess the uncertainty associated with the probabilistic nature of the input variables, the probabilities, costs, and utilities (with the exception of age, pharmaceutical prices, and days of hospitalization) were entered into the model as triangular probability distributions whose maximum is the basal value and the limits are the rank of uncertainty utilized in the analysis [35]. A one-way sensitivity analysis was performed for each one of the variables included in the model. Second, the joint effect of the main determinants of the ICER, identified by the one-way sensitivity analysis (age, TIMI score [15], and effectiveness of the antiplatelet therapy), was examined in different scenarios. Third, the simultaneous effect of all the variables (distributions) included in the model was analyzed using Monte Carlo probabilistic sensitivity analysis [35]. This method yields a distribution of effectiveness and cost values and 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).

Results

The survival predicted by the Markov model was reasonably comparable to that reported in diverse cohorts of patients admitted with NSTE-ACS [12,19,31–34].

In comparison with strategy C (double antiplatelet therapy), under the base case, by each 1000 patients treated with strategy A (upstream GPIIB/IIIA inhibitor) 16 adverse cardiac events would have been avoided, with a cost per event avoided (discounted) of €37,640. Depending on the basal risk, the cost per avoided event ranked from €13,009 to €91,924 (for patients with a TIMI of 6–7 and 0–1, respectively).

In terms of the expected survival, the adverse events avoided with strategy A would be translated into a life expectancy (discounted) 6 months higher that with strategy C, with a cost per year of life gained of €12,120.

In terms of utilities, the improvement was of 0.04 QALYs, with an incremental cost of €15,150 per QALY gained thanks to the upstream use of a GPIIb/IIIa inhibitor (Table 4). This estimation did not change significantly when the costs were adjusted using the Spanish medical inflation index instead of the consumer price index.

Strategy B was slightly less costly but was also less effective than strategy A, with an incremental cost-effectiveness of €22,350 (higher than that of strategy A

