Master's Degree Dissertation

A cost-effectiveness analysis in a Norwegian setting: Introducing genotyping to patients with ACS treated with PCI before prescribing antiplatelet therapy

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Abstract

Background: The use of CYP tests is under investigation for a more extensive use in the Norwegian health sector. One possible application could be the genotype-guided selection of oral P2Y12 inhibitors for patients undergoing primary percutaneous coronary intervention (PCI). Those patients receive today mostly clopidogrel, which has been accepted as the standard treatment.

Objective: The purpose of this study is to conclude as to whether it is cost-effective to introduce genotyping in the Norwegian clinical practice in the case of acute coronary syndrome, as a guide of pharmacotherapy decision making after a percutaneous coronary intervention.

Methods: A two-part model consisting of a 1-year-long decision tree and a 40-year-old Markov model was developed to simulate the short-term and long-term outcomes of the following treatment strategies: 1) universal clopidogrel treatment 2) universal ticagrelor treatment and 3) CYP2C19 genotype-guided treatment. Probabilities, costs and utilities were identified through systematic literature review. Data comparing the clinical performance of ticagrelor and clopidogrel were derived from the Platelet Inhibition and Patient Outcomes trial (PLATO). Cost-effectiveness is expressed as the incremental cost-effectiveness ratio (ICER) of QALYs in the genotype-guided therapy case versus the other two strategies, as this is the suggested measure of effectiveness by the Norwegian Health Authorities.

Results: This analysis shows that the genotype guided strategy is cost effective in most of the simulations at an incremental cost-effectiveness ratio (ICER) of 4,500 NOK compared to universal clopidogrel strategy. The second strategy evaluated in the deterministic analysis was universal ticagrelor. As it is more expensive and less effective than the genotype guided therapy, it is dominated by the last one. Given a Norwegian cost-effectiveness threshold of 500,000 NOK per QALY, the genotype guided therapy appears to be clearly cost effective.

Conclusions: The genotype-guided strategy is a cost effective treatment compared to universal clopidogrel and universal ticagrelor for patients who have undergone PCI. Given the assumptions and limitations of this analysis, further research is suggested, as well as real world evidence in order to confirm the above results.

Keywords: Clopidogrel, Ticagrelor, Percuntaneous coronary intervention, economic evaluation, cost.effectiveness, CYP, antiplatelets

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1. Background and Objectives

Cardiovascular disease is a leading cause of mortality and morbidity worldwide (AHA Statistical Update 2019; European Heart Network, 2019). The most frequent cardiovascular diseases are angina pectoris (angina), myocardial infarction, heart failure and stroke. Morbidity is mainly associated with atherosclerosis, which is the result of fat disposition, narrowing and blockage (blood clots or thrombosis) of the vessel wall. According to WHO figures from 2015, an estimated 17.7 million people die of cardiovascular disease each year. In Norway, approximately 40,000 people yearly receive specialist healthcare services related to angina or myocardial infarction; 16,000 for heart failure; and 11,000 for stroke (FHI).

Acute coronary syndrome (ACS) is a subcategory of cardiovascular disease. It has a high mortality, morbidity and economic burden as well. It is usually caused by ischemic heart disease and atherosclerotic plaque rupture in the coronary arteries causing platelet activation, aggregation and the formation of a thrombus. Acute coronary syndrome is the term for acute chest pain that is due to narrowing of one or more of the heart's coronary arteries, and which without prompt treatment can lead to a heart attack. It can be described as a group of heart problems that include heart attacks and unstable angina. Some patients are in need of a stent. In that case, a short tube is placed in an artery to prevent it from closing up, following percutaneous coronary intervention (PCI). Non-ST-elevation myocardial infarction (NSTEMI), ST-elevation MI (STEMI), and unstable angina are the three traditional types of ACS.

The clinical use of the troponin test has changed the diagnosis of unstable angina to NSTEMI in almost all patients formerly diagnosed with unstable angina. Patients formerly called for suffering from unstable angina, actually have abnormally elevated high-sensitivity troponin values. Unstable angina used to be defined by clinical and electrocardiographic (ECG) findings in the absence of an elevated biomarker level. Few if any patients with clinical and ECG evidence of myocardial ischemia have normal high-sensitivity troponin levels. They actually demonstrate elevated levels of this biomarker, resulting to the confirmation of the presence of myocardial cell death induced by ischemia. Almost all of these patients do not show a STEMI pattern on their ECG, and should thus get diagnosed as an NSTEMI (Braunwald et al., 2013).

A large number of patients is admitted annually to Norwegian hospitals with acute coronary heart disease. The incidence of ST-elevation myocardial infarction has decreased over the last 20 years, especially in younger age groups (FHI). However, the number of heart attacks without ST elevation has increased. This is related to new criteria for the infarction diagnosis with the use of sensitive markers on myocardial damage (troponins), as mentioned above. According to the Norwegian Medicines Handbook, myocardial infarction with ST elevation accounts for 25–30% of the total number of myocardial infarctions in Norway. From 2012 to 2016 the incidence rate for first-time cases of acute stroke and acute myocardial infarction decreased by approximately 8% and 15% (retrieved from the Norwegian Hjerte og kar register). Primary and secondary prophylaxis aims to modify major risk factors. Antiplatelet therapy results to improvement of the survival of people with manifest cardiovascular disease (Patrono et al., 2011). For decades, antiplatelet agents have been the cornerstones of management of ACS and dual antiplatelet therapy with aspirin and P2Y12 receptor blocker have been the standard of care for patients with ACS with or without percutaneous coronary intervention.

The antithrombotic anti-platelet agents, aspirin and clopidogrel are widely used when treating patients with atherothrombotic disease in cardiovascular or other vascular beds. Whether administered alone or in combination, both have proven efficacy when it comes to reducing the risk of adverse events, such as myocardial infarction, stroke or vascular death (Meta-analysis, 2002). Several molecules that inhibit platelet aggregation are currently available in clinical practice, in particular the oldest one, clopidogrel and the new (prasugrel,

ticagrelor)

P2Y12 inhibitors. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances (Baigent et al., 2009) by inhibiting platelets by two different mechanisms (Squizzato et al., 2007). Aspirin has an antiplatelet effect by inhibiting the production of thromboxane, whereas other antiplatelet drugs are adenosine diphosphate (ADP) receptor/P2Y12 inhibitors.

