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Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study

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Aims The efficacy and safety of ticagrelor vs. clopidogrel in patients with acute coronary syndromes (ACS) are well documented in the PLATelet inhibition and patient Outcomes trial (PLATO). The aim of this study was to assess the long-term cost-effectiveness of treating ACS patients for 12 months with ticagrelor compared with generic clopidogrel.

Methods and results Event rates, health-care costs, and health-related quality of life during 12 months of therapy with either ticagrelor or generic clopidogrel were estimated from PLATO. Beyond 12 months, quality-adjusted survival and costs were estimated conditional on whether a non-fatal myocardial infarction (MI), a non-fatal stroke, or no MI or stroke occurred during the 12 months of therapy. Lifetime costs, life expectancy, and quality-adjusted life years (QALYs) were estimated for both treatment strategies. Incremental cost-effectiveness ratios were presented from a health-care perspective in 2010 Euros (€) applying unit costs and life tables from a Swedish setting in the base-case analysis. Treatment with ticagrelor was associated with increased health-care costs of €362 and a QALY gain of 0.13 compared with generic clopidogrel, yielding a cost per QALY gained with ticagrelor of €2753. The cost per life year gained was €2372. The results were consistent in major subgroups. Sensitivity analyses showed a cost per QALY gained with ticagrelor of ∼€7300 under certain scenarios.

Conclusion Based on clinical and health-economic evidence from the PLATO study, treating ACS patients with ticagrelor for 12 months is associated with a cost per QALY below generally accepted thresholds for cost-effectiveness.
ClinicalTrials.gov Identifier: NCT00391872.

Keywords Acute coronary syndrome • Ticagrelor • Clopidogrel • Cost-effectiveness analysis • Quality-adjusted life years

Introduction

In patients who have acute coronary syndromes (ACS) with or without ST-segment elevation, the current clinical practice guidelines recommend dual antiplatelet treatment with aspirin [acetylsalicylic acid (ASA)] and clopidogrel.[1–3] The PLATelet inhibition and patient Outcomes trial (PLATO) recently showed that in patients with ACS, treatment with ticagrelor when compared with clopidogrel significantly reduced the rate of the composite endpoint of death from vascular causes, myocardial infarction (MI), or stroke without an increase in the rate of overall major bleeding.[4] A comprehensive cost study based on PLATO reported that 12-month treatment with ticagrelor was associated with a reduction in health-care costs compared with clopidogrel treatment when excluding study drugs.[5] In order to prioritize treatments among scarce health-care resources, the long-term costs and health outcomes of different treatment strategies need to be assessed and compared.[6] In this study, we synthesize the risk of cardiovascular events, costs, and quality-of-life data from the PLATO study with drug costs and long-term extrapolation data

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in order to determine the long-term cost-effectiveness of treating ACS patients for 12 months with ticagrelor according to the European label.

Methods

Overview of cost-effectiveness

The treatment strategies under investigation are ticagrelor in addition to ASA and clopidogrel in addition to ASA for a 12-month duration according to the PLATO study (NCT00391872), of which the design[7] and clinical results[4,8] have been extensively reported. In brief, the PLATO trial randomized 18 624 patients with ST-segment elevation or non-ST-segment elevation ACS, with onset during the previous 24 h to ticagrelor or clopidogrel as soon as possible after admission.[7] The key clinical findings from PLATO were a reduction in the rate of the composite endpoint of death from vascular causes, MI, or stroke [hazard ratio (HR) = 0.84; 95% confidence interval (CI): 0.77–0.92], and also a reduction in death from vascular causes (HR = 0.79; 95% CI: 0.69–0.91) without an increase in the rate of overall PLATO-defined major bleeding (HR = 1.04; 95% CI: 0.95–1.13).[4] In Europe, ticagrelor is indicated for the prevention of atherothrombotic events in adult patients with ACS [unstable angina, non-ST-elevation MI (NSTEMI) or ST-elevation MI (STEMI)], including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting.[9] Therefore, the base-case analysis was carried out on the full ACS population. The analysis was undertaken from a health-care perspective. In some jurisdictions, a societal perspective is preferred, but in this particular application, the difference between a societal and a health-care perspective is likely to be small. Costs and life table data required for extrapolation were based on Swedish sources. Costs are expressed in Euros (€) at 2010 prices and were, when required, converted to Euros using the average exchange rate in 2010 according to the European Central Bank (€1 = 9.5373 Swedish kronor).[10] Health outcomes were estimated in terms of life expectancy and quality-adjusted life years (QALYs). Costs and health outcomes were discounted by 3.0% per annum.

