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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Cost-effectiveness of clopidogrel vs. ticagrelor in patients of 70 years or older with non-ST-elevation acute coronary syndrome

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Objective The POPular AGE trial showed that clopidogrel significantly reduced bleeding risk compared with ticagrelor without any signs of an increase in thrombotic events. The aim of this analysis was to estimate the long-term cost-effectiveness of clopidogrel compared with ticagrelor in these patients aged 70 years or older with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Methods and results A 1-year decision tree based on the POPular AGE trial in combination with a lifelong Markov model was developed to compare clopidogrel with ticagrelor in terms of clinical outcomes, costs, and quality-adjusted life years (QALYs) in elderly patients (above 70 year) with NSTE-ACS. Cost-effectiveness was assessed from a Dutch healthcare system perspective. Events rates and utility data observed in the POPular AGE trial were combined with lifetime projections to evaluate costs and effects for a fictional cohort of 1000 patients. Treatment with clopidogrel instead of ticagrelor led to a cost saving of €1484 575 (€1485 per patient) and a decrease of 10.96 QALYs (0.011 QALY per patient) in the fictional cohort. In an alternative base case with equal distribution over health states in the first year, treatment with clopidogrel led to an increase in QALYs. In all scenario analyses, treatment with clopidogrel was cost-saving.

Conclusion Clopidogrel is a cost-saving alternative to ticagrelor in elderly patients after NSTE-ACS, though regarding overall cost-effectiveness clopidogrel was not superior to ticagrelor, as it resulted in a small negative effect on QALYs. However, based on the results of the alternative base case and clinical outcomes of the POPular AGE trial, clopidogrel could be a reasonable alternative to ticagrelor for elderly NSTE-ACS patients with a higher bleeding risk.

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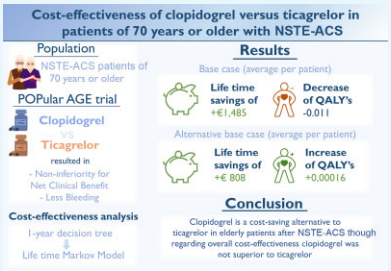
Graphical Abstract



This cost-effectiveness analysis was based on the data of the POPular AGE trial, in which clopidogrel was compared to ticagrelor in patients of 70 years or older with non-ST-elevation acute coronary syndrome (NSTE-ACS). The analysis showed that clopidogrel is a cost-saving alternative to ticagrelor in this population, though regarding overall cost-effectiveness clopidogrel was not superior to ticagrelor, as it resulted in a small negative effect on Qualtiy Adjusted Life Years (QALYs). However, based on the results of the alternative base case and clinical outcomes of the POPular AGE trial, clopidogrel could be a reasonable alternative to ticagrelor for elderly NSTE-ACS patients with a higher bleeding risk.

Keywords NSTE-ACS • Coronary artery disease • $P2Y_{12}$-inhibitor • Elderly • Cost-effectiveness

Introduction

As stated in the ESC guidelines on acute coronary syndromes (ACS), the optimal choice of antiplatelet therapy is the treatment with the optimal balance between ischaemic risk and bleeding risk.[1] Ticagrelor and prasugrel are preferred over clopidogrel due to an associated reduction in thrombotic events, though the guidelines also state that ticagrelor and prasugrel are associated with a higher bleeding risk. The preferred P2Y12 inhibitor for patients with low bleeding risk are ticagrelor or prasugrel, while clopidogrel is preferably used in patients with a higher bleeding risk. This advice for ticagrelor builds on results of the Platelet Inhibition and Patient Outcomes (PLATO) trial, which proved superiority of ticagrelor vs. clopidogrel on thrombotic events.[2]

Age is one of the intrinsic variables that change the balance of ischaemic and bleeding risk, though little research is conducted on the optimal P2Y12 inhibitor in the elderly population. In the PLATO trial the beneficial effect of ticagrelor was not found to be age dependent, however ticagrelor-related bleeding occurred more frequently, especially in the older patients, than did clopidogrel related bleeding.[2] The main aim of the POPular AGE trial was to determine the optimal P2Y12 inhibitor in elderly patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).[3] In this randomized trial the researchers presented clopidogrel as preferable alternative to ticagrelor for elderly patients after NSTE-ACS. Clopidogrel showed a net clinical benefit (NCB) that was non-inferior to ticagrelor with a significantly lower bleeding rate compared with ticagrelor.

Looking at the cost-effectiveness of ticagrelor in the PLATO trial when compared with clopidogrel, ticagrelor was below the accepted thresholds in this trial.[4] As clopidogrel reduced bleeding events in the POPular AGE trial compared with ticagrelor while being non-inferior regarding NCB, we determined the cost-effectiveness of clopidogrel vs. ticagrelor in the elderly after a NSTE-ACS, using the data from the POPular AGE trial.