Worldwide, clopidogrel is the most frequently used P2Y12 inhibitor for cardiovascular disease prevention. Clopidogrel, also known with the brand name Plavix, is an antiplatelet agent used to prevent problems by blood clots in adult patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease. Indications include a condition known as "acute coronary syndrome" and atrial fibrillation. Dual antiplatelet therapy with aspirin and clopidogrel is standard for prevention of thrombotic complications of percutaneous coronary intervention (PCI) (Levine et al., 2013). Clopidogrel, is an inactive pro-drug, which needs to undergo an oxidative process by the hepatic CYP system to become an active substance. It is well known that patients who carry a common reduced-of-function CYP2C19 allele have a lower level of active metabolite of clopidogrel, diminished platelet inhibition, and furthermore, higher rate of major adverse cardiovascular events than noncarriers (Scott et al., 2013). Genetic variations of the cytochrome P450 (CYP) 2C19 enzyme have been associated with individual response to clopidogrel, and thus indicating the need to evaluate the use of genetic tests to identify patients who may be preferably treated with other alternatives (Moon et al., 2018).

Prasugrel or Efient (by Daiichi Sankyo) combined with acetylsalicylic acid is new type P2Y12 inhibitor indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (ie unstable angina, myocardial infarction without ST-segment elevation or myocardial infarction with ST-segment elevation undergoing primary or delayed percutaneous coronary intervention). Prasugrel is a prodrug that is converted in vivo to an active metabolite, but its activation occurs in a way that is not influenced by functional variants of CYP enzymes (Mega et al., 2009). Prasugrel may be more effective on average than clopidogrel, but is unfortunately associated with an increased risk of bleeding (Wiviott et al., 2006).

Ticagrelor, also known as Brilique, branded by AstraZeneca, is the newest oral P2Y12 receptor antagonist which varies from the thienopyridine antiplatelets by not requiring an activation step and by exhibiting reversible receptor binding (O'Connor et al., 2017). As with prasugrel, ticagrelor is proved to be efficacious regarding reduction of cardiovascular events, but has been associated with a significantly higher minor and major bleeding risk compared to clopidogrel. (Wallentin et al., 2009, Guan et al., 2018).

There is therefore some uncertainty with regards to the cost-benefit relationship of replacing the standard therapy with clopidogrel with the above alternatives. Another issue is the price of the newest P2Y12 inhibitors, which after clopidogrel not being patented any more has been quite higher, and more than four times as expensive in Norway specifically (Wisløff et al., 2015). From the Norwegian prescription registry, we see that almost 46,000 patients used either clopidogrel, prasugrel or ticagrelor. Of these, 75% received clopidogrel, 21% percent received ticagrelor and only 4% received prasugrel. For years 2015 to 2019, a significant increase in the use of clopidogrel is present, with some increase in the use ticagrelor and actually a reduction in the use of prasugrel. Clopidogrel is still the preferred antiplatelet agent by Norwegian prescribers, even though the latest ESC guidelines suggest prasugrel and ticagrelor as the standard treatment for NSTE-ACS patients. Clopidogrel

should only be used when a contraindication for the other alternatives exists, or cannot be tolerated (Collet et al., 2020).

The CYP2C19 genotype could be a predictor of adverse cardiovascular events in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) treated with clopidogrel. A number of cost–effectiveness analyses have been published assessing the use of CYP2C19 genotype to guide P2Y12 receptor antagonist therapy (Crespin et al., 2011, Reese et al., 2012, Panattoni et al., 2012, Sorich et al., 2013, Patel et al., 2014). The PLATelet inhibition and patient Outcomes trial (PLATO) 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 (Wallentin et al., 2009). The fact that the CYP genotype testing is available for a better price than earlier, enables clinicians to personalize antiplatelet therapy so the more potent and expensive alternatives to clopidogrel can be selected and prescribed to those patients that are most likely to derive an inadequate response to clopidogrel (Scott et al., 2013).

The current term paper aims to utilize the estimates of the PLATO trial and genetic substudy in order to assess the cost–effectiveness of using CYP2C19 genotype to guide clopidogrel and ticagrelor therapy for the individuals who are most likely to benefit from being tested in advance. This analysis could be of assistance to decisions makers regarding the introduction of genotype-guided therapy as the new standard clinical practice in the Norwegian Healthcare system for patients with ACS undergoing PCI. The remaining of the paper is organised as follows. The model and the methods are presented in the next section. In sections 3 and 4, we present the result of this analysis and the discussion part. Tables and figures, as well as tables from the original excel file are to be find in the end of this file.

2. Methods

Data, sources and search strategy

PubMed, MEDLINE and the Cochrane library were searched for relevant publications (between the years 2009 and 2020) comparing clopidogrel with ticagrelor following coronary stenting. Terms and p

hrases searched were: “clopidogrel and ticagrelor”. The term “percutaneous coronary intervention” and “acute coronary syndrome” were also used in this search strategy, as well as “genotyping” and “CYP2C19”.

Model Cohort

Patients in Norwegian hospitals who undergo invasive coronary procedures such as coronary angiography (coronary artery radiography), percutaneous coronary intervention (PCI) and trans-catheter aortic valve implantation (TAVI) are registered in NORIC. In 2018, 28,346 patients were registered in NORIC who were examined and/ or treated using invasive coronary procedures at Norwegian hospitals. Some patients have been through several procedures during the same hospital stays and others have been hospitalized several times. On a national basis, it is more men than women who have had the aforementioned procedures performed, and the average age among men is somewhat lower than among women. The median age is 66 years for men and 69 years for women. From a total 32,101 invasive coronary procedures, 41.1% involved treatment with PCI and angiography or isolated PCI.

A Norwegian simulated population, with figures based on the latest report, for the year 2018, from the Norwegian Register for Invasive Cardiology (NORIC) is analyzed. The population modeled is a hypothetical cohort of 1,000 patients aged 65 years who underwent PCI after ACS. All patients received dual antiplatelet therapy with one of the previously mentioned agents and aspirin for 12 months after the last PCI or MI and low-dose aspirin thereafter unless contraindicated. We modeled the genotype-guided regimens on the basis of the recently published guidelines of the Clinical Pharmacogenetics Implementation Consortium (Scott et al., 2013). Folowing Wallentin et al. (2009), we did not distinguish between patients who presented with or without ST-segment elevations because this did not modify the effect of ticagrelor in the PLATO study.