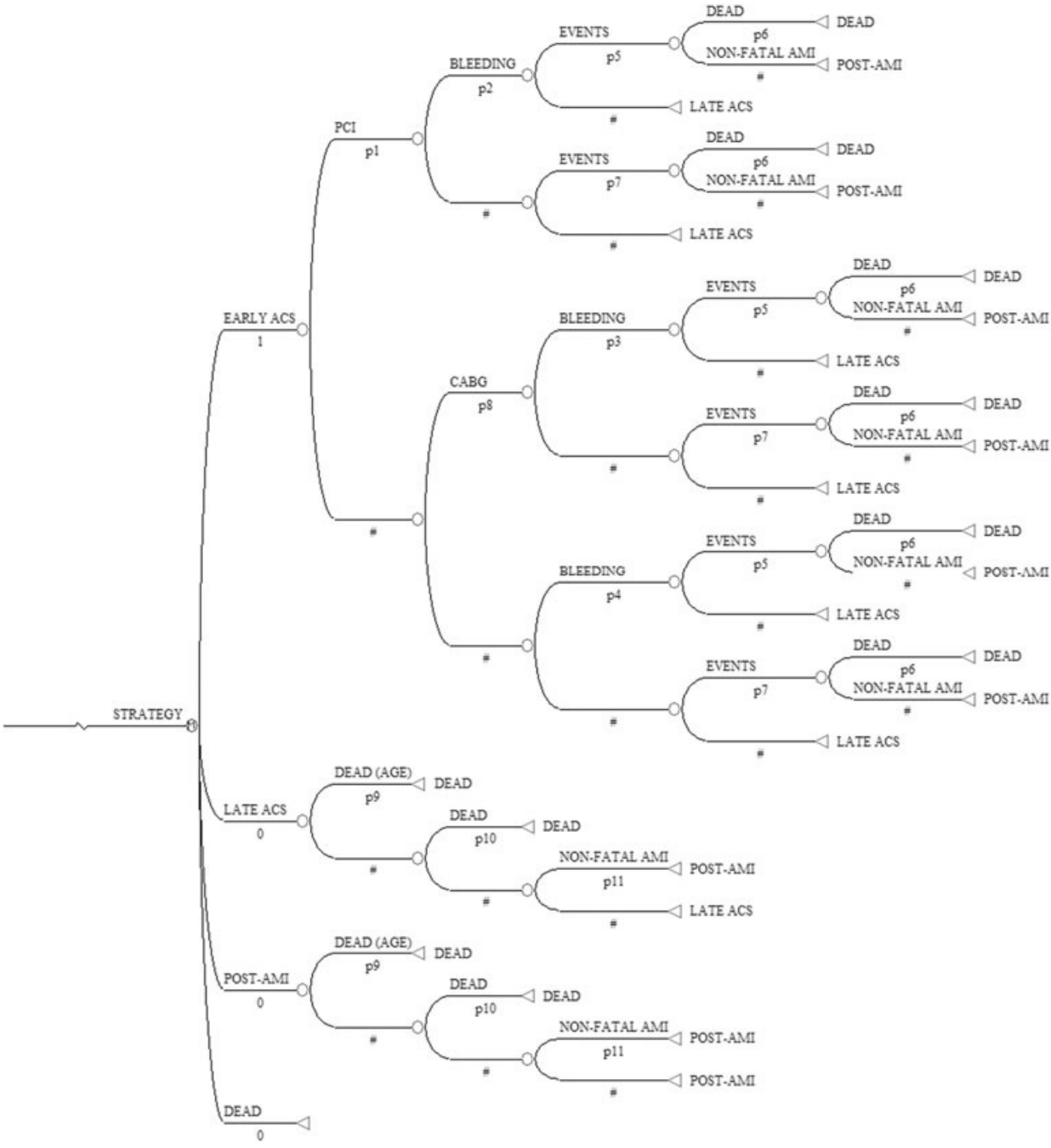

Figure 2 Decision tree. p1, probability of percutaneous revascularization after coronary angiography; p2, basal risk of major bleeding after coronary angiography × Relative risk (RR) of major bleeding with clopidogrel × RR of major bleeding with triple versus double antiplatelet therapy; p3, basal risk of major bleeding after coronary artery bypass graft × RR of major bleeding with clopidogrel; p4, basal risk of major bleeding after coronary angiography × RR of major bleeding with clopidogrel; p5, risk of events during the first year (according to TIMI score) × RR of adverse cardiac events with clopidogrel × RR of adverse cardiac events with glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors in patients treated with clopidogrel + absolute risk of events increase after an episode of major bleeding; p6, proportion of adverse cardiac events with death; p7, risk of events during the first year (according to TIMI score) × RR of adverse cardiac events with clopidogrel × RR of adverse cardiac events with GPIIb/IIIa inhibitors in patients treated with clopidogrel; p8, probability of Coronary artery bypass graft after coronary angiography; p9, age-specific mortality rate during year 2005 (for basal age + Markov cycle number); p10, late mortality because of coronary artery disease (total mortality − mortality due to age); p11, risk of late nonfatal myocardial infarction. #, complementary probability (1 minus probability).

Table 4 Estimated costs and effects for the referent case

Strategy	Cost (€)	Cardiac events (%)	Survival (years)	QALYs	Cost per QALY (vs. strategy C)
A	21,599	37.12	12.73	10.33	15,150
B	21,440	37.80	12.71	10.31	22,350
C	20,993	38.73	12.68	10.29	–

A 3% discount rate is applied to all the estimates.
QALY, quality-adjusted life-year.

vs. strategy C). This situation of *extended dominance* [36] featured in every type of analysis (cost per QALY, cost per year, and cost per event avoided) and for all the levels of TIMI.