Methods

Study design

The details on the design, methods, and results of the POPular AGE trial have been published previously.[3,5] In brief, it was an open label, assessor blinded, randomized controlled trial performed in 12 centers in the Netherlands between 2013 and 2018. Patients of 70 years and older were randomized to either treatment with clopidogrel, or to treatment with ticagrelor or prasugrel on top of standard care after NSTE-ACS or unstable angina. Follow-up duration was 12 months. At 1 month and 1 year after hospital admission a questionnaire was sent to all patients, containing questions about therapy adherence, hospital readmissions, and bleedings. The questionnaire also contained the EQ-5D-5L, which was used to objectify the health utilities. All study sites approved the trial and all patients provided written informed consent.

Model overview

The goal of the current analysis was to determine the cost effectiveness of clopidogrel in comparison with ticagrelor in elderly patients with NSTE-ACS. As <95% of the included patients in the ticagrelor/prasugrel arm of the POPular AGE trial were prescribed ticagrelor, we used ticagrelor as a reference in comparison with clopidogrel.

For the cost effectiveness study we developed a two-part decision-analytic model consisting of a 1-year decision tree followed by a Markov-model. The decision tree was used to determine the initial distribution of the cohort over the different Markov states (*Figure 1A*). The Markov model was used to simulate the lifelong costs and effects in both treatment groups (*Figure 1B*). In the decision tree, all patients could experience minor or major bleeding independent of experiencing any of the other events. During the first year patients who experienced a myocardial infarction (MI) or stroke entered corresponding health states, patients who died from other causes as well as cardiovascular causes entered the all-cause death state, all other patients entered the no-event state. After the 1-year decision tree period, patients transitioned between the different Markov states based on the different transition probabilities. The different health states consisted of the no event, non-fatal stroke, non-fatal MI, post-stroke, post-MI, and all-cause death state. These health states reflected the lifetime progression of patients after NSTE-ACS. The post-MI and post-stroke states were so called 'tunnel states', meaning that patients could only remain in each state for one cycle. The Markov-model structure was comparable with previously published and clinically validated models.[4,6,7] The model design allowed for a recurrence of stroke and MI for patients in the (post-)stroke and (post-)MI health states. In this analysis a hypothetical cohort of 1000 patients was used to simulate the progression and transition through the different health states. In the base-case analysis the cut-off of the lifetime horizon was set at the age of 100 years.