Model Structure and Inputs

We used a hybrid decision tree/Markov model to analyze the cost-effectiveness of genotype driven antiplatelet therapy for ACS. Thus, a two-part analysis model was developed consisting of a one year decision tree and a Markov model for maximum of 40 years, which represents a lifetime or until our patients reach the age of 100 years, with yearly cycle developed in Microsoft Excel 2016. The model has therefore been able to capture both short-term and long-term costs and health outcomes for ACS patients. As presented in the decision tree in Figure 1, our model allows healthcare providers the choice of genetic testing or the choice of 2 other universal treatments. In specific, three alternative strategies emerge 1) universal clopidogrel treatment, 2) universal treatment with alternative P1Y12 inhibitor, in this case ticagrelor, and 3) genetic testing for CYP2C19, which further indicates the choice of clopidogrel or ticagrelor.

There are two alternative antiplatelet agents in the market that are used as a substitute for clopidogrel, prasugrel and ticagrelor. In this analysis, it is chosen to analyse ticagrelor as ticagrelor and prasugrel have equal values at the different endpoints in the different studies that have been assessed in this analysis (Bundhun et al., 2017). For genotype-driven treatment each patient is tested for CYP2C19*2 mutations and prescribed clopidogrel in their absence and ticagrelor in the presence of any CYP2C19*2 mutation.

The decision tree was used to establish the proportion of patients who reached the various endpoints after the first 12 months with universal clopidogrel, genotype-guided clopidogrel and universal ticagrelor. The Markov model was used to calculate the expected costs and quality-adjusted life years depending on the events that occurred in the decision tree (Petrou et al., 2011). The decision tree has some limitations, which makes it natural in this process to use a Markov model in addition and in general in other issues within economic evaluation (Barton et al., 2014). The model structure and the majority of transition and utility parameters were based on the report of the PLATO economic substudy. The event rate probabilities for death, nonfatal myocardial infarction and nonfatal stroke at year 1 were obtained from the results of the cost-effectiveness study of Nikolic et al. The transition probabilities for ticagrelor patients were calculated by applying the HRs from the PLATO trial to the probabilities for clopidogrel patients, after converting such probabilities to rates (Grima et al., 2014).

There are 4 different events an ACS patient can end up in the first year:

1. Death, including cardiovascular death or because of severe bleeding
2. Non-fatal myocardial infarction (MI)
3. Non-fatal stroke (ST)
4. No event

All patients entered one of the initial three health states of Markov model corresponding to the clinical end points in the decision tree: "stable/No event" (including patients who experienced stroke or bleeding but survived), "Post MI" (patients surviving a myocardial infarction and having an increased risk for future MI, strokes or cardiovascular death) or "Post stroke" (patients surviving a stroke and having an increased risk for future strokes or cardiovascular death). The conditions "Non-fatal myocardial infarction" and "non-fatal stroke" in the Markov model represent the first year's forecast of survival, costs and quality-adjusted life years after survival of a non-fatal event. These conditions are so-called "tunnel" conditions, which patients can only be in for one cycle. Patients who are alive after one year in these two the conditions will make a transaction to the conditions "post MI", "post stroke". Patients in the non-fatal conditions can also make another transaction to death. Patients could not enter the nonfatal MI state from the post-stroke state because this would allow stroke patients to transition to a health state characterized by an improved quality of life and lower associated costs, following the example of other studies in this field. In addition, bleeding was not taken into account from the second year, because it is quite rare at this point. Lastly, half-cycle corrections are performed in the Markov models for a better representation of reality.

The following outcome measures were included: overall death, MI (non-fatal), stroke (non-fatal), life years gained (LYGs), quality-adjusted life years (QALY) and costs from the perspective of the health care provider. Adverse and subsequent events were not explicitly included in the analysis. The costs used in the analysis were measured in 2018 Norwegian crones. Costs were obtained from the NorCaD model (Norwegian Cardiovascular Disease Model), which referred to year 2015. Those were therefore adjusted to year 2018 using an annual inflation rate of 2,06%. Both costs and QALYs were discounted at 4% per annum as suggested by the guidelines for health technology assessments in Norway. The health outcomes in this analysis are based on quality-adjusted life years (QALY). The choice was changed from the initial proposal in order to follow the recommendation of the Norwegian Medicines Agency on economic analyses. QALY is an economic outcome that combines preferences for both the length of life and the health-related quality of life into one measuring instrument (Drummond et al., 2015). For the different values of the endpoints and the values in the Markov model, I have assumed a beta distribution, the same applies to QALYs, while for costs I have assumed lognormal distributions. For the parameters where the standard error was not available, it was assumed a 25% standard error from the deterministic value.

The QALY estimates for the people in the conditions stable/no event, nonfatal myocardial infarction and nonfatal stroke are taken from the PLATO study, where the average of clopidogrel and ticagrelor patients has been used for patients under 70 years and is therefore just an average approach. The QALY reduction signed to the conditions "post MI" and "post stroke", where obtained from Burström et al, which are based on Swedish population and on estimates from EQ-5D data. The Swedish population is a good reflection of the Norwegian population, and the values can thus be considered relevant for this analysis.

Assumptions

The genotype based strategy involved genotyping specifically for the CYP2C19*2 polymorphic variant, which accounts for 95% of loss of function mutations (Mega et al., 2009). The CYP test was assumed to be taken only once, and both its sensitivity and specificity were assumed to be 100%. This simplification is acceptable since the sensitivity and specificity of the test were determined to be 99% and 99%, respectively, based on

available data (Daly et al., 2007, Dumaual et al., 2007). Since they are not included, they are not varied in the sensitivity analyses. It was also assumed that information on genotype would be available quickly as to not delay initiation of therapy, which is not always the case in reality.

Under the Genetic substudy of the PLATO trial ticagrelor demonstrated a reduction on risk of cardiovascular events compared with clopidogrel, irrespective of the carriage of a CYP2C19 loss-of-function allele. As the pharmacologic effect of ticagrelor is unaffected by genotype, the event rates in carriers and wild-type subjects were assumed to be the same (Wallentin et al., 2010). The Markov model also assumed the post one year event rates to be equal regardless of the initial treatment strategies. Furthermore, we assumed the probabilities of event occurrence where constant through time, but time is a factor that modulates the probability of death. To minimize the effect of this on our results, we regulated the probability of death in accordance to mortality rate of the simulated population. While the patients remain in the event free state they are being applied the same mortality rate as the general population of the same age. This is not the truth in reality as mortality is also affected by disease. The Markov chain is a simplification for reflecting reality, as expected.

