ORIGINAL ARTICLE

Cost-effectiveness of antiplatelet drugs after percutaneous coronary intervention

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Aims	Clopidogrel has, for long time, been accepted as the standard treatment for patients who have undergone a percutaneous coronary intervention (PCI). The introduction of prasugrel—and more recently, ticagrelor—has introduced a decision-making problem for clinicians and governments worldwide: to use the cheaper clopidogrel or the more effective, and also more expensive prasugrel or ticagrelor. We aim to give helpful contributions to this debate by analysing the cost-effectiveness of clopidogrel, prasugrel, and ticagrelor compared with each other.
Methods and results	We modified a previously developed Markov model of cardiac disease progression. In the model, we followed up cohorts of patients who have recently had a PCI until 100 years or death. Possible events are revascularization, bleeding, acute myocardial infarction, and death. Our analysis shows that ticagrelor is cost-effective in 77% of simulations at an incremental cost-effectiveness ratio of €7700 compared with clopidogrel. Ticagrelor was also cost-effective against prasugrel at a cost-effectiveness ratio of €7800. Given a Norwegian cost-effectiveness threshold of €70 000, both comparisons appear to be clearly cost-effective in favour of ticagrelor.
Conclusion	Ticagrelor is cost-effective compared with both clopidogrel and prasugrel for patients who have undergone a PCI.
Keywords	Percutaneous coronary intervention • Economic evaluation • Cost-effectiveness • Antiplatelets

Introduction

Each year, >10 000 Norwegians have a percutaneous coronary intervention (PCI) after either a myocardial infarction (MI) or angina. Antiplatelet therapy with 12 months use of the antiplatelet drug clopidogrel has, for decades, been considered the standard treatment after a PCI in order to prevent MI and death. Recently, two new antiplatelet drugs, prasugrel and ticagrelor, have been introduced. Both of these two drugs have proved to be efficacious with regards to, for example, MIs, but some concerns have also been raised with regards to increased risk of bleeding.[1,2] Hence, there is uncertainty as to the risk−benefit trade-off. Prices of the drugs are also an issue. Clopidogrel is no longer patented and prices have decreased considerably. The more newly developed prasugrel and ticagrelor are considerably more expensive; for instance, these cost >20 times as much in the UK (http://www.nice.org.uk/guidance/ta236/resources/ta236-acute-coronary-syndromes-ticagrelor-costing-template),

and in Norway, these are >4 times as expensive (http://legemiddelverket.no/Blaa_resept_og_pris/Helseoekonomiske%20rapporter/Documents/2012-2011/Brilique_Akutt-Koronarsyndrom_2011.pdf). Similar differences are seen all across Europe.

In 2014, >36 000 patients in Norway used either clopidogrel, prasugrel, or ticagrelor. Of these, 71% used clopidogrel, 24% used ticagrelor, and 5% used prasugrel.[3] Hence, it seems that clopidogrel still is the preferred antiplatelet therapy among doctors.

Given the risk−benefit trade-off generated by the fact that each of the three available drugs are significantly better than at least one of the other drugs, and considerable cost difference, there is great uncertainty with regards to which of the three antiplatelet drugs offer the greatest value for money. Although some cost-effectiveness analyses have been conducted comparing each of the new drugs with clopidogrel,[4] no health economic evaluation has compared the cost-effectiveness of all these drugs with each other.

Our objective was to compare the cost-effectiveness of different antiplatelet drugs for patients who have undergone PCI.

Methods

We modified a previously developed probabilistic Markov model (MOCCA—Model Of Cost-effectiveness of CArdiac Disease) to fit the current research question.[5] The model applies a lifelong healthcare payer perspective after a PCI operation, including risk of MI, major bleeding, new revascularization (PCI or coronary artery bypass graft), and death (*Figure 1*).