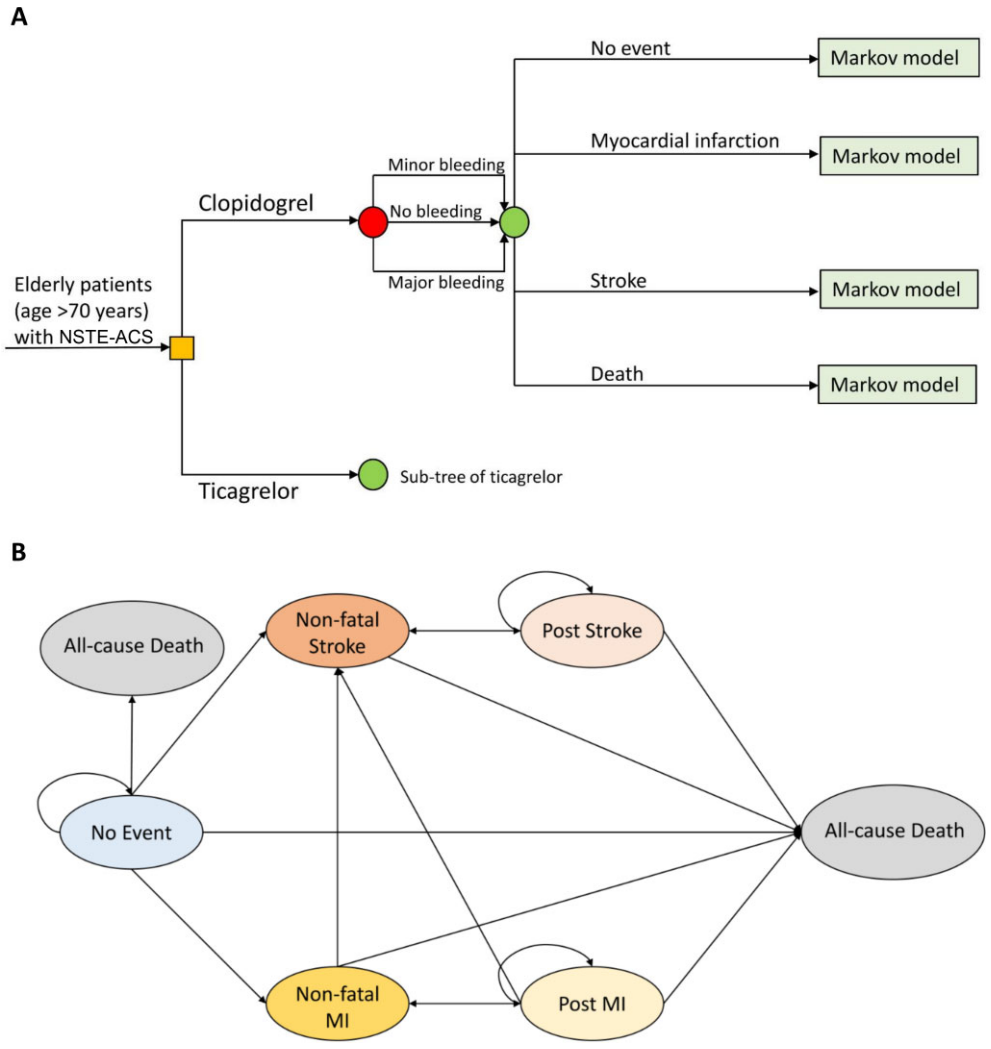


Figure 1 Cost-effectiveness model (*A*): 1-year decision tree based on the POPular AGE trial. (*B*): Long-term Markov model. MI: myocardial infarction, NSTE-ACS: non-ST-elevation myocardial infarction.

Model assumptions

We made the assumption that in patients of both groups, aspirin treatment after the 1-year follow-up was continued, in line with current ESC guidelines.[1,8] Because the use of anticoagulants was similar in both groups, no difference in bleeding rates was expected in the Markov model after the first year.

Another assumption, in line with previously published literature, was that bleeding decreased quality of life (QoL) for only a short period of time.[4] Thus, bleeding was not included as a separate health state in the Markov model. In the base-case analysis we assumed that adverse events, such as dyspnoea and bleeding events, were not prognostic in terms of long-term effects on survival, QoL and costs. Though adverse events that lead to death are accounted for in the analysis of mortality, patients could not develop multiple events during the 1-year trial, they could only experience a recurrent stroke or MI with a minimum interval of 1 year.

Population

For the current model we used the intention-to-treat population from the POPular AGE trial (Supplementary material online, Table S1). The mean age of the trial population was 77 years old, 36% was female and 26% had a prior history of MI. All individuals of the hypothetical cohort were at the age of 77 at the start of the decision tree.

Model input parameters

Transition probabilities

We based the probabilities for the distribution in the 1-year decision tree on the POPular AGE trial results. After the end of the decision tree, patients were assigned to their respective health state in the long-term Markov model. Onwards, a Markov-model with yearly cycles was used to simulate disease progression of elderly patients over their lifetime. Patient in each health state could experience a stroke, MI, or death in each year. The transition probabilities were derived from a previous cost-effectiveness analysis with a similar population.[9] The probabilities for MI and stroke increased with age, based on the yearly increase in risk for MI and stroke, derived from the QRISK3 calculator.[10] We calculated the yearly increase in risk with the following variables: age, gender, blood pressure, weight, and height derived from the POPular AGE trial. Patients in the 'Post-MI' and 'Post-stroke' health states had a higher risk of subsequent events than patients in the 'No-event' health state. The transition probabilities of experiencing subsequent events were derived by multiplying the baseline probabilities by the relative risk factors (Table 1). The mortality rate increased with age and was based on age specific data from Dutch population lifetables.[11] Patients could not transition from the post-stroke state to the post-MI state, since the post-stroke state had a higher subsequent event risk and