A two-part cost-effectiveness model comprising a short-term decision tree and a long-term Markov structure was utilized to estimate long-term costs and health outcomes (*Figure 1*). The aim of the modelling exercise was to adhere closely to the PLATO study and the model structure is based on the key clinical outcomes of PLATO. Data from PLATO were used to estimate rates of cardiovascular events, health-care costs, and health-related quality of life for the 12 months of therapy. Although these estimates were incorporated into the first part of the cost-effectiveness model (decision tree in *Figure 1*), the first year of the analysis is not regarded as a model as it is based solely on randomized data from PLATO. For Year 2 and onwards (Markov model in *Figure 1*), necessary assumptions and external data sources were utilized to extrapolate quality-adjusted survival and cost conditional on whether a non-fatal MI, a non-fatal stroke, or no MI or stroke occurred during the 12 months of therapy. Further details are available in the Supplementary material online.

Data

Key data inputs are summarized below. In the Supplementary material online, a full description of data sources, statistical analyses, and uncertainty around parameter estimates is provided.

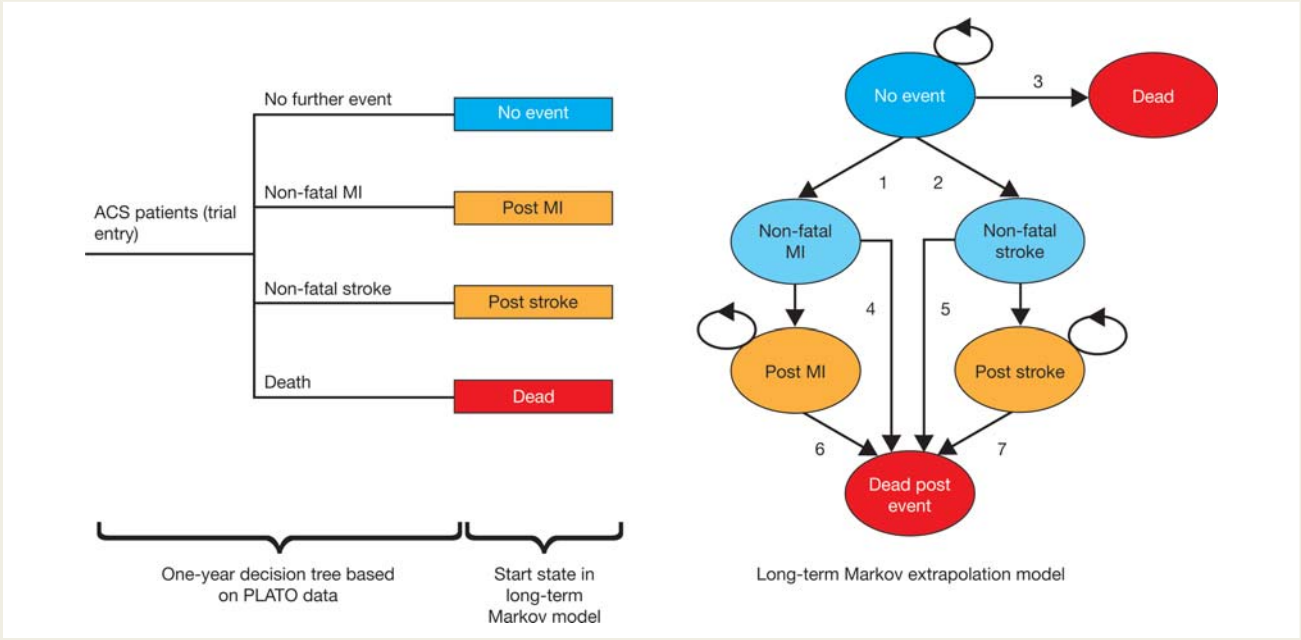

Figure 1 Model structure. Markov model transitions in figure: (1) risk of non-fatal myocardial infarction for patients with no myocardial infarction (MI) or stroke in the PLATO study. (2) Risk of non-fatal stroke for patients with no MI or stroke in the PLATO study. (3) Mortality risk for patients with no MI or stroke in the PLATO study. (4) Mortality risk at the first year after a non-fatal myocardial infarction. (5) Mortality risk at the first year after a non-fatal stroke. (6) Mortality risk at second and subsequent years after a non-fatal myocardial infarction. (7) Mortality risk at second and subsequent years after a non-fatal stroke.