3. Results

Based on our model, we observe that genotype guided strategy has already better results during the first year of treatment with a lower rate of death after a cardiovascular event and fewer non-fatal strokes and heart attacks than the other two strategies. As a result, lower costs and higher QALYs are also observed during the first year of genotype guided treatment. The results of the deterministic analysis showed that universal clopidogrel is the cheapest treatment, with the highest rate of cardiovascular events and death, the lowest life years gained and QALYs. Ticagrelor is cost-effective compared to clopidogrel, with an ICER of 317,446 NOK per QALY, but is dominated by the cheaper and more effective genotype guided treatment strategy. The genotype guided strategy results to the lowest rate of cardiovascular events and the highest number of QALYs gained.

Sensitivity or uncertainty analyses must be carried out in health economic analyses. Those can be made both deterministic and probabilistic. The purpose of this type of analysis is to look at the effect of the uncertainty around one parameters "true value", these can be parameters that estimate costs, quality of life, treatment effect and probabilities of events. One of the main goals of implementing sensitivity analyses are to contribute to better decisions, as well as to assure the analyst that the model works (Drummond et al., 2015). The sensitivity analyses in this paper were performed in Microsoft Excel 2016. In the one-way sensitivity analysis, the probability of suffering a non-fatal myocardial infarction affected the ICER to some extend in the case of universal clopidogrel and to a much smaller extend in the case of genotype guided clopidogrel. The same applies for the probability of getting a stroke. The utility of the state “No event/Stable”, and the probability of dying during the first year of treatment showed also great variation in the sensitivity analysis. Furthermore, the impact of reducing price of clopidogrel and ticagrelor was also explored. The reduction seemed to not make any difference for the final results, as the main differences in costs between the strategies are those resulting from reduction of clinical events, and cardiovascular death.

The result of the probabilistic sensitivity analysis showed that the optimal strategy is the third one, the genotype guided therapy. With a willingness to pay of 500,000 NOK/QALY genotype guided therapy was the dominant strategy. The choice of ticagrelor as the universal treatment was dominated by the genotype-guided strategy which resulted to more LYGs and QALYs for a lower price than universal ticagrelor. With a limit value of 4,500

NOK/QALY, clopidogrel is the most cost-effective treatment, but with an increasing value from, the probability of the genotype guided treatment to be the most cost-effective choice increases. The probability of ticagrelor being more cost-effective than clopidogrel is also observed at a limit value of 30.000 NOK per QALY, dominated still by strategy 3.

This overall analysis showed that the genotyped guided therapy is cost-effective compared to universal clopidogrel, with an incremental cost per life year gained of 109,943 nok and an incremental cost per QALY of 31,125 nok over a period of 40 years. The genotype guided therapy is the most cost-effective choice and has an ICER which is under the WTP (willingness to pay) assumed in this analysis.

4. Discussion

Dual antiplatelet therapy, usually accompanied with a P2Y12 receptor antagonist and aspirin, is generally acknowledged as the best approach in treating ACS patients. Dual antiplatelet therapy has been also regarded as a standard therapy especially after PCI according to several clinical guidelines. (Collet et al., 2020). Clopidogrel, a P2Y12 receptor antagonist, has been generally utilized with aspirin as prescribed antiplatelet agents in order to decrease the probability of myocardial infarction and stent thrombosis in patients with acute coronary syndromes with or without ST elevation. Clopidogrel requires a hepatic metabolism of 2 steps to be activated, as it is an inactive pro-drug. Ticagrelor is a direct-acting oral P2Y12-receptor antagonist with reversibility and without the need of a catabolite activation, which can explain it's faster and greater platelet inhibition than clopidogrel.

A growing body of literature suggests that *CYP2C19* genotype-guided antiplatelet therapy improves patient outcomes following a percutaneous coronary intervention (O'Connor et al., 2017, Limdi et al., 2020). Recent economic evaluations consistently demonstrate that a genotype-guided approach could be a cost-effective approach in guiding the selection of medication given to patients with ACS following PCI (AlMukdad et al., 2020). A number of institutions has also shown that the clinical application of *CYP2C19* genotype-guided antiplatelet therapy in PCI patients is feasible and sustainable in the real world as well (Lee et al., 2018). Personalized medicine can thus be adapted into medical care delivery. The results of large, ongoing, randomized studies comparing a genotype-guided strategy to standard dual antiplatelet therapy suggest a potential positive change on how DAPT is selected in cardiovascular patients, as a risk reduction of major cardiovascular events for carriers of a CYP2C19 loss-of-function allele is observed (Klein et al., 2019).

Our results are generally concordant with other published analyses that have found that genotype-based antiplatelet treatment is cost effective. There is however a number of limitations to be found in this analysis.

The overall mortality in the Markov models was estimated conservatively, and the increasing mortality rate due to previous cardiovascular events was not included to the Norwegian standard mortality. In addition, probabilities of events occurring were assumed to be stable through all years regardless of disease history and age, which does not reflect reality. A cycle length of one year was used in this model analysis, with half-cycle correction to make it more accurate. A shorter cycle length would be more appropriate, and might have been preferable. Moreover, the time frame of the simulation is 40 years, which is a long period and is based on assumptions. This is because follow-up data on patients over such long periods are scarce. A separate simulation with shorter periods is suggested for more detailed results. The present model is based in life years gained, myocardial infarctions and strokes prevented and QALYs, as health outcomes. Events during the first year of treatment, such

as hemorrhagic and ischemic stroke, gastrointestinal bleeding, revascularization and dyspnea have not been included in this analysis. Their impact has shown to not be statistical significant in other studies, and thus would probably have a minimal impact to the ICER.

In the cost-effectiveness plane most of the simulations are located in area I, which represents the more effective and costly alternatives. We find some simulations in other quadrants as well, but most of them are in the first and below the acceptable threshold of 500,000 NOK per QALY. Given the above threshold, ticagrelor is cost-effective in comparison to universal clopidogrel with a cost per QALY ratio of 330,467 NOK and 0.14 QALY gained. Ticagrelor is preferred above the limit value of 30,000 NOK per QALY with regards to clopidogrel (Figure 5). Nevertheless, the genotype-guided strategy is clearly the most cost-effective alternative. The cost per QALY ratio of 31,124 NOK (0.56 QALY gained) versus generic clopidogrel is well below accepted thresholds for cost-effectiveness evaluations, and supports the introduction of CYP testing in clinical practice regarding ACS patients and antiplatelet therapy choice for the Norwegian population.