Table 1 Model input parameters

Parameters	Base-case value	Range	Distribution	Source
Probabilities (decision tree)				
Ticagrelor treatment				
Minor bleeding	0,147	0,111–0,184	Beta	Trial
Major bleeding	0,106	0,079–0,132	Beta	Trial
MI	0,074	0,055–0,092	Beta	Trial
Stroke	0,020	0,015–0,025	Beta	Trial
All-cause death	0,068	0051–0,085	Beta	Trial
Clopidogrel treatment				
Minor bleeding	0,114	0,086–0,143	Beta	Trial
Major bleeding	0,076	0,057–0,095	Beta	Trial
Myocardial infarction	0,074	0,056–0,093	Beta	Trial
Stroke	0,010	0,008–0,013	Beta	Trial
All-cause death	0,074	0,056–0,093	Beta	Trial
Probabilities (Markov model)[a]				
Annual risk from ' No-event' to ' MI'	0,040	0,030–0,050	Beta	12
Annual risk from ' No-event' to ' Stroke'	0,020	0,015–0,025	Beta	12
Annual risk from ' No-event' to 'Non-CV death'	Age specific mortality rate		Beta	11
Increased risk of a subsequent event after having an event	2,0	1,0–4,0	LOGNORMAL	13
Increased risk of death in 'No-event'	2,0	1,5–2,5	LOGNORMAL	4
Increased risk of death in 'Non-fatal MI'	6,0	4,5–7,5	LOGNORMAL	4
Increased risk of death in 'post MI'	3,0	2,25–3,75	LOGNORMAL	4
Increased risk of death in 'Non-fatal stroke'	7,43	5,57–9,29	LOGNORMAL	4
Increased risk of death in 'post stroke'	3,0	2,25–3,75	LOGNORMAL	4
Age dependent increase of annual MI risk	4,5%	3,4–5,7%	LOGNORMAL	10
Age dependent increase of annual stroke risk	2,3%	1,7–2,8%	LOGNORMAL	10
Costs (in euros)[b]				
1 year clopidogrel treatment	21,90	16,43–27,38	Gamma	14
1 year ticagrelor treatment	788,40	591,30–985,50	Gamma	15
1 year prasugrel treatment	525,60	394,20–657,00	Gamma	16
Minor bleeding	321,03	195,26–447,89	Gamma	17
Major bleeding	5601,92	2856,98–8346,87	Gamma	18
MI	5734,33	2924,51–8544,22	Gamma	19
Post-MI	2620,61	2445,42–2755,95	Gamma	20
Stroke	29166,05	18985,97 –40088,00	Gamma	20
Post-stroke	11932,74	7979,54–15078,59	Gamma	20
All-cause death	3558,19	3109,12–3353,35	Gamma	21
Utilities[c]				
No event	0,76	0,74–0,77	Beta	Trial
Myocardial infarction	0,69	0,67–0,70	Beta	Trial
Post-MI	0,69	0,67–0,70	Beta	Trial
Stroke	0,62	0,60–0,64	Beta	4
Post-stroke	0,62	0,60–0,64	Beta	4
Death	0	NA	NA	
Minor bleeding (disutility 2 days)	0,06	0,03–0,09	Beta	22
Major bleeding (disutility 14 days)	0,1385	0,11–0,17	Beta	22

Table 1. Cost-effectiveness model input parameters. CI, confidence interval; CV, cardiovascular; NA, not applicable; MI, myocardial infarction
[a] Range indicating min/max as provided by paper. If min/max was unavailable, ranges where calculated with 25% of the base-case value.
[b] Range is based on 95% CI. If 95% CI was unavailable, ranges were calculated with standard error of 25% of the mean
[c] Range is based on 95% CI

was more costly than the MI health state. All model inputs are presented in Table 1.[12–16,18–21]

Costs

The cost-effectiveness analysis was performed from the healthcare perspective. Costs were inflated to 2021 using the consumer price index inflation from the Dutch Central Bureau of Statistics (Table 1).[23] All costs were based on the Dutch healthcare system and obtained from literature or Dutch governmental agencies. They consisted of treatment costs of the different antiplatelet drugs and costs associated with the cardiovascular events (minor bleeding, major bleeding, non-fatal MI, non-fatal stroke, post-MI, post-stroke, and death). The assumption was made that patients in the decision tree used the adjudicated antiplatelet medication during the whole year. We based the costs of treatment with $P2Y_{12}$-inhibitors on the adjudicated treatment in the POPular Age trial and discounted these using an annual rate of 4% in accordance with existing Dutch guidelines for conducting health-economic evaluations.[24]

Health utilities

Health utilities were measured in QALYs and derived from the POPular AGE trial (using the EQ-5D-5L questionnaire) if applicable. The health utilities were dependent on the different events that patients experienced. In case data were not available from the trial, utility estimates in similar populations were derived from literature (Table 1). During the first year, bleeding led to a temporary disutility, based on previously published literature.[22] Adverse events caused by antiplatelet therapy, such as dyspnoea or bruises, were not prognostic in terms of long-term (beyond one year) effect on QoL and therefore we did not include these events in the calculation of the utilities for the base-case values.[4]