The model was built to model half-year cycles from the age of 50 onwards to 105 years old. In our base case analysis, we analysed 60 year olds until aged 100, hence 80 cycles. Within-cycle correction was done using Simpsons 1/3rd methods, as recommended by Elbasha and Chhatwal.[6]

Efficacy data of prasugrel and ticagrelor compared with clopidogrel were based on the two licensing phase III randomized controlled trials including 13 608 and 18 624 participants, respectively.[1,2] Outcomes included significant reductions in risk of MI for both drugs, increased risk of bleeding and reduced risk of revascularization with prasugrel, and

reduced overall mortality with ticagrelor (*Table 1*). Due to different reporting in trials, effect on revascularization in our model was based on data on urgent target vessel revascularization from TRITON Thrombolysis in Myocardial Infarction Study Group (TIMI) 38 and recurrent ischaemia from PLATO invasive, as has also been done in a meta-analysis of these drugs.[7]

Costs of all three antiplatelet drugs are based on current prices from the Norwegian Medicines Agency:[8] €207 per year for clopidogrel (300 mg loading dose, thereafter 75 mg per day), €509 per year for prasugrel (60 mg loading dose, thereafter 10 mg per day), and €817 per year for ticagrelor (180 mg loading dose, thereafter 90 mg per day). Costs of treatment [acute myocardial infarction (AMI), revascularization and bleeding] were based on items from the original publication,[5] but all costs of services were based on fees for 2015 (*Table A2*). We have chosen a Norwegian healthcare sector perspective for our analyses, as recently suggested in a Norwegian white paper on prioritizing.[9] Costs are converted into Euros (€) using average rate of 2014 (€1 = NOK 8.35).

Effectiveness is in our base case analysis measured as life years gained (LYG), which is one of the two acceptable measures in Norwegian cost-effectiveness analyses.[10] The other acceptable measure of effect in Norwegian health economic evaluations is quality-adjusted life years (QALYs). All weights were based on EQ-5D data, health states as derived in a Norwegian study by Pettersen *et al.*[11] and events as used in a previous Norwegian economic evaluation.[12]

Incremental cost-effectiveness ratios (ICERs) are regarded as cost-effective if below NOK 588 000 (€70 000) per LYG or QALYs, as recommended by the Norwegian Directorate of Health.[13] Recently, it was suggested in a white paper that the Norwegian threshold should rather be NOK 250 000 (€30 000) to better be in line with the opportunity cost.[9] We compared our results also with this suggested threshold. All costs and health benefits were discounted at 4% as recommended in Norwegian guidelines for health economic evaluations.[10]

We incorporated probability distributions on all parameters in the model that were considered uncertain (*Table 1, A1,* and *A2*). Choice of distribution types was based largely on knowledge of how data of different types are usually distributed, as recommended by Briggs *et al.*[14] Uncertainty within each distribution was based on confidence intervals, where available. All results shown are based on probabilistic analyses, meaning that we sampled 10 000 times from all probability distributions in the model and calculated means of model outcomes based on these samples.

When modelling disease progression with different health states, there is often a possibility of double counting. In our model, and in
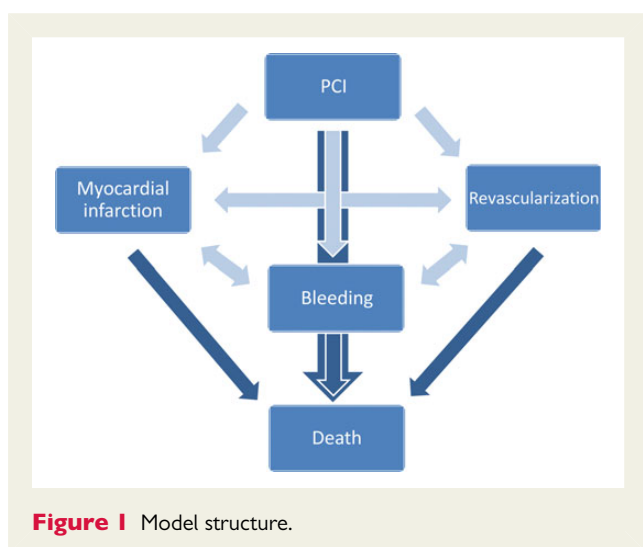

Figure 1 Model structure.