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Tables

Table 1. Model Inputs I

Parameters	Mean Value	Range		Source
Probabilities first year after PCI		**Minimum**	**Maximum**	
Base case: Universal Clopidogrel				
Nonfatal MI	0,0575	0,0498	0,0659	PLATO Study
Nonfatal Stroke	0,0088	0,0054	0,0132	PLATO Study
All-cause death	0,0586	0,0419	0,0746	PLATO Study
Strategy 2: Universal Ticagrelor				
Nonfatal MI	0,0497	0,0000	0,4941	PLATO Study
Nonfatal Stroke	0,0096	0,0000	0,1270	PLATO Study
All-cause death	0,0462	0,0000	0,5387	PLATO Study
Hazard ratios of LOF carriers vs non carriers				
Nonfata MI	1,45	1,090	1,920	Mega et al., 2010
Nonfatal Stroke	1,73	0,680	4,380	Mega et al., 2010
Cardiovascular death	1,84	1,030	3,280	Mega et al., 2010
Year 2+ transitions probabilties		**Minimum**	**Maximum**	
Risk of death in No event state	2			Nikolic et al., 2012
Hazard ratios over standard mortality				
Risk of death in the Nonfatal MI state	6	0,6 (standard error)		Nikolic et al., 2012
Risk of death in Post MI state	3	0,15 (standard error)		Nikolic et al., 2012
Risk of death in the Post Stroke state	3	0,15 (standard error)		Nikolic et al., 2012
Risk of death in the Nonfatal Stroke state	7,43	0,35 (standard error)		Nikolic et al., 2012
Increased probability of having a subsequent event	2			Lala et al., 2012
Annual risk of non-fatal MI in the no event state	0,019	0,0000	0,7497	Nikolic et al., 2012
Annual risk of nonfatal stroke in the no event state	0,03	0,0021	0,0040	Nikolic et al., 2012
Crude annual mortality rate of Norwegian population	7,6			Statistisk sentralbyrå
Utilities		**Minimum**	**Maximum**	
No event	0,8763	0,1648	1,0000	Nikolic et al., 2012
Nonfatal MI	0,8136	0,1327	0,9990	Nikolic et al., 2012
Nonfatal Stroke	0,7379	0,1565	0,9877	Nikolic et al., 2012
Potst MI	0,868	0,1579	1,0000	Nikolic et al., 2012
Post Stroke	0,735	0,2693	0,9801	Nikolic et al., 2012
Death	0			By definition
Costs (NOK)				
Clopidogrel (per month)	129,2	95,89	179,43	SLV
Ticagrelor (per month)	742,4	561,47	960,48	SLV
Acute nonfatal MI	149806	86 493,18	150 246,91	NorCad
Acute nonfatal stroke	213764	101 709,39	179 971,66	NorCad
Cardiovascular death	56601,87	32 721,69	56 678,20	NorCad
ACS annual ongoing	4731	3 399,80	6 235,81	NorCad
Post MI annual ongoing	2980	2 201,61	4 121,38	NorCad
Post stroke annual ongoing	213764	1 657,71	2 943,62	NorCad
Genotyping	434	334,65	584,10	Rikshospitalet

Table 2. Results of the cost-effectiveness analysis. Clopidogrel & tigracrelor compared to the genotype guided treatment following ACS with expected PCI. Ticagrelor is a more expensive strategy with a lower QALY gain, thus the negative ICER

	Clopidogrel	Ticagrelor	Genotype-guided therapy
Costs	1 627 134,28	1 674 786,04	1 644 578,34
MI & stroke (events)	0,09	0,08	0,06
LYGs	13,60	13,76	13,76
QALYs	11,89	12,03	12,45
Incremental			
Costs		- 30 207,69	17 444,07
MI & stroke reduction	-	0,02	0,03
LYGs	-	-	0,16
QALYs	-	0,42	0,56
Cost/QALY (NOK)	-	- 72 569,20	31 124,80