Outcomes

The outcome measures in this study were costs, QALYs, incremental cost-effectiveness ratios (ICERs) presented in euros per QALY gained and net monetary benefit (NMB). If both incremental costs and QALYs were positive the ICER would be calculated. If either incremental costs or the incremental QALYs were negative the intervention dominated the comparator (i.e. decreased costs and added QALYs) or was dominated by the comparator (i.e. added costs and decreased QALYs). If both incremental costs and incremental QALYs were negative, the NMB would be calculated, as the resulting ICER was not informative.[25] In our analysis a positive NMB indicated that the intervention treatment (clopidogrel) is cost-effective compared with the standard treatment (ticagrelor) at the given willingness-to-pay threshold. A reference value of €20.000/QALY was chosen, because the overall burden of disease was estimated to be low as the treatment was for secondary prevention.[26]

Sensitivity and scenario analysis

We based the base-case analysis on the model inputs as shown in Table 1. Univariate deterministic (DSA) and probabilistic sensitivity analyses (PSA) were performed to accommodate for uncertainties in the model. The range of each parameter was based on the 95% confidence interval (CI) or on a standard error of the mean of 25%. To assess the influence of individual parameters, each of the parameters were varied one by one over the 95% CI or over the fixed range of +/- 25% in an univariate DSA. The PSA was performed using a Monte Carlo simulation with 10.000 iterations, in which all parameters were randomly and simultaneously varied over their 95% CI or fixed ranges. The different distributions used for each parameter are mentioned in table 1. In the base case model we used the exact distribution of patients over the different health states at the end of year 1 of the POPular AGE trial. As the POPular AGE trial showed no statistically significant difference between both groups regarding the incidence of MI, stroke or death [both cardiovascular (CV) death and non-CV death], we performed an alternative base case scenario in which the distribution of the cohort over the MI, stroke, and all-cause death state were equal.

Scenario analyses were performed to assess robustness of the results in different time horizons (scenario 1) and to mimic availability of generic variants for ticagrelor and prasugrel by equalising all prices (scenario 2). The POPular AGE trial showed, as seen in other studies, that many patients discontinued ticagrelor due to side-effects (often dyspnoea), providing a rationale for the hypothesis that that the QoL in the ticagrelor treatment arm could be lower than in the clopidogrel arm.[27–29] Therefore, a third scenario analysis would be performed in case of a statistically significant difference in utilities between patients treated with clopidogrel and ticagrelor based on the questionnaires. The fourth scenario analysis accounted for a prolonged duration of disutility of bleeding, as both minor and major bleeding have been associated with increased morbidity and lower QoL for a prolonged time.[30–32]

Model validation

To check the internal validity of the model, two independent researchers altered all input values in a step-by-step manner. They checked whether setting input values to unrealistic values (e.g. zero or very large costs or utilities) provided results that were logical. This internal validity check demonstrated no major flaws in the model. The external validity of the model was checked by comparing the results with literature (Supplementary Appendix).

Results

Base-case and alternative base case analyses

In a cohort of 1000 elderly patients with NSTE-ACS based on the POPular AGE trial, antiplatelet therapy with clopidogrel instead of ticagrelor resulted in a decrease of 10.96 QALYs, while saving €1484 575. This translates to a reduction of 0.011 QALYs and €1485 saved per patient. The NMB of clopidogrel was €1265. In the alternative base case scenario clopidogrel dominated ticagrelor due to cost savings (€808 per patient) and slightly higher QALYs per patient (0,00 017) due to the lower bleeding rates. The results of the univariate DSA are depicted in a tornado diagram displayed in *figure 2*. This analysis showed that distribution over the different health states (all-cause death, MI, and stroke) had the largest impact on the output of our model. Results of the PSA are plotted in a cost-effectiveness plane (*Figure 3*). Treatment with clopidogrel was cost saving in each iteration (100%) of the Monte Carlo simulation, whereas it increased QALYs in 44% of the iterations.

Scenario analyses

Table 2 shows the results of the different scenario analyses. In scenario 1 varying the time horizon did not change the conclusions regarding cost-effectiveness. The difference in QALYs gained was lower with a time horizon of 1 and 5 years, but after 10 years the results of the scenario analysis were comparable with the base-case analysis. Treatment with clopidogrel remained cost-saving in scenario 2, where prices for all $P2Y_{12}$-inhibitors were equal. As there was a statistical difference in utilities between clopidogrel and ticagrelor in patients who did not experience an event, scenario 3 was performed. In this scenario 46.67 QALYs were gained, while saving €1484 575 with clopidogrel compared with ticagrelor. In this scenario, in which our own observed QoL data for the utilities in the 'no event' group were used, clopidogrel dominated ticagrelor. In the fourth scenario the period of the disutility of bleeding was prolonged. This reduced the decrease in QALYs associated with clopidogrel from 10.96 (base case) to 8.23 (182 days) and 5.32 (365 days), in line with expectations as clopidogrel causes fewer bleeding events.