Event risks, costs, and quality of life from the PLATO study

The risk of the following clinical pathways, by treatment strategy, was estimated for the 12 months of therapy: a non-fatal MI occurring before a potential non-fatal stroke with no subsequent fatal event; a non-fatal stroke occurring before any potential non-fatal MI with no subsequent fatal event; death occurring at any point in the study follow-up; no further event, which is one minus the combined risk of the other three clinical pathways. Survival analysis[11] was employed to determine the risk of events, and the results of this analysis were incorporated into the model.[12] For selected subgroups, survival models were run to estimate different baseline event rates (clopidogrel group) associated with each subgroup. Based on the fact that there was no statistically significant interaction for the primary endpoint between treatment and the final index hospitalization diagnosis ($P = 0.41$), between treatment and medical history of diabetes mellitus ($P = 0.49$), and between treatment and planned treatment approach ($P = 0.88$), the HRs for the overall population were used to generate the event rates for ticagrelor-treated patients.[4] The importance of this assumption for the final results was investigated in alternative scenarios. The estimated risk of all-cause death for all ACS patients while on therapy was 0.046 and 0.059 for ticagrelor- and clopidogrel-treated patients, respectively. The corresponding risk of the MI clinical pathway was 0.050 and 0.058 for ticagrelor- and clopidogrel-treated patients, respectively. The risk of the stroke clinical pathway was 0.010 for ticagrelor-treated patients and 0.009 for clopidogrel-treated patients.

The cost estimates for the 12 months of therapy were based on the resource-use data collected in PLATO. Days on study drug, bed days due to hospitalizations, investigations, interventions, blood products and re-operations due to bleeding were recorded in the trial. The total health-care costs per patient, calculated by multiplying resource use by unit costs based on a Swedish setting, were used to estimate the mean per-patient health-care costs for each treatment group. A cost of generic clopidogrel (€0.06 per day, lowest available price in July 2011) and ticagrelor (€2.21 per day, reimbursed price in Sweden) was applied. In the trial-based cost analysis, the daily drug price was multiplied by the number of days patients were on the study drug. In order not to underestimate drug costs with ticagrelor in the cost-effectiveness analysis, the cost of study drugs was entered as a separate parameter and applied as long as patients remained alive during the 12 months of therapy. Due to administrative censoring (patients were followed until 6, 9 or 12 months when the pre-specified number of endpoints had occurred in the study), patients eligible for 12 months of follow-up (randomized before 18 January 2008) were included in the analysis of 12-month costs. The results showed that the mean per patient cumulative health-care cost at 12 months were €96 (95% CI: −360 to 553, $P = 0.679$) higher with ticagrelor-treated patients compared with clopidogrel-treated patients (*Table 1*). As expected, drug costs were higher with the ticagrelor strategy (mean difference = 590; 95% CI: 582 to 598, $P < 0.001$). Non-drug health-care costs were numerically lower with the ticagrelor strategy, mainly due to the reduced number of bed days and interventions. For reasons of power, caution is warranted in the interpretation of *P*-values in the analysis of costs. Although not statistically significant, the results indicate that ticagrelor treatment is associated with an increase in health-care costs when compared with clopidogrel treatment; a trend evident in most of the analysed subgroups (*Table 1*).

Table 1 Mean per patient health-care costs at 12 months

Health-care costs and cost categories (€)	Ticagrelor (*N* = 5347)	Clopidogrel (*N* = 5339)	Difference (95% CI)	*P*-value
Bed days	7455	7800	−345 (−700 to 10)	0.057
Investigations	1480	1493	−14 (−48 to 21)	0.435
Interventions	3568	3701	−134 (−298 to 31)	0.112
Bleeding related	83	84	−1 (−24 to 22)	0.934
Study drug	606.4	16.7	590 (582 to 598)	0.000
Total costs	13 192	13 095	96 (−360 to 553)	0.679
Health-care costs by selected subgroups (€)	**Ticagrelor**	**Clopidogrel**	**Difference (95% CI)**	***P*-value**
Female (*n* = 3088)	12 767	12 820	−53 (−961 to 855)	0.909
Male (*n* = 7598)	13 366	13 206	160 (−365 to 686)	0.550
Age: <75 years (*n* = 8972)	12 961	12 862	98 (−384 to 581)	0.689
Age: ≥75 years (*n* = 1712)	14 450	14 292	158 (−1155 to 1471)	0.813
Diabetes (*n* = 2646)	14 754	14 633	122 (−1018 to 1261)	0.834
No diabetes (*n* = 8034)	12 693	12 586	107 (−368 to 583)	0.658
Intent for medical management (*n* = 3015)	12 268	12 190	79 (−775 to 933)	0.856
Intent for invasive management (*n* = 7671)	13 551	13 455	97 (−443 to 637)	0.725
Final diagnosis unstable angina (*n* = 1800)	11 141	10 887	254 (−717 to 1224)	0.608
Final diagnosis STEMI (*n* = 3947)	13 813	13 850	−37 (−806 to 732)	0.925
Final diagnosis NSTEMI (*n* = 4655)	13 771	13 451	320 (−388 to 1027)	0.376

Unit costs to value resource use based on a Swedish setting (see Supplementary material online, *Table S5*) and detailed resource use for all PLATO patients (see Supplementary material online, *Table S8*) are available. Note that *N* is lower than 18 624 patients enrolled in PLATO as patients eligible for 12 months of follow-up were analysed due to administrative censoring. Patients eligible for 12-month follow-up had similar characteristics to those not eligible for 12-month follow-up (see Supplementary material online, *Table S7*). The mean difference in health-care costs using the full sample (corresponding to the average length of follow-up in the trial rather than 12 months treatment) was 116 (95% CI: −224 to 455).

