Cost-effectiveness of the Pharmacogenetic Passport as guidance for dual antiplatelet therapy in acute coronary syndrome patients undergoing primary percutaneous coronary intervention

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Rotterdam, 2020-2021
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Word count: 19199 (main text)

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Summary

The pharmacogenetic passport is a document that contains a standardized overview of genetic variations that affect drug response. The passport as designed by the Dutch Pharmacogenetics Working Group currently covers 58 variant alleles relating to 49 frequently prescribed drugs, one of which is the $P2Y_{12}$ inhibitor clopidogrel. $P2Y_{12}$ inhibitors are a component of dual antiplatelet therapy in acute coronary syndrome patients undergoing primary percutaneous coronary intervention. Today, prasugrel and ticagrelor are usually prescribed to rule out any pharmacogenetic interaction, while for certain patients the cheaper drug clopidogrel may be just as effective and may present less risk of clinical events. In this economic evaluation, the cost-effectiveness of a pharmacogenetics-guided treatment strategy was assessed by means of a cost-utility analysis.

A cohort Markov model was developed to carry out the analysis, consisting of a partitioned survival model informed by a combination of short-term and long-term pseudo patient-level survival data. The cohort of 1,000 patients was assumed to enter the post-acute state after primary percutaneous coronary intervention at the age of 65 and patients were followed until they entered the death state or when the end of the time horizon of 40 years was reached, whichever came first. The analysis was performed from a societal perspective. Adverse event incidences, utility and disutility values were retrieved from available meta-analyses and literature. With a few exceptions, all data was specifically applicable to acute coronary syndrome patients undergoing primary percutaneous coronary intervention. Relevant healthcare cost categories were based on Dutch clinical guidelines on medication, treatment, and follow-up. National data on volume and price was utilized, with attention for uptake of certain treatments. Costs of life years gained, travel, informal care and productivity losses were included in the evaluation as well.

The main outcome of this economic evaluation is that the pharmacogenetic-passport-guided treatment strategy costs € 2,342 per quality-adjusted life year based on the deterministic analysis. On average, the costs for pharmacogenetic-passport-guided treatment are € 77,249 per patient over a lifetime, accumulating 12.7 quality-adjusted life years. The costs for the standard treatment are € 75,768 per patient over a lifetime, accumulating 12 quality-adjusted life years. The probabilistic sensitivity analysis shows that there is a 70% chance the intervention is cost-effective at a threshold of € 20,000 and 46% of the simulations indicate the intervention is cost-saving. The parameters affecting the deterministic ICUR the most are the costs related to life years gained in both arms, the costs of the pharmacogenetic passport and the utility values of acute coronary syndrome patients.

Comparison with related works reveals this economic evaluation is unique in several ways. It is the first Dutch economic evaluation on pharmacogenetic-guided dual antiplatelet therapy compared with the current standard treatment. Next to that, none of the related works did operationalize a societal perspective. Limitations of this economic evaluation are that several assumptions made regarding survival data, interpolation and extrapolation thereof, and the choice of parametric curve might have led to an overestimation of survival rates. The deterministic results are valid only for the examined proportions of antiplatelet drugs and generalization to largely diverging genotype-guided treatment strategies is limited. The results may be subject to biases that are inherent to applied methods of utility measurement. Several recommendations have been made regarding reimbursement decisions and future research on the pharmacogenetic passport.

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List of abbreviations

ACS	acute coronary syndrome
ACE	angiotensin converting enzyme
AF	atrial fibrillation
AIC	Akaike Information Criterion
ADP	adenosine diphosphate
AMI	acute myocardial infarction
CABG	coronary artery bypass grafting
CBA	cost-benefit analysis
CCS	chronic coronary syndrome
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CMA	cost-minimalization analysis
CU	cost-utility
CUA	cost-utility analysis
DAPT	dual antiplatelet therapy
DNA	deoxyribonucleic acid
DPWG	Dutch Pharmacogenetics Working Group
DTC	Diagnosis Treatment Combination
EQ-5D	EuroQol 5D
ESC	European Society of Cardiology
GP	general practitioner
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
iDBC	Disease Burden Calculator
iPCQ	Productivity Cost Questionnaire
KM	Kaplan-Meier
LOF	loss-of-function
LY	life year