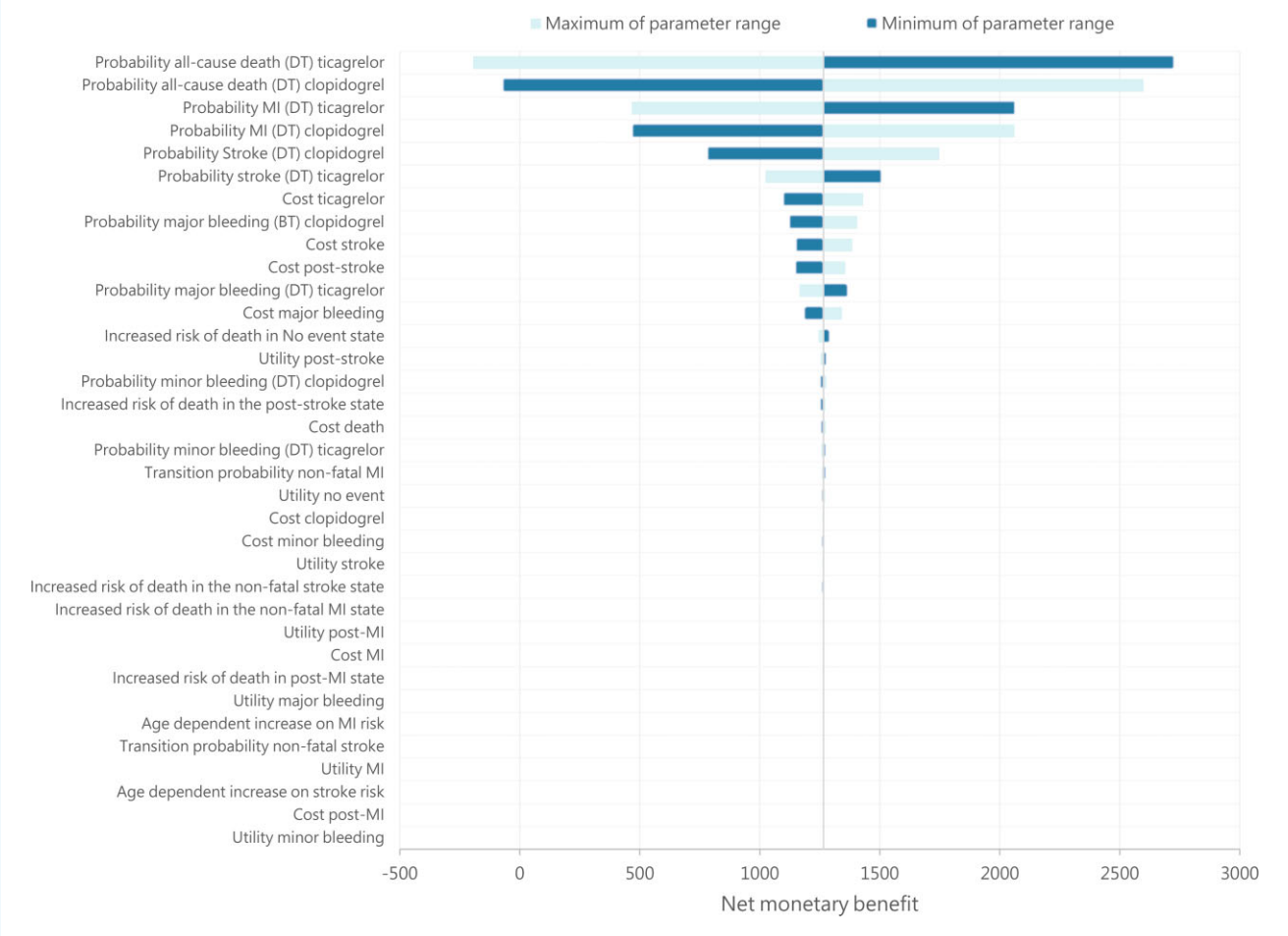


Figure 2 Deterministic sensitivity analysis. Figure 2. Tornado-plot showing the net monetary benefit (NMB). In the deterministic sensitivity analysis (DSA) the minimum and maximum value of the parameter range of every individual parameter are alternately put into the model. The results of the DSA depict the influence on the NMB when the minimum or maximum value of the individual parameter is used, while all other parameters stay the same. The base case value of the NBM was 1265. DT: decision tree, MI: myocardial infarction.