Figures

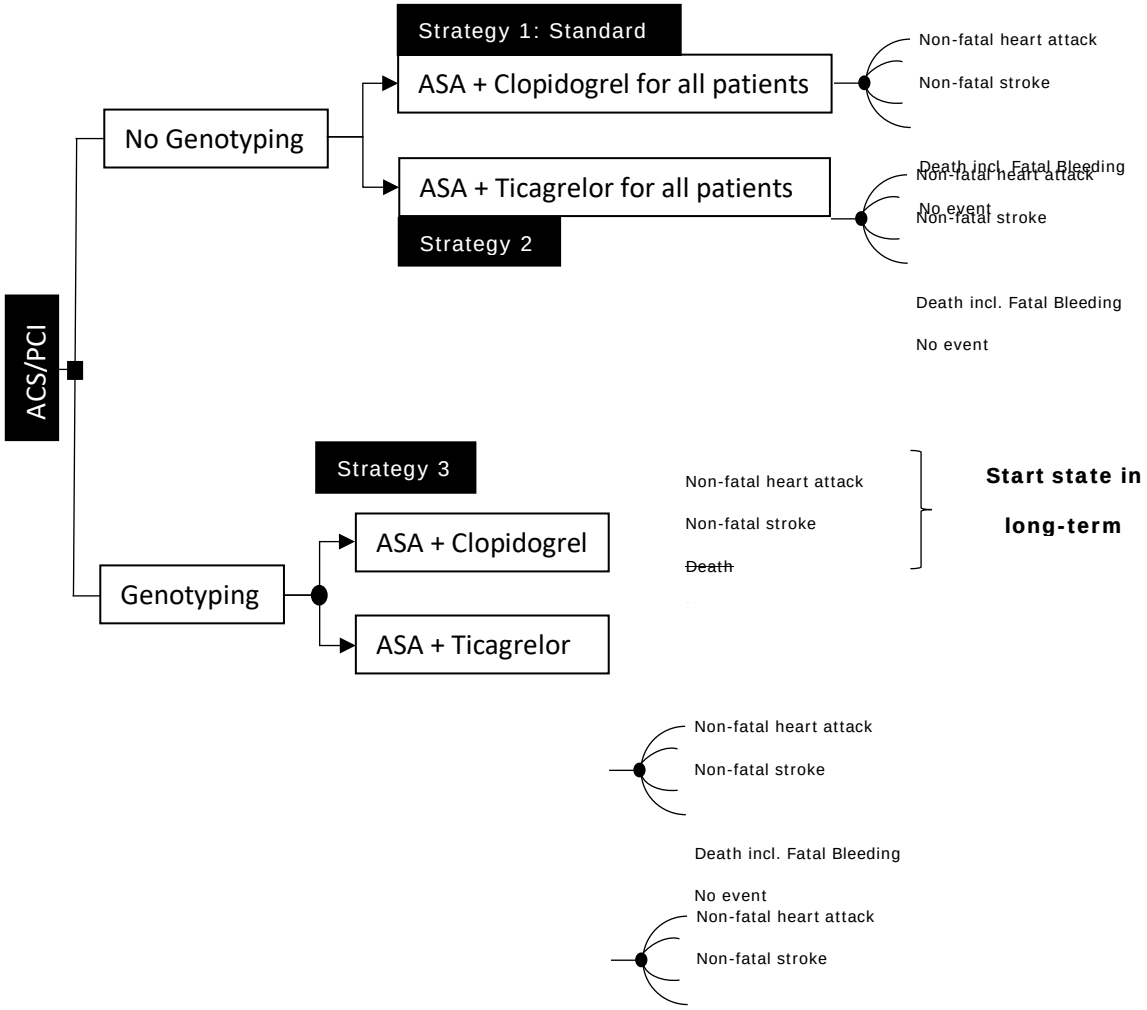

Fig.1 Decision tree outlining treatment options under comparison. Patients either receive CYP2C19*2 mutation testing and have antiplatelet therapy selected by testing result or receive ticagrelor or clopidogrel without genetic testing. Individuals may end up in death including death due to fatal bleeding and cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or no event. The events that occur in the first year affect the start state of the Markov model.

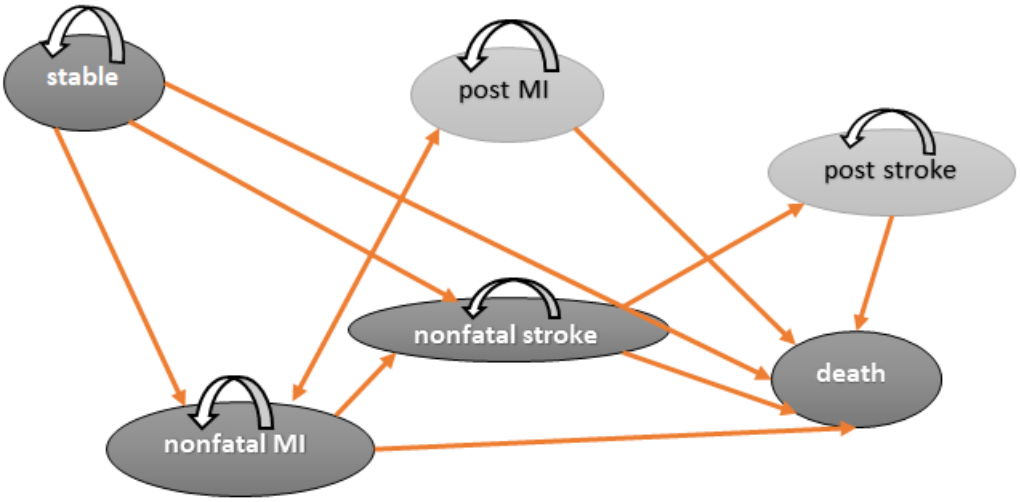

Fig.2 The Markov Model used in this analysis with all the states and transitions taken into consideration