Table 1 Effect of new drugs compared with clopidogrel

	Hazard ratio	Confidence interval	Distribution	Source
Prasugrel vs. clopidogrel				
Urgent target vessel revascularization	0.66	0.54–0.81	Log-normal (−0.4155, 0.1034)	TRITON TIMI-38[1]
Death from cardiovascular causes	0.89	0.70–1.12	Log-normal (−0.1165, 0.1199)	TRITON TIMI-38[1]
Non-fatal MI	0.76	0.67–0.85	Log-normal (−0.2744, 0.0607)	TRITON TIMI-38[1]
Major TIMI bleeding	1.32	1.03–1.68	Log-normal (0.2776, 0.1248)	TRITON TIMI-38[1]
Ticagrelor vs. clopidogrel				
Recurrent ischaemia	0.93	0.82–1.05	Log-normal (−0.0726, 0.0631)	PLATO invasive[2]
Death from cardiovascular causes	0.79	0.69–0.91	Log-normal (−0.2357, 0.0706)	PLATO invasive[2]
Non-fatal MI	0.84	0.75–0.95	Log-normal (−0.1744, 0.0603)	PLATO invasive[2]
Major TIMI bleeding	1.03	0.93–1.15	Log-normal (0.0296, 0.0542)	PLATO invasive[2]

Table 2 Lifetime costs and effects (incrementals compared with strategy above)

	Lifetime cost (€)	Incremental cost (€)	Life expectancy	Life years gained	Incremental cost-effectiveness ratio
Clopidogrel	19 929		11.96		
Prasugrel	22 649	2720	12.32	0.36	7505 €/LYG
Ticagrelor	25 612	2963	12.70	0.38	7820 €/LYG

the trials we based the difference in effectiveness on, there are possibilities that patients were classified as having both MI and revascularization or both MI and death. In addition to our base case simulation, we therefore performed scenario analyses with effect on fewer outcomes in the model. We did analyses eliminating either effect on revascularization or mortality or both, due to the possibility of overlap between these outcomes and AMI.

Risk of revascularization and bleeding was assumed to be the same in the first half year and in later half-year periods due to lack of data. Since these risks are likely to be lower in later half-year periods after the initial PCI, we performed separate analyses with these probabilities being 0 in all years post the first year.

We also conducted analyses where the model was run for only 5 years to explore whether results differ between a model based mostly on data (5 years) and a model based on assumptions with regards to extrapolation.

To explore whether cost-effectiveness would be different across ages, we also performed simulations for 50-, 70- and 80-year olds.

We performed one deterministic sensitivity analysis reducing the prices of the drugs not considered cost-effective in our base case analysis, to see how low these prices had to be for the drugs to be cost-effective.

Results

Sixty-year-old patients undergoing PCI had a life expectancy of 11.96 years (discounted) if treated with clopidogrel the first year. The treatment with prasugrel increased the life expectancy to 12.32 years, while ticagrelor resulted in 12.70 years. Prasugrel was cost-effective compared with clopidogrel, and ticagrelor was cost-effective compared with both prasugrel and clopidogrel (*Table 2*).

Monte Carlo simulations show that at an assumed Norwegian cost-effectiveness threshold of EUR 70 000 per life year gained, 76, 24, and 0.1% of simulations indicated that ticagrelor, prasugrel, and clopidogrel were cost-effective, respectively (*Figure 2*). If we rather compared with the suggested threshold of EUR 30 000, these percentages would be 72, 27, and 0.4%. The cost-effectiveness acceptability frontier gives that clopidogrel is cost-effective for cost-effectiveness thresholds lower than €7505 per LYG, prasugrel is cost-effective for threshold between €7505 per LYG and €7820 per LYG, and that ticagrelor is cost-effective for threshold above €7820 per LYG (*Figure 3*).

When including only efficacy data on MI and bleeding, *prasugrel* dominated the other two drugs with both lowest costs and highest effectiveness. When including efficacy on revascularization as well as bleeding and MI, *clopidogrel* was the most effective and least costly. When including efficacy only on death, bleeding, and MI, ticagrelor was the most effective and cost-effective. When excluding the
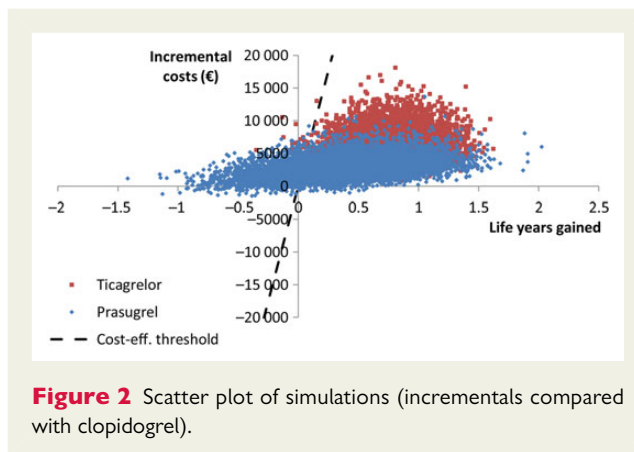