Discussion

This cost-effectiveness analysis of the POPular AGE trial showed that clopidogrel is a cost-saving alternative to ticagrelor in elderly patients with a NSTE-ACS. This finding was consistent across different sensitivity and scenario analyses. Clopidogrel was associated with a small decrease in QALYs compared with ticagrelor in the base case analysis. To put this in perspective, the small decrease in QALYs translates to a gain of 4 days in good health. In *figure 3*, the 44% of iterations falling in the southeast quadrant indicate clopidogrel would dominate (higher QALYs, lower costs), whereas the 56% of iterations in the southwest quadrant indicate that treatment with clopidogrel resulted in lower costs but also a decrease in QALY's. The implication of this finding is difficult to establish because the favorability of this scenario should be based on willingness-to-accept thresholds, for which guidance is currently lacking. With cost savings of €1483 per 0.011 QALY lost, the ratio is around €135 000 per lost QALY. This is substantially higher than normal WTP thresholds, indicating that the QALY loss might be acceptable, but without any guidance on willingness-to-accept thresholds it is difficult to come to any conclusions besides the fact that the lost QALYs are on average very small even in the most conservative scenario and therefore the use of clopidogrel seems a reasonable alternative to ticagrelor in the elderly patient after an NSTE-ACS.[33] In addition, the alternative base case analysis showed a small increase in QALYs with clopidogrel compared with ticagrelor.

The results of the base-case analysis are predominantly driven by the observed event rates of all-cause death, myocardial infarction, and stroke in the POPular AGE trial (*figure* 2). To stay on the conservative side of the spectrum, we stayed as close as possible to the POPular AGE trial in this base case analysis, by using the exact observed incidences of thrombotic events, which differed between both groups in the POPular AGE. All-cause mortality was numerically lower in the ticagrelor group (37/500 in the clopidogrel and 34/502 in the ticagrelor group). Consequently, after 12 months the proportion of patients alive was larger in the ticagrelor group than in the clopidogrel group. In our analysis this difference in mortality was the major contributor to the estimated higher QALYs with ticagrelor treatment, since death has a much greater impact on QALYs than the occurrence of a cardiovascular event.

In the POPular AGE trial the NCB met non-inferiority and although the study was not powered to examine differences for the thrombotic endpoints or mortality, analysis of the secondary endpoints regarding the individual thrombotic outcomes suggested that the incidence of thrombotic events in both treatment arms did not differ. So it is plausible that the results of the alternative base case, in which there were no differences in health states at the start of the Markov model, are closer

Figure 3 Probabilistic sensitivity analysis. Figure 3. Results of the probabilistic sensitivity analysis (PSA) on the cost-effectiveness plane. The scatterplot depicts results of the Monte Carlo analysis (10 000 iterations) per patient when all model inputs are randomly varied according to their uncertainty distributions. In the figure both the mean PSA value and the base-case outcomes are depicted. QALY: quality-adjusted life year.

to daily practice. In this alternative base case clopidogrel dominated ticagrelor (being cost-saving as well as providing higher QALYs), which was due to the reduction in bleedings in the clopidogrel arm. The gain in QALYs is relatively small due to the limited impact of short-term reductions in QoL of bleeding events (2–14 days) as compared to the quality-adjusted life years accrued over a lifetime.

The DSA showed that the probability for all-cause death had the largest impact on the results of the model, leading to large differences on the NMB in both treatment arms. The latter was also the case for the probability for MI and stroke. This can be explained by the fact that the minimum and maximum range has a greater impact on the model results as the probability gets lower. The larger variability in the DSA due to treatment costs can be explained by the higher costs of ticagrelor treatment compared with clopidogrel. Changes in costs of events and utilities had little impact on the results of the model, presumably because the values of these parameters did not differ between both groups.

In scenario 2 the daily costs of ticagrelor were identical to clopidogrel to account for generic variants of ticagrelor in the future. Treatment of clopidogrel remained cost-saving, which was mainly driven by higher costs due to more bleeding and stroke events in the ticagrelor group. Scenario 3 was performed knowing that ticagrelor is often discontinued due to side-effects, of which dyspnoea is the most common.[3,28,29] In this scenario, clopidogrel dominated ticagrelor, as it was cost-saving and led to an increase in QALYs. We conducted scenario 4 as it is likely that bleeding can lead to a longer disutility than 2 or 14 days.[30,31] In a sub-analysis of the TRANSLATE-ACS trial even minor bleeding events were associated with worse health-state utilities and patient reported QoL.[31] Minor bleeding during one year follow-up has also been associated to a lower QoL, measured at 1, 6, and 12 months.[32] Due to the higher bleeding incidence in the ticagrelor arm, the incremental QALYs increased in this scenario, though remaining favourable for ticagrelor. In accordance, in the POPular AGE trial the average utility at 12 months was lower in patients who experienced a bleeding event at any time during the year follow-up, further substantiating the hypothesis that bleeding can reduce QoL over a longer period of time.