MACE	major adverse cardiovascular event
MI	myocardial infarction
NVKC	Nederlands Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde
NVVC	Nederlandse Vereniging voor Cardiologie
NZa	Nederlandse Zorgautoriteit
PAID	Practical Application to Include future Disease costs
PCC	patient-centered care
PCI	percutaneous coronary intervention
PGx	pharmacogenetic
PLATO-criteria	Platelet Inhibition and Patient Outcomes
PPI	proton pump inhibitor
PSA	probabilistic sensitivity analysis
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life year
RNA	ribonucleic acid
SF-36	36-Item Short Form
SF-6D	Short Form 6D
SNP	single nucleotide polymorphisms
STEMI	ST elevation myocardial infarction
TECH-VER	TECHnical VERification
TIA	transient ischemic attack
TIMI-criteria	Thrombolysis in Myocardial Infarction criteria
TTO	time-trade-off
UAP	unstable angina pectoris
US	United States
VAS	visual analogue scale

1. Introduction

The concept of personalized medicine is emerging in the field of patient-centered care (PCC). PCC pays substantial attention to tailoring healthcare for each patient's particular needs. PCC relates to improved patient experience,(1) higher adherence(2) and cost-effective healthcare.(3) A specific form of PCC is personalized medicine, encompassing diagnostics, treatment and care adjusted to characteristics of individuals. It has been argued that the individual characteristics considered should consist of a multitude of factors in order to fully optimize individual patient treatment, see Figure 1.

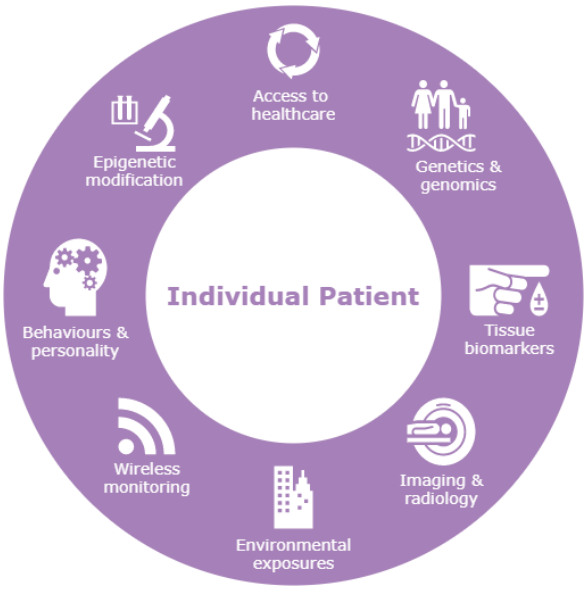

Figure 1. ''Graphical depiction of elements in need of integration and assessment in pursuing truly personalized medicine'' according to Goetz and Schork, adapted image.(4)

The element of genetics and genomics is the topic of interest in pharmacogenomics. Pharmacogenomics analyzes in what way drug metabolism and response are affected by deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) characteristics.(5) Such DNA characteristics can for example consist of single nucleotide polymorphisms (SNPs), variabilities in sequences (genetic variation), haplotypes or cytogenetic rearrangements. RNA characteristics can include RNA sequences, expression levels and processing. Pharmacogenetics is a subset of pharmacogenomics, studying genetic variation in relation to drug response.(6) The field of drug response research includes connecting genetic variation to incidence of adverse events and drug efficacy. Pharmacogenetic research can contribute to personalized drug therapy through informing the clinician on appropriate dosage and/or appropriate drug selection and possible interaction or side effects, improving the traditional trial-and-error drug prescription approach.

Pharmacogenetic information of individuals can be accessed through pharmacogenetic testing. Testing can be done on different moments in time. A distinction can be made between preemptive and reactive testing. If testing is done before the onset of the disease course, i.e., the testing is conducted preemptively, and no manifestation of disease has occurred yet. Reactive testing is done in the stadium before prescription to attempt maximal treatment effectiveness of the indicated drug for the condition of the patient.(7) Analysis can be performed for a singular gene or multiple genes using a panel-based approach.(8) The panel-based approach allows for standardization in terms of which genetic variants are tested for. Researchers have created a so-called pharmacogenetic passport

(PGx-Passport) that contains a standardized selection of variant alleles for which clinical guidelines of the Dutch Pharmacogenetics Working Group (DPWG) are available.(9) This PGx-Passport currently covers 58 variant alleles relating to 49 frequently prescribed drugs.