The sensitivity analysis identified three critical determinants of the efficiency of the triple antiplatelet therapy: the basal risk of events (TIMI score), the incremental effectiveness of the GPIIb/IIIa inhibitor, and the age of the patient (Table 5, Fig. 3). Combinations of these three variables arranged some scenarios with different cost-effectiveness. Indeed, costs per QALY gained ranked between €3919 (for a 55-years-old patient with a TIMI score of 6–7) and €53,570 (for an 85-year-old patient with a scoring of 0–1). According to the commonly accepted willingness to pay, strategy A was cost-effective in patients with TIMI score equal to or higher than 3 (especially in young patients) and was not cost-effective in patients with low TIMI score (especially in the elderly).

According to the Monte Carlo simulation, the strategy of the upstream GPIIb/IIIa inhibitor would be cost-effective in 91.2% of the cases (Fig. 4). This percentage varied from 26.0% for patients with TIMI 0 to 1 and 99.6% for patients with TIMI 6 to 7.

Discussion

To date, the available studies that analyze the cost-effectiveness of GPIIb/IIIa inhibitors in NSTE-ACS patients rely on placebo-controlled clinical trials [10,19,37–40], which do not inform about the incremental benefits and risks of GPIIb/IIIa inhibitors. Fortunately, some recent studies provide adequate evidence on the efficacy and safety of triple antiplatelet therapy in these patients [8,9]. This evidence allows the assessment of the efficiency of this therapy in patients already treated with clopidogrel.

The results of the reference case analysis show that the use of upstream GPIIb/IIIa inhibitors in medium- to high-risk NSTE-ACS patients pretreated with clopidogrel who undergo an early invasive strategy, is cost-effective according to the threshold recommended for the adoption of health-care interventions in Spain (€30.000 per saved life-year) [41]. As expected, the ICER is attractive in patients with high TIMI score, while it is unacceptable in patients with a TIMI score lower than 3.

Although these data refer to the Spanish environment, the economic evaluations on clopidogrel [42,43] and GPIIb/IIIa inhibitors [7,40] in NSTE-ACS patients conducted in different countries provide results that are remarkably similar. On the other hand, the sensitivity analysis (Table 5) shows that the ICER of the triple antiplatelet therapy in moderate- to high-risk patients is beneath the commonly accepted boundary of 50,000 dollars per QALY gained. This suggests that the results of our study can be extrapolated to other Western countries.

Current guidelines recommend administration of GPIIb/IIIa inhibitors, either upstream to all high-risk patients before angiography or deferred for selective use in the catheterization laboratory just before angioplasty. Our study shows that, although the selective use of abciximab is something less costly than strategy A (upstream therapy with eptifibatide or tirofiban), the ICER of the selective strategy is higher. In other words,

Table 5 Sensitivity analysis: cost per quality-adjusted life-year according to TIMI score, age, and GPIIb/IIIa effectiveness

TIMI	Age		
	55	70	85
0–1	30,347 (20,943; 63,725)	44,621 (30,536; 95,534)	53,570 (36,517; 115,917)
2	22,377 (15,720; 44,068)	32,677 (22,761; 65,376)	39,105 (27,142; 78,851)
3	11,104 (7,973; 20,201)	15,918 (11,291; 29,430)	18,910 (13,355; 35,182)
4	6,736 (4,851; 11,984)	9,467 (6,689; 17,221)	11,167 (7,839; 20,475)
5	5,095 (3,659; 9,028)	7,049 (4,937; 12,848)	8,270 (5,741; 15,223)
6–7	3,919 (2,800; 6,952)	5,319 (3,673; 9,785)	6,199 (4,229; 11,548)

Figures between parentheses correspond to the predicted values for the 95% confidence limits of the relative risk of the reduction of events because of the GPIIb/IIIa inhibitor in patients previously treated with clopidogrel.
Because of the inherent variability of the method, the values cannot coincide exactly with the values predicted by the Monte Carlo simulation.
GPIIb/IIIa, glycoprotein IIb/IIIa.