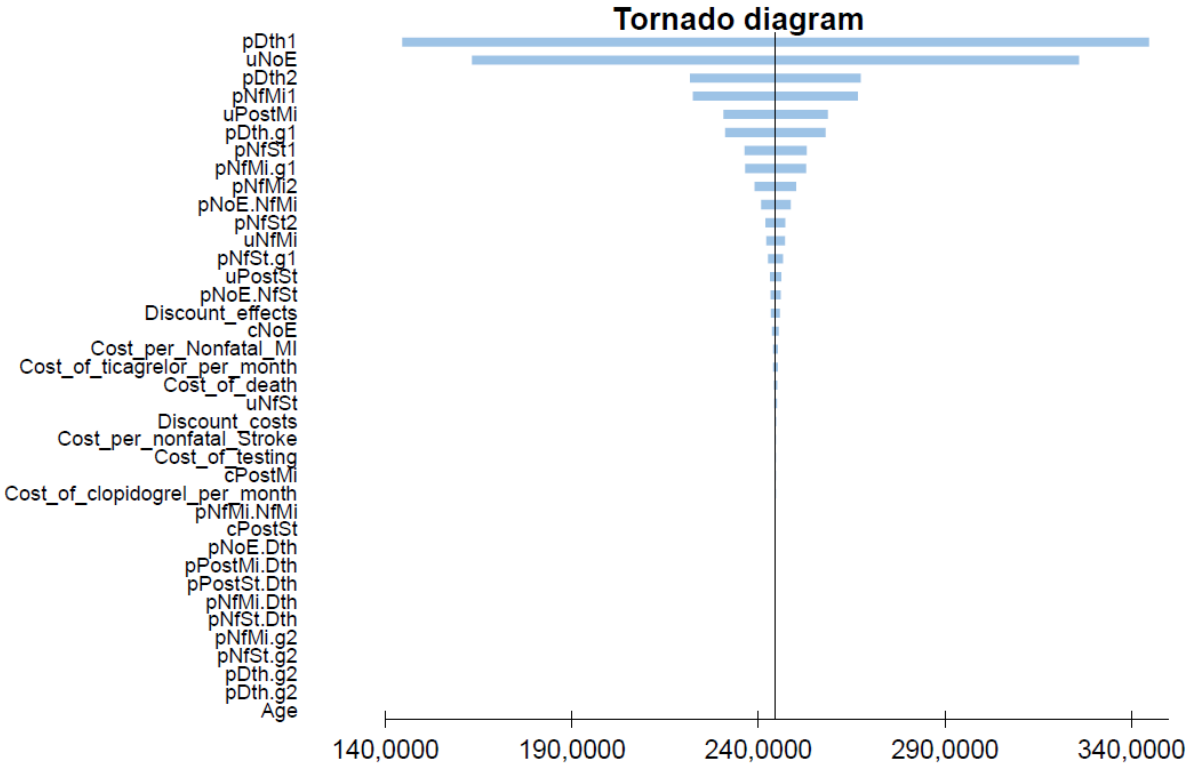

Fig.3 One-way sensitivity analysis results presented as a tornado graph

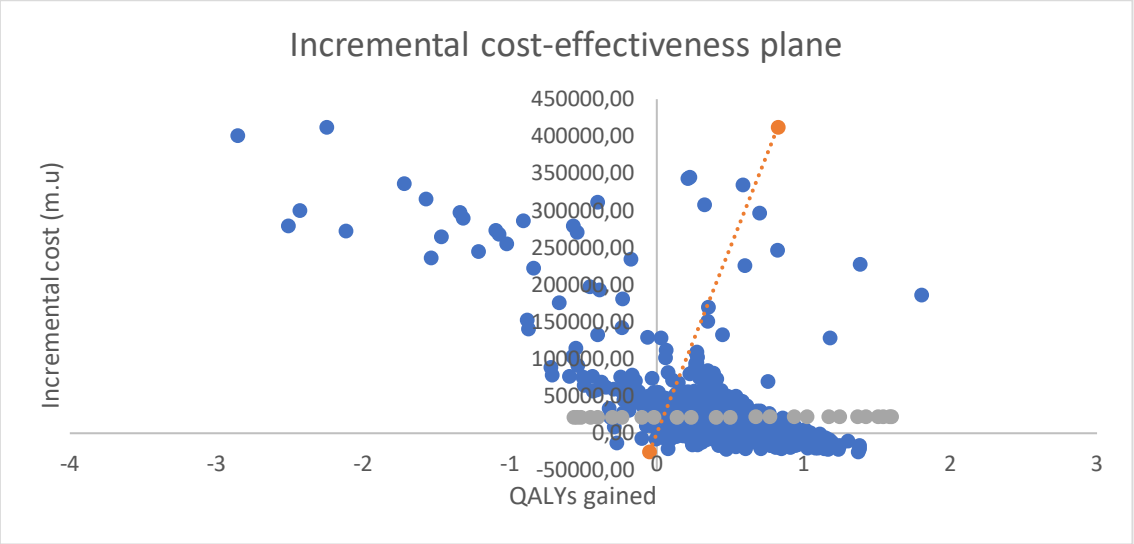

Fig.4 Cost-effectiveness plane of 1000 Monte Carlo simulations representing the distribution of costs and effects while comparing genotype guided treatment to universal clopidogrel. The threshold of 500,000 NOK per QALY is also included in the figure.

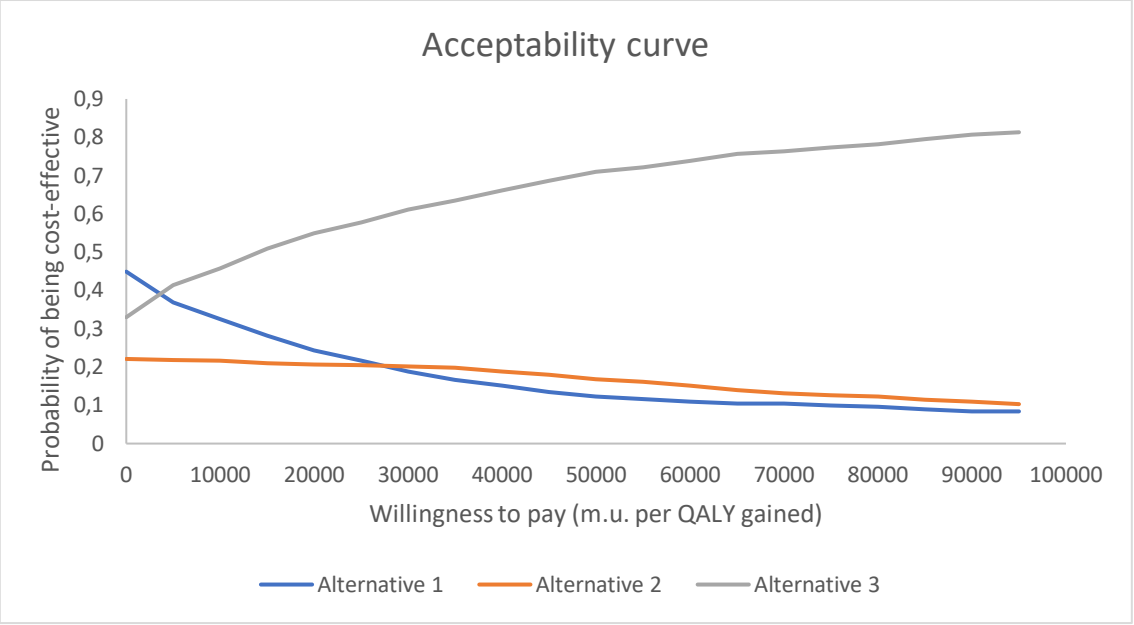

Fig.5 Cost-effectiveness acceptability curve

RESULTS FROM EXCEL FILE

RESULTS OF COST-EFFECTIVENESS ANALYSIS (Deterministic model)

	Costs	MACE occurence %	Life Years	QALYs	
Universal Clopidogrel	1 645 118,11	0,0977	13,335	11,632	
Universal Ticagrelor	1 696 361,20	0,0897	13,526	11,794	
Difference	51 243,09	0,0081	0,191	0,161	
ICER 2 VS 1		**6 364 315,65**	**268 264,47**	**317 446,18**	m.u./QALY
Universal Clopidogrel	1 645 118,11	0,0977	13,335	11,632	
Gen. Guided Treatment	1 665 068,08	0,0684	13,526	12,161	
Difference	19 949,97	0,0293	0,191	0,529	
ICER 3 VS 1		**681 008,18**	**104 440,76**	**37 701,74**	m.u./QALY
Universal Ticagrelor	1 696 361,20	0,0897	13,526	11,794	
Gen. Guided Treatment	1 665 068,08	0,0684	13,942	12,161	
Difference	- 31 293,12	0,0212	0,416	0,368	
ICER 3 VS 2		**- 1 473 094,02**	**- 75 192,79**	**- 85 098,21**	m.u./QALY

Monetary benefit

Alternative 1	Alternative 2	Alternative 3	Maximum benefit
-497541	-531494	-461741	-443366
204914	220881	231902	220432
-1294524	-1368108	-1293608	-1293608
-147255	-111106	-38161	-38161