One of the barriers that prevents implementation of pharmacogenetics in routine care, is the yet to be made reimbursement decision about pharmacogenetic tests.(10) An important factor in reimbursement decisions is information on the cost-effectiveness of pharmacogenetic testing.(11)

This economic evaluation focused on one medicine that is included in the PGx-Passport: clopidogrel. Clopidogrel is a $P2Y_{12}$ inhibitor. $P2Y_{12}$ inhibitors selectively inhibit the $P2Y_{12}$ adenosine diphosphate (ADP) receptor of platelets. Inhibition results in a decrease of the binding of fibrinogen to the GPIIb and GPIIIa receptors on the platelets' surface. This way, $P2Y_{12}$-dependent platelet activation, platelet aggregation, and thrombus formation are prevented.(12)

In patients with acute coronary syndrome (ACS) undergoing primary percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is indicated. DAPT consists of the combination of aspirin and a $P2Y_{12}$ inhibitor. ACS is an unstable ischemic heart disease. The definition of ACS includes acute myocardial infarction (AMI, both with ST elevation, STEMI, and without, non-STEMI) and unstable angina pectoris (UAP). A partially or completely occluded coronary artery causes oxygen imbalance. Several factors, such as the degree of coronary occlusion and the pre-existing cardiac condition, determine the degree of ischemia and myocardial necrosis.(13) STEMI is visible on the electrocardiogram as ST elevation and is caused by complete occlusion of the coronary vessels.(14) Non-STEMI does not cause ST elevation and can happen due to intermittent or incomplete occlusion. The definition of UAP is myocardial ischemia at a resting state or during minimal exertion, without myocardial necrosis. No elevated cardiac biomarkers point by definition in the direction of a UAP.(13) It is common for a STEMI to occur after a non-STEMI or a UAP, in 5% to 40% of the cases.(15)

A PCI is the deployment of a stent in the stenosis. Via a guide wire that is inserted through the stenosis, a catheter with a stent is brought in on a balloon. Inflation of the balloon opens the stent in the stenosis.(16) There are thirty Dutch heart and angioplasty centers that perform PCIs. Between 2015 and 2019, the yearly number of registered PCIs in the Netherlands remained quite constant: between 40,134 and 41,048 interventions are performed. The average number of treatments per unique patient per year is approximately 1.13.(17) In-hospital mortality in the Netherlands is 4-12% in AMI patients, which makes AMI one of the most common causes of death. Those numbers illustrate the importance of the common clinical choice for a type of antiplatelet therapy.

There are several $P2Y_{12}$ inhibitor options to choose from. In the Netherlands, clopidogrel, prasugrel, ticagrelor and cangrelor are available.(12) The Dutch Society for Cardiology (Nederlandse Vereniging voor Cardiologie, NVVC) prescribes which guidelines must be followed in the field of cardiology. For ACS, the European cardiology guidelines of the European Society of Cardiology (ESC) must be adhered to.(18) The European guidelines prefer prasugrel or ticagrelor before and after primary PCI in case of a STEMI.(14) In non-STEMI patients, the same recommendation has been made.(13) Antiplatelet therapy for UAP follows the applicable standards for non-STEMI treatment.(19) Cangrelor is, unlike the other three $P2Y_{12}$ inhibitors, administered parenterally and therefore recommended for consideration if the patient is unable to absorb oral agents.(14)

For a long time, clopidogrel was the mainstay of PCI related therapies. However, the extent to which clopidogrel is enzymatically activated differs among people depending on their genotype. The enzyme CYP2C19 dominantly determines the activation of clopidogrel and there is interindividual variability in CYP2C19 production. Loss-of-function (LOF) alleles of a CYP2C19 mutation cause lower clopidogrel

active metabolite levels. The LOF variants lead to impaired clopidogrel activation, causing the drug to not work as well as in patients without a mutation. Especially LOF CYP2C19*2 and *3 variants have been associated with an increased risk for major adverse cardiovascular events (MACEs).(20) Even though the efficacy of clopidogrel is similar to that of prasugrel and ticagrelor in patients without a mutation,(21) the latter two have become a standard part of DAPT for all ACS patients after primary PCI. Prasugrel and ticagrelor do not show pharmacogenetic interaction, but the downside is that these drugs impose a higher risk of bleeding,(22) and are more expensive compared to clopidogrel.(23)

Pharmacogenetic testing can be used to identify CYP2C19*2 and *3 carriers, personalizing antiplatelet therapy based on the patients' genotype. The PGx-Passport proposed by the DPWG currently contains nine variant alleles of the CYP2C19 gene, including the alleles interacting with clopidogrel.(9) In this context, the PGx-Passport could function as guidance in selecting patients that will not benefit from clopidogrel so that prasugrel or ticagrelor can be prescribed to them. The less expensive clopidogrel could be prescribed to the rest of the patients, preventing them from being exposed to unnecessary increased bleeding risks. However, the costs of the PGx-Passport could outweigh the added value of pharmacogenetic information guiding antiplatelet therapy.