Figure 2 Scatter plot of simulations (incrementals compared with clopidogrel).
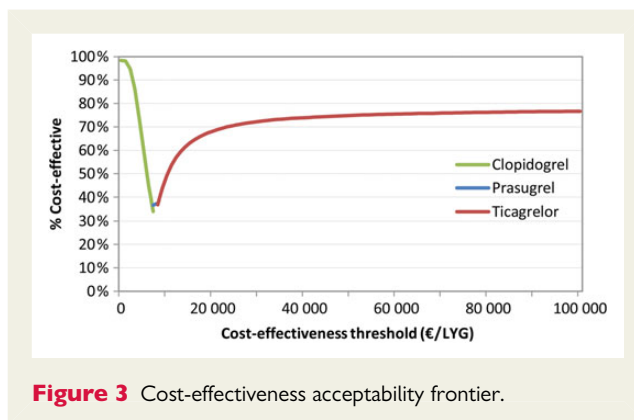

Figure 3 Cost-effectiveness acceptability frontier.

probability of bleeding and revascularization after the first year, analyses gave that ticagrelor was the most effective and cost-effective.

In analyses of expected value of perfect information on parameters, we found that the relative effect on death of ticagrelor and prasugrel compared with clopidogrel was the only parameter with any value of gathering new evidence. The per person expected value of partial perfect information was €3220 and €580 for prasugrel and ticagrelor, respectively, indicating that for each person in Norway who experience a PCI, up to €3220 could be used to reduce the decision uncertainty, if this was completely removed by the research.

In sensitivity analyses without discounting health, life expectancy with clopidogrel, prasugrel, and ticagrelor was 17.52, 18.23, and 19.05, respectively. Applying discounted costs to these life expectancies gave ICERs of 3840 €/LYG of prasugrel

compared with clopidogrel and 3620 €/LYG of ticagrelor compared with prasugrel.

When incorporating health-related quality of life in the model, expected discounted remaining QALYs were 9.54, 9.82, and 10.12 for clopidogrel, prasugrel, and ticagrelor, respectively. The cost-utility of prasugrel compared with clopidogrel then becomes 9531 €/QALY. Ticagrelor compared with prasugrel gives a cost-utility of 9987 €/QALY.

We explored the impact of reducing price of clopidogrel and prasugrel. Not even reducing prices to €0,- would make prasugrel or clopidogrel cost-effective, because the main differences in costs between the strategies are those resulting from reduction of clinical events.

In simulations of 50-, 70-, and 80 year-olds, we also found that ticagrelor was cost-effective compared with the other two drugs. Probabilities of ticagrelor being cost-effective were 76, 78, and 79% for 50-, 70-, and 80-year olds, respectively. Probability of clopidogrel being cost-effective was <0.3% in all cases.

We performed a separate simulation with only 5-year time horizon. In these analyses, ticagrelor was also the most cost-effective option, but the probability of being cost-effective was lower at 61%.

Discussion

Our base case analysis based on efficacy data on four different outcomes showed that ticagrelor is clearly cost-effective compared with prasugrel and clopidogrel. Simulations gave a 77% that ticagrelor is cost-effective, given the current evidence base. Considering that only 24% of users of these drugs use ticagrelor, it may be time for a change in practice.

Interpretation of the analyses did not change for different suggested cost-effectiveness thresholds. Results were also extremely robust with regards to choice of starting point for the model. Having a PCI at 50, 60, 70, or 80 did not change conclusions; ticagrelor is cost-effective and clopidogrel is clearly not.