Limitations

Besides the fact that to estimate long-term cost-effectiveness, making assumptions and using other data sources is inevitable, this analysis is subject to several limitations. First, the POPular AGE trial had a high discontinuation rate, especially in the ticagrelor group. We assume this hardly affects the validity of our analysis, as the consequences of the discontinuation rate are incorporated in the incidence of the events during follow-up, which makes our results closer to clinical practice. However, the higher discontinuation may impact cost-savings, as most patients switched to clopidogrel or discontinued ticagrelor, reducing costs in the ticagrelor arm. As the median duration of exposure to the study drug was 324 days in the ticagrelor group, the impact of the high discontinuation rate is expected to be low. In addition, in scenario 2 clopidogrel still led to cost-savings. Secondly, the POPular AGE trial was not powered to detect a difference in thrombotic events, affecting the interpretation of these results for our analysis. Thirdly, in our analysis we mainly focused on the comparison between ticagrelor and clopidogrel, as <5% of the patients in the ticagrelor or prasugrel arm were prescribed prasugrel. Consequently our results are primarily applicable to treatment with clopidogrel and ticagrelor. Fourthly, although we based the analysis on the Dutch healthcare system, the transition probabilities for stroke and MI in the Markov model were based on a similar population in the United Kingdom, since no comparable data were available from a Dutch population. [34] Because in both countries the quality of the health care systems and the cardiovascular risk profile are comparable, we assumed this data to be representative for our analysis. Lastly, this analysis was performed using a health-care perspective, whereas a societal perspective is sometimes preferred. In a societal perspective further assumptions regarding non-healthcare costs are made, of which loss of work productivity due to disease is an important component. However, as the loss of work productivity due to disease is negligible in the elderly population, since patients of 75 years or older have a labour market participation of <1%, incorporating non-healthcare costs were not expected to affect the results of our analysis.[17]

Table 2 Lifetime cost-effectiveness results for base-case and scenario analyses.

	Cost Clopidogrel (€)	Cost Ticagrelor (€)	ΔCost (€)	QALY's Clopidogrel	QALY's Ticagrelor	ΔQALY	ICER[a] (€/QALY)
Base case	€12.387.434	€13.872.009	−€1.484.575	4064,15	4075,10	−10,96	NA
Alternative base case	€12.726.115	€13.534.125	−€808.010	4069,72	4069,56	0,16	Dominating
Scenario analyses							
Scenario 1 Different time horizons							
1 year	€2.458.744	€3.651.999	−€1.193.255	1313,40	1318,57	−5,18	NA
5 years	€7.813.162	€9.218.691	−€1.405.529	3087,09	3096,86	−9,77	NA
10 years	€11.710.939	€13.190.107	−€1.479.168	3948,06	3959,07	−11,01	NA
20 years	€12.387.312	€13.871.895	−€1.484.583	4064,14	4075,10	−10,96	NA
Scenario 2							
Identical prices for $P2Y_{12}$ inhibitors	€12.356.533	€13.197.007	−€840.474	4064,15	4075,10	−10,96	NA
Scenario 3							
Different health utilities in the clopidogrel and ticagrelor arm	€12.387.434	€13.872.009	−-€1.484.575	4081,02	4034,35	46,67	Dominating
Scenario 4 Prolonged duration of bleeding disutility							
182 days[b]	€12.387.434	€13.872.009	−€1.484.575	4056,54	4064,76	−8,23	NA
365 days[b]	€12.387.434	€13.872.009	−€1.484.575	4048,47	4053,80	−5,32	NA

Table 2. Cost-effectiveness analysis outcomes of the base-case and sensitivity analyses based on the POPular AGE trial. The results in the table are based on the full fictional cohort of 1000 patients.

[a] When both the incremental costs and QALY's were negative, the ICER could not be calculated.

[b] Disutility for both minor and major PLATO bleeding.

ICER, incremental cost-effectiveness ratio; NA, not applicable; QALY, quality-adjusted life year.

Conclusion

Clopidogrel is a cost saving alternative to ticagrelor in elderly patients with a NSTE-ACS, though regarding overall cost-effectiveness clopidogrel was not superior to ticagrelor, as it resulted in a small negative effect on QALYs. However, based on the results of the alternative base case and clinical outcomes of the POPular AGE trial, clopidogrel could be a reasonable alternative to ticagrelor for elderly NSTE-ACS patients with a higher bleeding risk.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data that support the findings of this study are available from the corresponding author, R.V., upon reasonable request.

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