A cost-utility analysis (CUA) of the PGx-Passport contributes to informed political decision-making, and reimbursement decisions for new interventions, which reflects the practical relevance. CUA-results are therefore relevant as well for clinical protocols and in the end, patients. The CUA could contribute to knowledge-improvement regarding the PGx-Passport, since not a lot is known about it in clinical practice, which shows potential theoretical relevance. Furthermore, a literature review (which will be discussed in greater detail in the Discussion section) has demonstrated that no economic evaluation on this intervention has been performed yet for the Netherlands, or for any European country. The results of the available economic evaluations do not unambiguously agree on the cost-effectiveness of the PGx-Passport. The objective of this study was to contribute to providing evidence for the cost-utility of PGx-Passport-guided antiplatelet therapy to inform reimbursement decisions, thereby possibly accelerating clinical implication of preemptive pharmacogenetic testing. The research question was the following:

''What is the cost-utility of PGx-Passport-guided antiplatelet therapy for ACS patients that underwent primary PCI with stent compared to regular antiplatelet therapy in the Netherlands?''

Secondary questions were:

- What are the health effects of PGx-Passport-guided and non-PGx-Passport-guided antiplatelet therapy?
- What are the costs of PGx-Passport-guided and non-PGx-Passport-guided antiplatelet therapy?
- What is the incremental cost-utility ratio (ICUR), using the abovementioned effects and costs?
- To what extent does the ICUR respond to changes in input parameters? (Sensitivity analysis)
- How could the results of this study inform a reimbursement decision concerning the PGx-Passport in the Netherlands?

In the Theoretical Framework, some important topics of health technology assessment are introduced. The Methods section elaborates on the data collection, creation of survival curves and model parameters, and the setup of the sensitivity analyses. The model outcomes are reported and interpreted in the Results section. The Discussion section elaborates on related work, assumptions made, and offers in-depth discussion of some assumptions in the light of behavioral decision theory. Several recommendations have been made.

2. Theoretical Framework

2.1 Economic evaluation

Health technology assessment is a systematic evaluation of properties, effects and impacts of health technologies with economic evaluation as its core. Economic evaluation deals with costs and consequences of alternative courses of action, thereby being suitable as transparent and unbiased policy tool for decision making guidance. An economic evaluation identifies, measures, values, and compares alternatives. Economic evaluations are thus by definition comparative, since the costs and effects of the intervention-strategy are compared with a comparator-strategy.(24) The intervention is the action that needs to be assessed. The comparator-strategy is the alternative strategy to which the intervention-strategy is compared. Common comparators are standard interventions or, if there is no available treatment, a placebo or non-treatment.(24)

Not all economic evaluations use the same techniques. Types of analyses are cost-utility analysis (CUA), cost-minimalization analysis (CMA), cost-benefit analysis (CBA), and cost-effectiveness analysis (CEA). Across those types, the identification of incremental costs and their measurement in monetary units is identical. The main difference is the nature of the consequences. In CUA, effects are expressed in quality-adjusted life years (QALYs) or utility values. In CMA, the effects are kept equal and only costs are reviewed. In CBA, the effects are expressed in monetary terms. CEA expresses incremental effects in natural units, which leads to multiple outcome measurements.(24) A great advantage of CUA stated in Dutch guidelines is the comparability of outcomes.(25) Next to that, QALYs encompass a multidimensional metric that allows for the consideration of both length of life and health-related quality of life.(26)

2.2 Effects and costs

Quality of life can be measured directly and indirectly. Direct valuation is done by patients themselves by valuing their own health condition. Indirect valuation entails a description of a condition by patients and valuation of said condition by the general public. Some methods that are frequently used in direct valuation are the time-trade-off (TTO), the standard gamble (SG) and the visual analogue scale (VAS).(24) All methods are accompanied by all types of advantages and disadvantages due to biases. In general, the TTO is considered to generate results that are the most consistent with individual preferences (although with a slight upwards bias).(27) Indirect valuation can be done through generic and disease-specific questionnaires. Disease-specific questionnaires are tailored towards a specific disease. Generic questionnaires are broad and more general in nature. An example of a generic questionnaire is the EuroQol 5D (EQ-5D) that connects TTO scores on five health dimensions: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. Other commonly used generic instruments are the Short Form 6D (SF-6D) and the Health Utilities Index (HUI).(24) Dutch guidelines appoint indirect valuation to assure an accurate societal perspective. A generic instrument is preferred because quality of life needs to be measured in a broad sense in a societal perspective and generic questionnaires allow for comparisons between interventions more easily. Furthermore, the EQ-5D is strongly preferred for its thorough development and the availability of Dutch valuations. For Dutch economic evaluations, it is advised to make use of valuations of the Dutch general public if possible.(28)