A similar approach to the cost analysis was used to estimate QALYs for the 12 months of therapy. The QALY estimates were based on EQ-5D[13] data collected within the PLATO study. EQ-5D was distributed in the index period and at 6 and 12 months. At each point of measurement, a QALY weight was derived applying the commonly used UK tariff.[13] A QALY estimate was calculated for each patient in the PLATO study who had a planned follow-up of 12 months (randomized before 18 January 2008). For patients alive at the end of the study and with all three EQ-5D measurements, the area under the curve was calculated assuming a linear relationship between QALY weight measurements at the index period and at 6 and 12 months. For patients who died in the study, the last QALY weight estimate was carried forward until the date of death in order to calculate the area under the curve. Overall, the estimated mean QALYs were similar between the treatment groups (ticagrelor 0.846 vs. clopidogrel 0.840, mean difference = 0.006, 95% CI: −0.016 to 0.004).

Long-term extrapolation

In order to estimate long-term cost-effectiveness, quality-adjusted survival and costs were estimated conditional on whether a non-fatal MI, a non-fatal stroke, or no MI or stroke occurred during the 12 months of therapy using a Markov model. No treatment effect was incorporated in the Markov model as patients are no longer on the study medications; hence, the Markov model is identical for ticagrelor- and clopidogrel-treated patients. For patients surviving and not suffering a non-fatal MI or stroke during the 12 months of therapy, the annual risks of non-fatal MI and non-fatal stroke (transitions 1 and 2 in *Figure 1*) were estimated by extrapolating out the observed hazard function of clopidogrel-treated patients in PLATO beyond 1 year of follow-up. The annual mortality risk (transition 3 in *Figure 1*) in the no event state was estimated using age-specific mortality rates from Swedish life tables[14] to which an HR based on data from a Swedish MI registry is applied.[15] Similarly, survival after non-fatal events was modelled by estimating the HR corresponding to the increased hazard of death following an MI or stroke relative to standard mortality rates from life tables. Different estimates were applied the first year after a non-fatal event [non-fatal MI state (transition 4 in *Figure 1*) and non-fatal stroke state (transition 5 in *Figure 1*)] when compared with the second year onwards [post-MI state (transition 6 in *Figure 1*) and post-stroke state (transition 7 in *Figure 1*)]. These data are summarized in *Table 2*.

For the purpose of estimating long-term costs, each state in the Markov model was assigned a cost estimate. Further analyses of the PLATO data were performed to estimate an annual cost associated with the no event state. The costs associated with a non-fatal event in the Markov model (non-fatal MI and non-fatal stroke states the first year, and the post-MI and post-stroke states the second year and onwards) were derived from the literature (*Table 2*).[16]

Regarding long-term QALYs, the QALY estimate for patients without an event in the PLATO study was applied in the no event state. The mean estimate of ticagrelor- and clopidogrel-treated patients was applied for patients aged <70 years. As patients grow older in the model, a proportional decrement due to age was applied.[17] For the non-fatal MI, non-fatal stroke, post-MI, and post-stroke states, the decrements associated with the non-fatal MI and non-fatal stroke clinical pathways in the PLATO study were applied. The decrements were subtracted from the QALY estimate applied in the no event state in the model. The QALY estimates for the long-term extrapolation are summarized in *Table 2*.

Table 2 Parameters for long-term extrapolation in the base-case analysis

Parameter	Mean value	Source
Annual risk of MI in the no event state	0.019	PLATO data
Annual risk of stroke in the no event state	0.003	PLATO data
Increased risk of death in the no event state[a]	2.00	Norhammar *et al.*[15] and Statistics Sweden[14]
Increased risk of death in the non-fatal MI state[a]	6.00	PLATO data
Increased risk of death in the post-MI state[a]	3.00	Assumption
Increased risk of death in the non-fatal stroke state[a]	7.43	Dennis *et al.*[29]
Increased risk of death in the post-stroke state[a]	3.00	Dennis *et al.*[29] and Olai *et al.*[30]
Annual cost in the non-fatal MI state (€)	15 656	Sigvant *et al.*[16]
Annual cost in the post-MI state (€)	4172	Sigvant *et al.*[16]
Annual cost in the non-fatal stroke state (€)	12 977	Sigvant *et al.*[16]
Annual cost in the post-stroke state (€)	3506	Sigvant *et al.*[16]
Annual cost in the no event state (€)	1376	PLATO data
Annual QALY weight in the non-fatal MI state age <69	0.8748	PLATO data
Annual QALY weight in the non-fatal MI state age 70–79	0.8430	Burström and Rehnberg[17]
Annual QALY weight in the non-fatal MI state age >79	0.7814	Burström and Rehnberg[17]
Annual QALY decrement non-fatal MI state	0.0627	PLATO data
Annual QALY decrement post-MI state	0.0627	PLATO data
Annual QALY decrement non-fatal stroke state	0.1384	PLATO data
Annual QALY decrement post-stroke state	0.1384	PLATO data

[a]Hazard ratio over standard mortality.