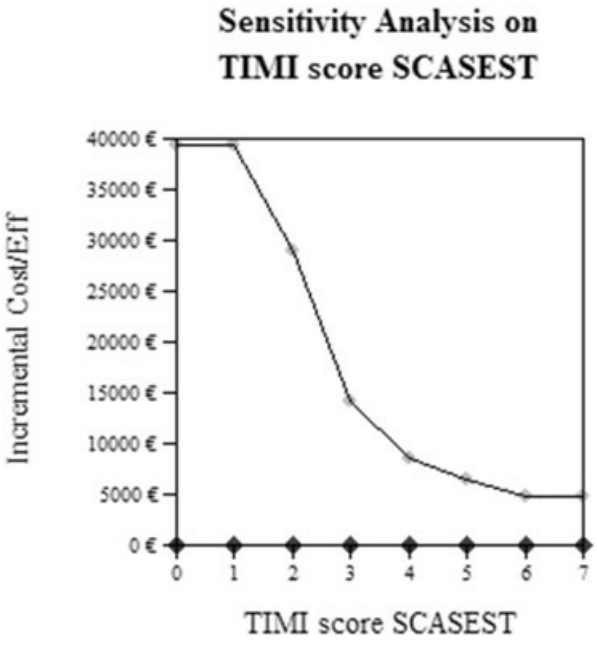

Figure 3 One-way sensitivity analysis for TIMI score. Circles, strategy A; rhombus, strategy C; cost/eff, cost-effectiveness ratio.

it is cheaper to gain a QALY with strategy A than with strategy B. This situation of extended dominance [35] means that, for a given closed budget, the overall health results applying strategy B are worse than when using strategy A for a specific segment of the population and strategy C for the remainder.

As with most studies based on models, our economic evaluation presents some limitations. First, the model considers only three strategies and ignores other alternatives (e.g., with bivalirudin [44,45] or fondaparinux [12]) that are recommended in the most recently published guidelines [3,4].

Second, the long-term modeling compels us to make some assumptions that are difficult to demonstrate. Nevertheless, the lifetime horizon should be long enough to capture all relevant future effects of the health-care intervention. Furthermore, survival predicted by the model is similar to the survival reported in other cohort studies and economic evaluations [12,19,31–34].

Third, data about probabilities, costs, and utilities are sometimes sparse and of low quality, requiring best guess estimates. Nevertheless, the sensitivity analysis shows that most of these variables had a limited impact on the output of the model, so the estimated ICER was robust over a wide range of values of these variables.

As counterpart, our study presents some strong points that deserve to be mentioned. First, this study, in contrast to others [10,19,38–40], used a comparison strategy that combined treatment with aspirin and clopidogrel, which is the currently relevant comparison, not just aspirin. In addition, the decision tree incorporates some important aspects such as the impact of increasing age and the effects of bleeding on the incidence of major cardiac events and long-term mortality [12].

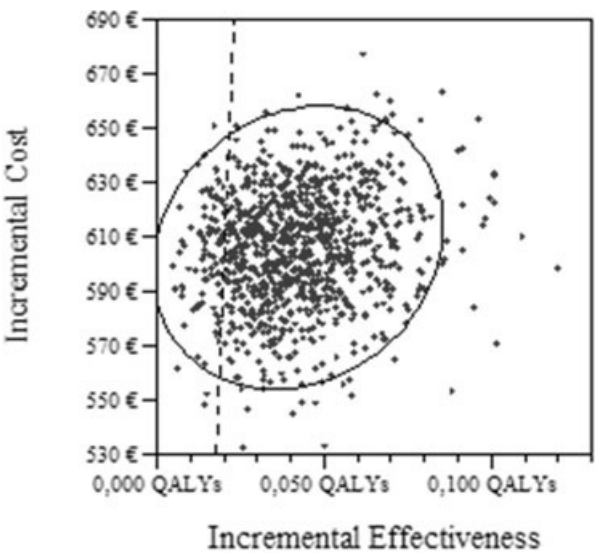

Figure 4 Cost-effectiveness function (Monte Carlo simulation). The discontinuous line represents the threshold cost-effectiveness ratio.

Conclusion

We conclude that the use of GPIIb/IIIa inhibitors upstream in high-risk NSTE-ACS patients pretreated with aspirin and clopidogrel is cost-effective, particularly in the younger age group.

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