What types of costs and effects are considered exactly depends on the chosen perspective. A societal perspective for example considers all costs no matter who carries the burden of those. Other perspectives are more limited. A healthcare perspective only considers costs and effects falling on the

healthcare budget of the government. A patient perspective examines costs and effects of the patient and a payer perspective revolves around the party that provides financing in healthcare.

There are several types of costs that should be reckoned with in economic evaluations with a societal perspective. First, costs within the healthcare sector are costs directly related to the intervention (and associated adverse events), diagnosis, therapy, treatment, and provision of regular care. Within this category, indirect medical costs related to life years gained also need to be considered. The relevant cost items can be identified by looking at the natural history of the disease and treatment pathways. Systematic literature reviews, treatment guidelines, pilot samples and expert opinions are useful sources.

Second, costs of patients and their family, such as travelling costs and costs of informal care could be considered. Informal care is care on a voluntary basis, provided within a prior social relationship. For caregiving activities to qualify as informal care, it is necessary it is provided due to health problems or ageing for more than two weeks.(29) The monetary value of informal care is calculated by multiplying the number of hours spent on it with the value of providing care. There are four methods on the valuation of formal care.(29) The opportunity cost method looks at what has been sacrificed for the informal care, like paid or unpaid work, or leisure time. The proxy good method looks at the shadow price of the specific care that has been provided, for example household activities or personal care. The contingent valuation method values informal care by looking at a hypothetical willingness to pay or willingness to accept of the caregiver. The conjoint measurement method measures preferences between different hypothetical situations that consist of attributes so that (dis)utility of providing informal care can be estimated. The proxy good method is commonly used in Dutch economic evaluations.(28)

Third, there could occur costs within other sectors, like productivity costs.(25) Productivity costs lead to real wealth decreases which is why it is considered a substantial societal cost. Productivity costs consist of the costs associated with production loss and replacement due to illness, disability, or death of productive persons. Reduced productivity is called presenteeism and being totally absent from work is called absenteeism. There are several methods on how to include productivity costs in an economic evaluation.(24) ''Transfer payments'' sets productivity costs equal to sick pay. The human capital method uses the prognosis of income as representation of productivity loss. The friction cost method differentiates between short-term and long-term absence and reckons with the vacancy period, level of unemployment and age and sex specific production.(30) The friction cost method is commonly used in Dutch economic evaluations.(28)

2.3 Discounting

Costs and effects will occur through several years. Discounting is necessary to convert costs and effects to present value. Time discounting is defined as reductions to a basic price of goods and services when they are received later in time compared to the same goods and services received immediately. In general, it is assumed rewards are preferred to be gained as soon as possible whereas costs are preferred to occur as late as possible. The underlying reason for these preferences is that we give less weight to the future than to the present. In behavioral economics, several explanations have been opted for giving less weight to the future.(31) One explanation is that investment opportunities lead to opportunity costs. If a budget is spent now, the money cannot be invested in attractive alternatives such as shares, stocks, and assets. Another explanation is uncertainty. The future is uncertain, which is generally disliked, which is why moving benefits to the future is undesirable.(31) There are several discounting theories. The neoclassical discounting theory entails that effects and costs in every period are multiplied by a time weight, so that the total discounted effects and costs of an outcome profile

can be calculated by summing up the periods. This results in a constant discounting rate.(32) Non-constant discounting rates result from hyperbolic discounting methods, like quasi-hyperbolic discounting (combination of a decreasing discounting rate and a constant discounting rate) or generalized hyperbolic discounting (continuously decreasing discounting rates). Differential discounting means that costs and benefits are discounted differently.(32) Dutch guidelines prescribe the use of differential constant discounting: 4% for costs and 1.5% for effects.(25)