Analysis

Costs and QALYs were calculated over a lifetime time horizon and are presented as mean outcomes per patient. The estimated mean costs and QALYs were combined into an incremental cost-effectiveness ratio (ICER) defined as:

$$\text{ICER} = \frac{(C_1 - C_0)}{(Q_1 - Q_0)} = \frac{\Delta C}{\Delta Q}$$

where C is the estimated mean cost, Q the estimated mean QALYs, and the treatment strategies are indexed 1 for ticagrelor and 0 for clopidogrel.[18]

Uncertainty in the estimated ICERs due to sampling uncertainty in the estimated input parameter values was evaluated by employing probabilistic sensitivity analysis.[19] In the probabilistic analysis, simulation was employed to propagate the uncertainty in single-model inputs through the model so that the uncertainty in the cost-effectiveness results indicates the uncertainty in the decision to implement a treatment strategy rather than the uncertainty surrounding single model inputs.[19] The probability of ticagrelor being cost-effective at different levels of willingness to pay, or threshold values, for a QALY was also assessed.[20]

Several alternative scenarios were analysed to assess uncertainty in the cost-effectiveness results related to model assumptions and data inputs that are not associated with sampling uncertainty. The patient characteristics in the base-case analysis were as observed in the PLATO study in which the clinical and economic evidence were generated.[4] Hence, the base-case analysis was based on the mean age (62 years) and the proportion of women (28.4%) enrolled in the PLATO study. It has been shown that 79% of the patients in Swedish clinical practice who were hospitalized with an index diagnosis of ACS in 2007 met the inclusion criteria in the PLATO study.[21] The impact of age and gender on the cost-effectiveness results was investigated in alternative scenarios. Tentative analyses of some key subgroups (STEMI, NSTEMI, unstable angina, intent for invasive management, and diabetes) were also performed in order to investigate the robustness of the cost-effectiveness results across a broad spectrum of ACS patients.

All statistical analyses were performed using Stata version 7 (Stata Statistical Software: Release 7.0. College Station, TX, USA: Stata Corporation). The decision-analytic model was programmed and analysed in Microsoft® Excel (Microsoft Corporation, Redmond, Washington, DC, USA).

Results

Base-case analysis

The ticagrelor strategy was associated with a QALY gain of 0.1316 at an incremental cost of €362, yielding a cost per QALY gained of €2753 when compared with the strategy of generic clopidogrel (*Table 3*). The cost per life year gained was €2372. The difference in total costs at different time horizons is presented in *Figure 2*. The cost-effectiveness model provides a higher incremental cost with ticagrelor at 12 months compared with the trial-based analysis presented in *Table 1* due the conservative approach of costing the study drugs. Uncertainty around the cost-effectiveness results is demonstrated by plotting the results from the probabilistic sensitivity analysis on the cost-effectiveness plane (*Figure 3*). It can be

Table 3 Results of cost-effectiveness analysis

	Ticagrelor	Clopidogrel	Ticagrelor − clopidogrel	ICER (€)
All ACS				
Costs (€)	35 553	35 191	362	
Life years	11.6056	11.4529	0.1527	2372
QALYs	9.7680	9.6365	0.1316	2753
Unstable angina				
Costs (€)	32 329	31 933	395	
Life years	11.7436	11.6136	0.1300	3039
QALYs	9.7339	9.6257	0.1082	3652
NSTEMI				
Costs (€)	37 802	37 438	363	
Life years	11.4662	11.3102	0.1560	2329
QALYs	9.4180	9.2847	0.1333	2727
STEMI				
Costs (€)	34 915	34 560	355	
Life years	11.7221	11.5753	0.1468	2421
QALYs	10.2120	10.0842	0.1278	2781
Planned invasive management				
Costs (€)	35 471	35 140	331	
Life years	11.7237	11.5917	0.1320	2509
QALYs	10.0255	9·9108	0.1147	2888
Diabetes				
Costs (€)	39 505	39 068	437	
Life years	11.1364	10.9203	0.2161	2023
QALYs	9.0704	8·8877	0.1827	2393