In a recent review of cost-effectiveness, four studies were found that evaluated prasugrel vs. clopidogrel and two studies that evaluated ticagrelor vs. clopidogrel.[15] None of these six evaluations had more than a 2-year perspective, so our 40-year perspective is probably not all that comparable, yet all these analyses found the analysed new drug to be cost-effective compared with clopidogrel. Cost-effectiveness analyses are usually reckoned to not be transferable across jurisdictions, although recent evidence may indicate otherwise.[16] That taken into account, in addition to our analyses showing that ticagrelor is cost-effective even if the prices of the two other drugs were €0,- are clear indications that ticagrelor is likely to be cost-effective regardless of jurisdiction.

Remaining life expectancy for patients who have recently undergone a PCI is reasonable to assume to be shorter than for the general population. Our analyses indicate a remaining life expectancy of 17.5 years with current treatment strategy (clopidogrel) for 60-year olds, compared with an average of 24.5 years for the general population at the same age. This indicates that our model gives results around what was reasonable to assume.

Limitations

We used a cycle length of 6 months in our model analyses. In this way, we distinguished clearly between those events patients are at risk of getting during the first days and months after a PCI, compared with risks later on. We acknowledge that a shorter cycle length is even more accurate, and might have been preferable.

We chose a 40-year perspective when modelling 60-year-old patients who had undergone a PCI. By the end of this period, 99.99% would be dead; hence, all relevant aspects should have been included, as for instance recommended by SMDM-ISPOR.[17] On the other hand, modelling such a long period is largely based on assumptions. We, therefore, conducted a separate simulation with only a 5-year perspective, although results differ, conclusions do not; ticagrelor is still the most cost-effective.

A limitation of our analysis is the lack of longer follow-up data on revascularization and bleeding. Here, we assumed that rates were similar in later periods compared with the first half year.

When creating models of disease progression, choice of which health states to include is essential and may very well influence results. In our model, we included AMI, revascularization, bleeding, and death, mainly because these trials have indicated that the most pronounced differences between the drugs are on these outcomes. We might also have incorporated other health states, for instance stroke, but chose not to do so, because P-values of 0.22 and 0.93 indicate that if there is a difference, it is probably not that substantial.[1,2] In analyses exploring whether *eliminating* any of the included health states would affect the results, we found that all three drugs evaluated could be considered cost-effective, depending on which health states that was included. All scenarios analysed here can be justified based on reasoning related to double counting of events and hence be used by pharmaceutical companies when applying for reimbursement. We therefore urge governmental institutions appraising reimbursement applications to be aware of the potential impact of structural uncertainty when making decisions on reimbursement.

The present model is based solely on life years as health outcome. In other model of patients receiving PCI, outcomes such as avoided revascularizations and QALYs have also been presented. We did not use revascularizations as outcome because it would not capture the time aspect. QALYs could have been used, because there might be a lower QALY with bleeding compared with AMI. This impact would, however, be only for a limited time after each episode, making the impact on the ICER minimal.

Conclusions

Ticagrelor is clearly cost-effective compared with prasugrel and clopidogrel for a Norwegian setting. Results can be easily modified by pharmaceutical companies who want to prove their drug being the most cost-effective.

Conflict of interest: D.A. reports personal fees from Astra-Zeneca, personal fees from Sanofi-Aventis, outside the submitted work.

Appendix

Table A1 Probabilities and proportions

Probability	Expectation	Distribution details	Source
AMI first 6 months after primary PCI	0.0639	Beta ($r = 823$, $n = 12\,880$)	SCAAR[18]
Revascularisation first 6 months after primary PCI	0.01978	Beta ($r = 232$, $n = 11\,730$)	WDHR[19]
Bleeding first 6 months after primary PCI	0.00068	Beta ($a = 11.620$, $b = 17\,027$)	Meta-analysis[20]
Death first 6 months	0.0316	Log-normal (1.6190, 0.0569)[a]	SCAAR[18]
AMI in later half-year periods	0.01614	Beta ($r = 507$, $n = 31\,409$)	SCAAR[18]
Revascularisation in later half-year periods	Assumed same as first half-year period		
Bleeding in later half-year periods	Assumed same as first half-year period		
Death in later half-year periods	0.01028	Log-normal(0.4856, 0.0489)[a]	SCAAR[18]
Mortality during PCI operation	0.005	Beta ($a = 30.710$, $b = 6111.3$)	Feiring Heart Clinic[21]
Mortality during CABG operation	0.008	Beta ($a = 37.567$, $b = 4658.3$)	Feiring Heart Clinic[21]
Bleeding mortality	0.00193	Beta ($r = 26$, $n = 13\,457$)	NOKC report[22]

[a]Distribution of a rate ratio which is multiplied by mortality rate to give age-dependence.