2.4 Modelling in health technology assessment

Usually there is no data that represents a patients' lifetime, which is where health economic modelling comes in. A cohort model characterizes the experience of the average patient from the population. There are cohort decision trees and cohort Markov models. Decision trees and Markov models are not mutually exclusive: they can be used jointly by combining one or more trees and models.(26) Decision trees are not a very convenient format for incorporating complexity and a multitude of aspects, since the number of branches could become unwieldy. A cohort Markov model allows analysis of a set of possible transitions between states of (ill-)health over a series of cycles.(26) The cycle length is the time interval between transitions. The Markov model allows one event to happen per cycle. Therefore, the cycle length should fit the nature of the disease. As for the timing of the transition between health states, bias could occur when it is assumed that all patients move at the beginning or the end of a cycle to another state. A half-cycle correction should be applied to account for the fact that some patients will move at the beginning and some at the end of the cycle. From a societal perspective, where all consequences of the intervention and the comparator must be taken into consideration, the time horizon of the model should be long enough to reflect all important differences in costs and outcomes between the intervention and the comparator.(33)

A Markov trace shows the number of patients in each health state at every cycle. To determine the time a patient will spend in a health state before transitioning to another health state or death, the survival function needs to be known. The survival function indicates the probability that there is no progression or death at least to a certain point in time. There are two ways to estimate the survival function. The first is the parametric approach. In this approach, a smooth curve is fitted through observed, empirical data. The non-parametric method looks at the observed data as it is.(34) Ideally, individual patient data is used for these estimations, but individual patient data is not always available. Pseudo individual patient-level data can be generated by reading published Kaplan-Meier (KM) graphs. KM graphs show times of events, the event usually being progression or death. KM graphs can contain censored events, which means that an observation is not complete, due to no follow-up, withdrawal from study or no event by the end of the study period.(35) A survival curve can be used to estimate the transition probability per cycle, or to directly estimate the Markov trace in a partitioned survival model.(34)

Often the pseudo patient-level data observed from the KM graphs does not reach the point where all patients have progressed or died. The solution for encountering gaps in empirical evidence is extrapolation.(26) Extrapolation can be done by using parametric functions that smooth out the KM curves. There are several parametric distributions, such as Weibull, exponential, lognormal, loglogistic, generalized gamma and Gompertz distributions. The statistical fit of those models can be assessed by the Akaike Information Criterion (AIC) value. The lower the AIC, the lower the loss of information. Next to the AIC value, clinical plausibility should be assessed before deciding on which function to use.(36)

Costs and utilities can be incorporated as a mean value per state per cycle. Expected values can be calculated by adding costs and outcomes across the states and weighted according to the time the patient is expected to be in each state.(26)

2.5 Uncertainty

Since a model is a simplified version of reality, assumptions and choices concerning the input values must always be made. Extrapolation adds to uncertainty as well. The uncertainty surrounding the inputs should be addressed using sensitivity analyses, since these inputs affect the outcome of the economic evaluation. The main outcome of a CUA is the incremental cost-utility ratio (ICUR). The ICUR shows the additional costs of a QALY when the comparator would be replaced by the assessed intervention. The ICUR can be compared with the threshold of the willingness to pay for a QALY. Quantifying the uncertainty surrounding the ICUR can aid decision makers. There are several types of sensitivity analyses.(24) Deterministic sensitivity analysis varies one (univariate) or a few parameters (multivariate) at the time to investigate the relative impact of parameters. A probabilistic sensitivity analysis (PSA) varies all parameters at the same time. For each input variable, a probability distribution is chosen. Drawing random numbers from each distribution repeatedly in a simulation and calculating the accompanying ICUR can be displayed in a cost-utility plane (CU-plane). By adding various thresholds to the results displayed in the cost-utility plane, it can be calculated which percentage of ICURs is acceptable given a certain threshold. A cost-effectiveness acceptability curve (CEAC) can be constructed. A CEAC displays the chance that an intervention is cost-effective for several thresholds.(37)

3. Research Methods

3.1 Framing & Model structure

The object of this economic evaluation was to assess the cost-utility of PGx-Passport-guided antiplatelet therapy for ACS patients that underwent primary PCI compared to regular antiplatelet therapy in the Netherlands. The audience of this CUA was the Dutch government. The Dutch government being the main user had the implication that a societal perspective was adopted as recommended by Dutch guidelines for health technology assessment.(25) As a consequence, healthcare sector costs, travelling costs, informal care costs, and productivity costs were considered relevant. National data on volume, price, and quality of life have been used as much as possible. Standard Dutch discounting and indexing percentages have been used. The intervention of interest is PGx-guided antiplatelet therapy on a background aspirin therapy. Since there are concise protocols guiding treatment after primary PCI, and Dutch guidelines on economic evaluation require comparison with usual care,(25) the comparator consisted of the standard treatment.(38) For ACS patients, this is antiplatelet therapy on a background aspirin therapy without any pharmacogenetic guidance.