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

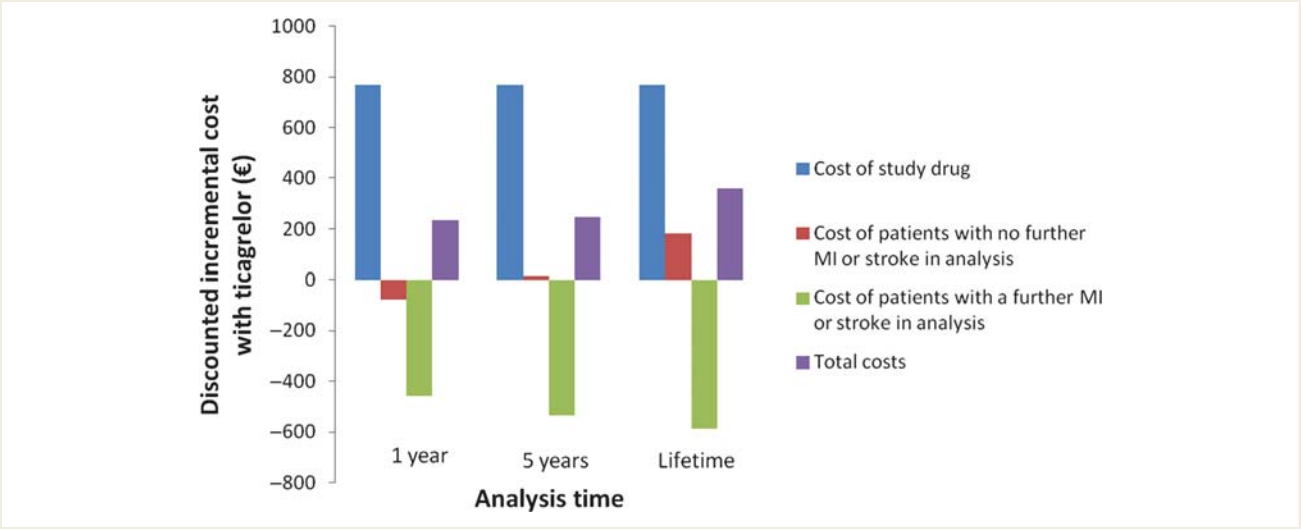

Figure 2 Detailed incremental cost with ticagrelor over time.

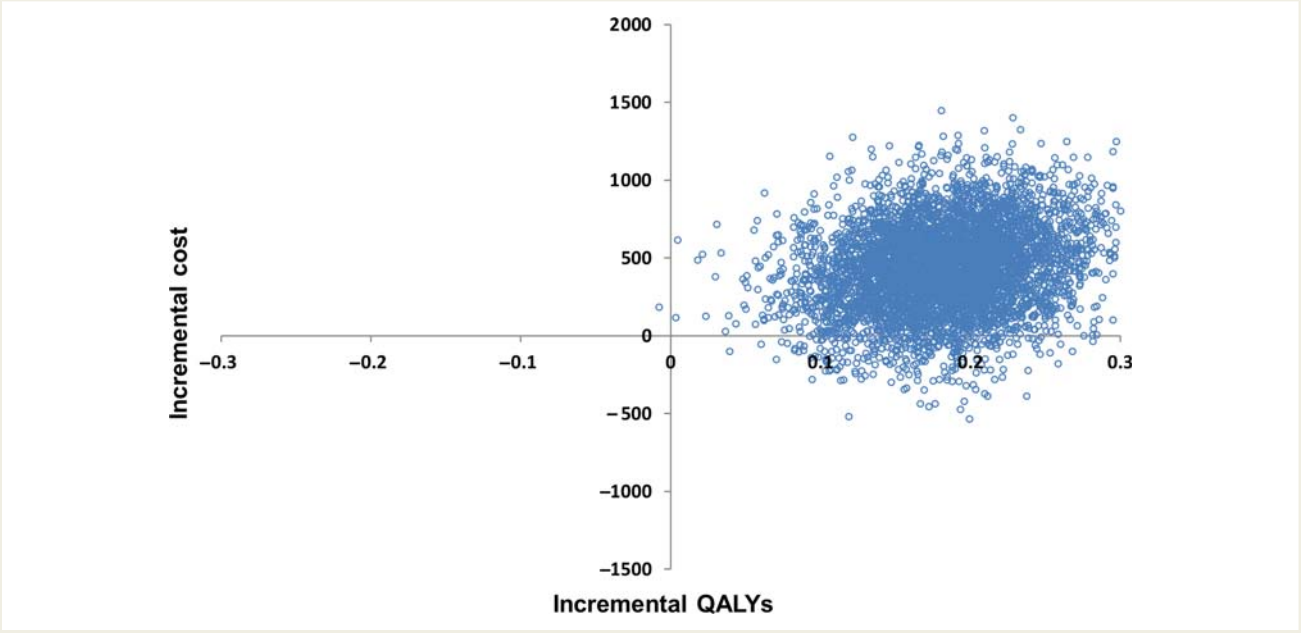

Figure 3 Results of the probabilistic analysis on the cost-effectiveness plane (all ACS). Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.

seen in *Figure 3* that treating ACS patients for 12 months with ticagrelor is associated with a gain in QALYs at an incremental cost in the majority of simulations. The probability of ticagrelor being cost-effective for different willingness to pay, or threshold values, of a QALY is presented in the cost-effectiveness acceptability curves in *Figure 4*. Applying conventional threshold values for a QALY, the probability of ticagrelor being cost-effective appears high.