Table A2 Cost items

| Cost item	Expectation	Distribution details	Source
Cost per half year of ACE inhibitor	1110.06	No	NoMA[8]
Cost per ground ambulance turn-out	11000.00	Gamma (4, 0.00036)	NorCaD[23]
Cost per half year of ASA use	145.13	No	NoMA[8]
Cost per half year of beta-blocker	341.76	No	NoMA[8]
Half year cost of clopidogrel	865.64	No	NoMA[8]
Cost per loading dose of clopidogrel (300 mg)	47.07	No	NoMA[8]
Cost per DRG-point	35127.00	No	DRG price list[24]
Cost per GP lab test with ECG and cholesterol	141.00	No	GP tariff[25]
Cost per GP visit	289.00	No	GP tariff[25]
Cost per half year of prasugrel	3413.13	No	NoMA[8]
Cost per loading dose of prasugrel (60 mg)	112.14	No	NoMA[8]
Cost per half year of statin	338.48	No	NoMA[8]
Half year cost og ticagrelor treatment	2124.53	No	NoMA[8]
Cost per loading dose of ticagrelor (180 mg)	23.27	No	NoMA[8]
Number of GP lab tests per half year with ECG and cholesterol	1.0	Gamma (4, 4)	NorCaD[23]
Number of GP visits per half year when asymptomatic	1.0	Gamma (4, 4)	NorCaD[23]
Number of GP visits with STEMI at intervention hospital	1.0	Gamma (4, 4)	NorCaD[23]
Number of ambulances when STEMI at intervention hospital	1.0	Gamma(4, 4)	NorCaD[23]
Number of DRG 112e when STEMI at intervention hospital	0.5	Beta ($r = 50$, $n = 100$)	NorCaD[23]
Number of DRG 112f when STEMI at intervention hospital	0.5	Beta ($r = 50$, $n = 100$)	NorCaD[23]
Number of ambulances with STEMI at other hospitals	2.8	Gamma (2.8, 1)	NorCaD[23]
Number of DRG 112e when STEMI at other hospitals	0.45	Beta ($r = 45$, $n = 100$)	NorCaD[23]
Number of DRG 112f when STEMI at other hospitals	0.45	Beta ($r = 45$, $n = 100$)	NorCaD[23]
Number of DRG 121 when STEMI at other hospitals	0.5	Beta ($r = 50$, $n = 100$)	NorCaD[23]
Number of DRG 122 when STEMI at other hospitals	1.4	Gamma (4.2, 3)	NorCaD[23]
Number of GP visits when STEMI without PCI facilities	1.0	No	NorCaD[23]
Weight for DRG 112e	1.19	Gamma (4, 3.3613)	DRG price list[24]
Weight for DRG 112f	1.46	Gamma (4, 2.7397)	DRG price list[24]
Weight for DRG 121	1.51	Gamma (4, 2.6490)	DRG price list[24]
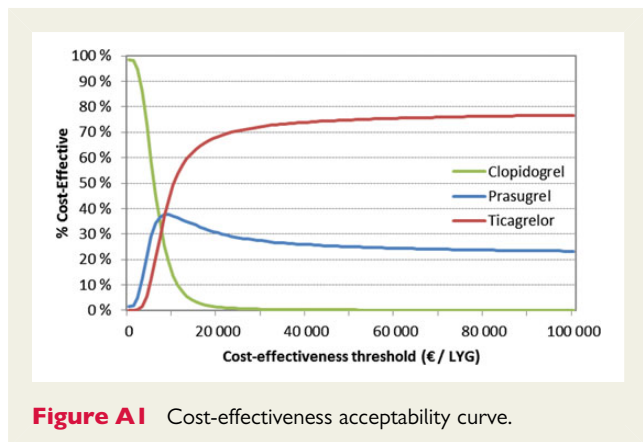
Figure A1 Cost-effectiveness acceptability curve.

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