The target population was a homogenous group of 65-year-old patients from the Netherlands. The male-female ratio is 3:1. All patients suffered from a STEMI, non-STEMI or UAP and were treated with PCI with stent placement. The implemented stents were drug-eluting or bare metal stents. The population was characterized by the presence of some cardiovascular risk factors such as smoking, diabetes mellitus or a family history of coronary artery disease. Some patients of the population have undergone a PCI with stenting before.

A time horizon of 40 years was applied, in other words, the cycle in which the remaining population turned 105 years old. The reason behind the choice for this time horizon lied in an inherent property of extrapolation: the mortality rate observed in trials is assumed to continue into the future. Although this could be a valid starting point for the first extrapolated years, and over the past couple of years the life expectancy of ACS patients has been improving, it is reasonable to expect that survival curves decline more rapidly in an elderly cohort after the follow-up period.(39) A time horizon of 40 years causes a proportion of patients still alive according to the extrapolated curve to be discarded. However, it was expected that the most important costs and effects of the intervention were captured within 40 years.

The CUA was carried out using a cohort Markov model. The cohort Markov model was developed in Microsoft Excel to evaluate the cost-utility of PGx-guided antiplatelet treatment compared to standard, non-PGx-guided treatment after primary PCI. The Markov model consists of two states: a post-acute state that patients enter after the primary PCI, and a death state, representing mortality of all causes. The Markov model is pictured in Figure 2. Patients only move from the post-acute state to the death state, or they stay in the post-acute state. No additional states were modelled for the occurrence of adverse events. Instead, utility decrement and costs were applied at defined incidence rates in the post-acute health state. The post-acute state was not split up into a separate DAPT state and a post-DAPT state, because DAPT is indicated for a fixed period time, which causes the absence of a transition probability. Even though costs and utilities differ during and after DAPT, they could be differentiated in the cycles so that a single post-acute health state sufficed.

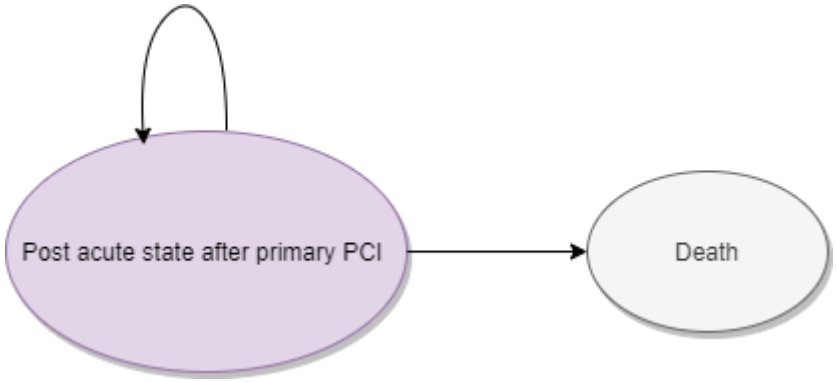

Figure 2. Markov model.

For the first year in the post-acute state, a cycle length of 4 weeks was applied. After the first year, the cycle length was changed into 12 weeks. The varying cycle length was deemed appropriate since the incidence of events is relatively high in the first year in the post-acute state and decreases afterwards, and a Markov model only allows for a single event to happen during a cycle.

3.2 Model inputs – Survival analysis

3.2.1 Collection of survival data

Estimating the probability of moving from the post-acute state to the death state has been based on several sources. The ''CYP2C19 Genotype-Guided Antiplatelet Therapy in ST-Segment Elevation Myocardial Infarction Patients — Patient Outcome after Primary PCI'' (POPular Genetics) clinical trial is an open-label, randomized, assessor-blinded trial in which patients undergoing primary PCI with stent implantation received genotype-guided treatment or standard DAPT in a 1:1 ratio.(40) The genotype-guided treatment arm entailed patients being tested for CYP2C19 LOF alleles. Patients with CYP2C19*2 and CYP2C19*3 variants received prasugrel or ticagrelor, patients without such LOF alleles received clopidogrel. The genetic testing resulted in 60.6% of patients receiving clopidogrel, 1.0% prasugrel and 38.1% ticagrelor in the genotype-guided group. Prasugrel or ticagrelor were prescribed to the standard treatment arm. In practice, 90.5% of patients in de standard treatment arm received ticagrelor, 2.3% prasugrel and 7.0% clopidogrel. See table 1. Next to a $P2Y_{12}$ inhibitor, aspirin was prescribed to all patients as a part of the DAPT. All patients enrolled had STEMI symptoms. The two primary combined outcomes measured consisted of 1. death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding (according to Platelet Inhibition and Patient Outcomes – PLATO – criteria) and 2. major and minor bleeding according to PLATO criteria.