Although minor variations in the estimated ICERs can be observed, the cost-effectiveness results appear consistent across the investigated subgroups (*Table 3*). Similar to the base-case analysis, the probability of the ticagrelor strategy being cost-effective is high in the investigated subgroups (*Figure 4*). The results of analysing men and women separately at different ages showed that age and gender were not heavily influencing the cost-effectiveness results (see Supplementary material online, *Table S23*).

Sensitivity scenarios

The sensitivity analyses indicate that the results of the base-case analysis are robust to plausible changes in input parameters.

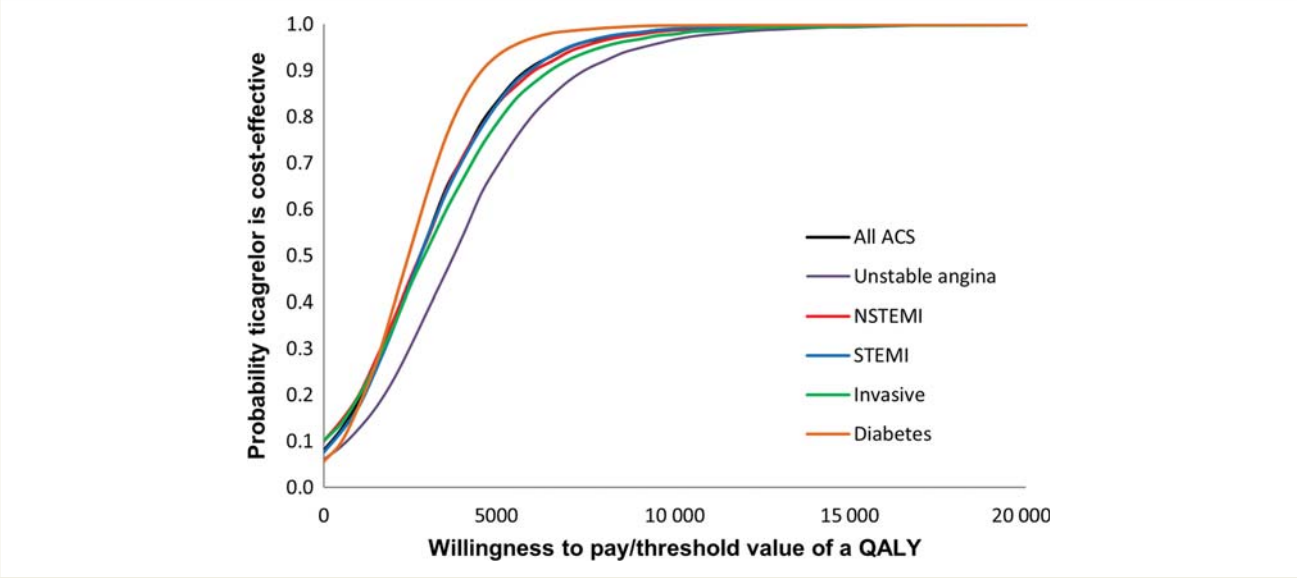

Figure 4 Cost-effectiveness acceptability curves for ticagrelor.

Applying a ticagrelor cost of €3 per day yielded a cost per QALY gained with ticagrelor of €4874. Setting the cost and QALY estimates from PLATO equal for both treatment strategies (i.e. the cost-effectiveness results are driven only by the difference in the rates of clinical events as observed in PLATO) showed a cost per QALY of €5204 with ticagrelor. Combining this analysis with a ticagrelor cost of €3 per day showed a cost per QALY of €7293. Furthermore, the results are robust when altering the parameters in the long-term Markov model and varying the discount rates (see Supplementary material online, *Table S25–S28*). Finally, allowing the treatment effect (including event rates, costs, and quality of life) to vary in the analysed subgroups did not alter the conclusions of the base-case analysis (see Supplementary material online, *Table S29*). The highest cost per QALY with ticagrelor was €6400 (unstable angina) and the lowest €102 (STEMI).

Discussion

The results of the cost-effectiveness analysis show that treatment with ticagrelor is associated with a cost per QALY of ∼€2800 when compared with generic clopidogrel. This finding was consistent across major subgroups, indicating that treating ACS patients with ticagrelor compared with generic clopidogrel will improve quality-adjusted survival at a cost below generally acceptable thresholds for cost-effectiveness.