Acceptability curve

Cratio	Alternative 1	Alternative 2	Alternative 3	EVPI
95000	0,084	0,103	0,813	18375,92

SUMMARY OF SIMULATION			
Dominated	99	285	72
Cost-effective	400	367	578
Dominant	338	333	331
% Dominated	0,099	0,285	0,072
% Cost-effective	0,4	0,367	0,578
% Dominant	0,338	0,333	0,331
	C/reduction MI and stroke	C/LYG	C/QALY

Results of the Simulation

	Parameters	Simulation	Average	Deviation	Minimum	Maximum
Year 1 probabilities: Universal Clopidogrel	pNfMi1	0,0575	0,0575	0,0025	0,0498	0,0659
	pNfSt1	0,0088	0,0088	0,0012	0,0054	0,0132
	pDth1	0,0586	0,0587	0,0054	0,0419	0,0746
Year 1 probabilities: Universal Ticagrelor	pNfMi2	0,0497	0,0507	0,0634	0,0000	0,4941
	pNfSt2	0,0096	0,0095	0,0156	0,0000	0,1270
	pDth2	0,0462	0,0486	0,0656	0,0000	0,5387
Year 1 probabilities: Genotype-guided	pNfMi.g1	0,0299	0,0271	0,1238	0,0000	0,9564
Clopidogrel	pNfSt.g1	0,0030	0,0030	0,0003	0,0022	0,0039
	pDth.g1	0,0111	0,0111	0,0011	0,0079	0,0155
Year 1 probabilities: Genotype-guided	pNfMi.g2	0,0497	0,0518	0,0661	0,0000	0,4140
Ticagrelor	pNfSt.g2	0,0096	0,0096	0,0009	0,0069	0,0128
	pDth.g2	0,0462	0,0457	0,0639	0,0000	0,4117
Year 2+ transition probabilities	pNoE.Dth	0,0200	0,0208	0,0879	0,0000	0,8519
	pNoE.NfMi	0,0190	0,0196	0,0618	0,0000	0,7497
	pNoE.NfSt	0,0030	0,0030	0,0003	0,0021	0,0040
	pNfMi.NfMi	0,0380	0,0380	0,0038	0,0273	0,0501
	pNfMi.Dth	0,0300	0,0299	0,0030	0,0187	0,0397
	pPostMi.NfMi	0,0390	0,0388	0,0039	0,0246	0,0540
	pPostMi.Dth	0,0600	0,0515	0,1106	0,0000	0,7820
	pNfSt.Dth	0,0743	0,0781	0,2169	0,0000	0,9993
	pPostSt.Dth	0,0300	0,0317	0,1165	0,0000	0,8919
Costs	Cost per nonfatal MI	114 932,0000	114 982,3073	10 222,1243	86 493,1758	150 246,9089
	Cost per nonfatal Stroke	139 093,0000	139 656,6373	12 825,4305	101 709,3940	179 971,6580
	Cost of death	43 425,0000	43 759,4081	4 074,0736	32 721,6882	56 678,2045
	Cost of testing	434,0000	435,7236	39,6048	334,6520	584,0989
	Cost of clopidogrel per month	129,2000	129,9586	12,5489	95,8944	179,4313
	Cost of ticagrelor per month	742,4000	744,5484	65,1539	561,4666	960,4798
Cost of states for 1 year	cNoE	4 731,0000	4 727,9414	419,9475	3 399,8034	6 235,8062
	cNfMi	149 806,0000	150 150,5007	13 616,1447	113 168,8280	196 424,9546
	cNfSt	213 764,0000	214 753,9713	19 613,9982	159 523,3268	298 198,2364
	cPostMi	2 980,0000	3 003,6765	279,8629	2 201,6115	4 121,3823
	cPostSt	2 163,0000	2 168,9995	201,2468	1 657,7140	2 943,6221
	cDth	56 601,8700	56 601,8700	0,0000	56 601,8700	56 601,8700
Utilities	uNoE	0,8763	0,8784	0,1542	0,1648	1,0000
	uNfMi	0,8136	0,8034	0,1542	0,1327	0,9990
	uNfSt	0,7379	0,7372	0,1387	0,1565	0,9877
	uPostMi	0,8680	0,8622	0,1515	0,1579	1,0000
	uPostSt	0,7350	0,7327	0,1431	0,2693	0,9801
MI and stroke occurence: **Base case**	MACE1	0,0977	0,0891	0,0232	0,0705	0,1876
Life years gained	LYG1	13,3350	13,6006	0,6799	11,3126	15,3566
	QALY1	11,6322	11,8905	1,8608	3,2465	14,6744
	COST1	1 645 118,1117	1 627 134,2769	65 109,5907	1 515 683,4574	1 899 112,5440
MI and stroke occurence: **Ticagrelor**	MACE2	0,0897	0,0822	0,0776	0,0027	0,6303
	LYG2	13,5260	13,7593	1,1776	6,9346	16,3997
	QALY2	11,7936	12,0347	2,0934	3,2952	15,7173
	COST2	1 696 361,2025	1 674 786,0356	130 068,0754	844 094,8307	2 025 407,7220
MI and stroke occurence: **Genotype**	MACE3	0,0684	0,0579	0,1056	0,0049	0,8278
	LYG3	13,5260	13,7593	1,1776	6,9346	16,3997
	QALY3	12,1614	12,4509	2,0122	3,2322	15,7243
	COST3	1 665 068,0785	1 644 578,3424	82 881,1436	1 506 695,0208	2 077 938,5983
Strategy 3 vs 2: Genotype vs base case	Incr MACE	0,0293	0,0312	0,1024	- 0,7458	0,0803
	Incr LYGs	0,1910	0,1587	0,9874	- 7,3965	1,2973
	Incr QALYs	0,5292	0,5605	0,4321	- 3,0607	4,7447
	Incr Cost	19 949,9668	17 444,0655	44 438,5323	- 27 121,4055	350 060,2398
	ICER(MACE)	681 008,1774	559 033,9236	8 597 020,4026	- 24 329 541,8917	193 914 368,8702
	ICER(LYG)	104 440,7602	109 943,6186	770 438,6427	- 3 826 865,1102	23 092 749,7464
	ICER(QALY)	37 701,7387	31 124,7975	560 738,1968	- 5 826 553,1885	10 885 110,7787