Although necessary assumptions and external data sources are inevitably employed to estimate long-term cost-effectiveness, the results are primarily driven by the clinical event rates observed in PLATO during the 12 months of therapy. In particular, the reduction in mortality is a key parameter. The long-term quality-adjusted survival in the larger proportion of patients alive at the end of 12-month treatment with ticagrelor when compared with clopidogrel is the major contributor to the estimated gain in QALYs with ticagrelor treatment.

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), it was reported that prasugrel is cost-effective compared with clopidogrel in ACS patients undergoing PCI.[22] In TRITON-TIMI 38, the majority of the estimated gain in life years with prasugrel compared with clopidogrel (0.074 out of the total 0.102 estimated gain in life years) was accrued due to a reduction in MIs. In the present study, the reduction in MIs with ticagrelor treatment compared with clopidogrel was not the major contributor to the long-term gain in life years (and QALYs). Rather, the majority of the gain in life years and QALYs was due to a reduction in mortality. It is difficult to find a detailed explanation for these differences in long-term prognosis after MI. The extrapolation after MI in the TRITON-TIMI 38 trial is based on other data sources where the long-term survival prognosis may have been worse compared with the present study. Possibly, the larger proportion of the reduction in MIs in the TRITON-TIMI 38 trial resulted from a reduction in procedure-related biomarker elevations,[23] which is now known to carry little consequences for long-term survival.[24]

The costs per gained health outcome demonstrated with ticagrelor are comparable with those reported when clopidogrel in addition to ASA was evaluated against ASA alone in non-ST-elevation ACS patients.[25] The economic evaluations of an early invasive treatment strategy compared with a conservative strategy in patients with unstable coronary artery disease showed similar or higher cost-effectiveness ratios compared with the results of the present study.[26–28]

The PLATO study was designed to reflect the current clinical practice in which ticagrelor was administered early in the acute phase of the ACS episode and compared with a flexible loading dose of clopidogrel. This may contribute to the generalizability of the results to a setting where ticagrelor is actually implemented in clinical care. It should be pointed out that the base-case analysis

used unit costs and data for extrapolation primarily from a Swedish setting. Several sensitivity scenarios indicate that the cost-effectiveness results should be valid for other settings as well. When the costs and QALYs of the clinical pathways in the first year of the analysis were set equal for ticagrelor- and clopidogrel-treated patients and at the same time applying a daily ticagrelor cost of €3 per day, the cost per QALY gained with ticagrelor (approximateley €7300) was below generally acceptable thresholds for cost-effectiveness. This analysis represents jurisdictions with a high cost of ticagrelor (€3) and where there is believed to be small differences in non-drug costs between ticagrelor- and clopidogrel-treated patients during the 12 months of therapy. Further sensitivity analyses indicated that the cost-effectiveness results are not sensitive to the estimated costs, quality-of-life and event risks required for extrapolation. The generalizability of the PLATO design to clinical practice together with the fact that the cost-effectiveness results appear robust to data sources that could potentially differ between countries imply that the the cost per QALY gained with ticagrelor should be below conventional thresholds for cost-effectiveness in most European settings.

Limitations

Regarding methodology, it should be pointed out that the current analysis took a health-care perspective, whereas a societal perspective is sometimes preferred for decision-making. The reason for applying a health-care perspective was to stay as close as possible to the PLATO study results and preserve internal validity of the findings. If a societal perspective is adopted, further assumptions regarding the occurrence and magnitude of non-health-care costs would have been required. In this particular case, non-health-care costs associated with cardiovascular events would have been included in the analysis. However, since ticagrelor reduces cardiovascular events, inclusion of further costs due to those events would likely enhance the findings of the present study.

It should also be pointed out that the drug prices applied in the present analysis are dynamic and may change. In the present analysis, a low generic clopidogrel price (€0.06 per day) was used, indicating that the results are not sensitive to a further reduction in the price of generic clopidogrel.

Conclusions

Based on the clinical and health-economic evidence from the PLATO study, treating ACS patients with ticagrelor for 12 months is associated with a cost per QALY below generally accepted thresholds for cost-effectiveness.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: M.J. has received lecture fees from Pfizer. O.H. is an employee of AstraZeneca and has equity ownership in AstraZeneca. L.W. has received research grants from AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, GlaxoSmithKline, and Schering–Plough; honoraria from AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, GlaxoSmithKline, Schering–Plough, and Eli Lilly; consultant fees from Regado Biotechnologies, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, and Eli Lilly; and lecture fees from AstraZeneca, Boehringer Ingelheim, and Eli Lilly. M.H. is an employee of AstraZeneca. E.N. has no conflicts of interest to declare.

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