	Clopidogrel	**Prasugrel**	**Ticagrelor**
Genotype-guided arm	60.6%	1.0%	38.1%
Standard treatment arm	7.0%	2.3%	90.5%

Table 1. Ratios of $P2Y_{12}$ inhibitor in the POPular Genetics treatment arms.

The POPular Genetics study had a follow-up of 12 months. The two arms were considered to be relevant for the research question central to this economic evaluation, since the genotype-guided

approach leads to the same treatment strategy as the use of the PGx-Passport would, assuming all doctors would adhere to the information in the PGx-Passport. Next to that, the control group received a standard treatment that accurately reflects that standard treatment in the Netherlands as prescribed by European guidelines. Furthermore, the clinical trial was performed at 10 European sites from which 8 in the Netherlands, 1 in Belgium and 1 in Italy. The patient population therefore is expected to reflect the baseline characteristics of the average Dutch patient. The average age of the Dutch patient who undergoes PCI is approximately 65 according to registrations of Dutch facilities.(17) The average age in the POPular Genetics study was slightly lower: 61.9 and 61.4 for the genotype-guided and standard treatment group, respectively.

Since no patient-level data of all patients until the whole cohort died was available, the empirical data had to be extrapolated. As the transition probabilities are prone to change as life years increase and extrapolation based on just a years' worth of data is expected to increase uncertainty, it was considered necessary to combine the POPular Genetics survival data with that of studies covering longer follow-up periods. Since no other studies with the same genotype-guided approach and the same standard treatment were available at the time of writing, it was opted for to select several studies with data on individual $P2Y_{12}$ inhibitors and combine those in the ratios as presented in table 1. Studies were searched for using the PubMed and Embase databases. Table 2 provides an overview of available studies that were eligible based on their patient population being sufficiently consistent with that from POPular Genetics, availability of outcomes as time-to-event data, and a follow-up duration longer than 12 months.

The limited number of studies could be attributed to the fact that most studies involve a year of follow-up, as DAPT is usually prescribed for approximately the first year after the primary PCI procedure. As for the long-term data concerning survival after clopidogrel as $P2Y_{12}$ inhibitor in DAPT, two studies were available. The ''Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel - Thrombolysis in Myocardial Infarction'' (TRITON-TIMI) 38 study was a phase 3 trial comparing clopidogrel and prasugrel regimens.(41) TRITON-TIMI 38 is regarded as one of the landmark studies for these two antiplatelet therapies. The other available study was a report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).(42) The SCAAR report is an observational analysis of data of hospitals in western Sweden, tracking long-term mortality rates of patients that have undergone primary PCI and DAPT with clopidogrel or ticagrelor. The data for patients treated with clopidogrel cover 11 years. While the demographic characteristics of the patients of TRITON-TIMI 38 are more similar to those in POPular Genetics, the SCAAR report was preferred as data source for clopidogrel overall survival estimates because 10 years of data has quite additional value compared to data covering only a 450-day period after PCI. Next to that, the SCAAR report is an unselected study with the advantage that it reflects clinical reality, since no exclusion criteria have been applied to the case mix. Lastly, TRITON-TIMI 38 not only included patients undergoing primary PCI, but also undergoing elective (staged) PCI, which could cloud the data in the sense that average mortality and stroke rates are lower after elective PCI.(43)

	Data		Source
Data up until 12 months	Primary combined outcome: -death from any cause (1.5% vs 1.5%) -myocardial infarction (1.5% vs 2.1%) -definite stent thrombosis (0.2% vs 0.2%) -stroke (0.6% vs 0.9%) Primary bleeding outcome: -PLATO major or minor bleeding (9.8% vs 12.5%)	KM curves (figure 2) + tables (table 2 and 3)	**POPular Genetics** (40) *Comparison: CYP2C19 genotype-guided vs standard ticagrelor/prasugrel + aspirin.* *Population: STEMI, undergoing primary PCI with stent implementation*
Data after 12 months	Primary efficacy end point: -death from cardiovascular causes (9.9% vs 12.1%) -myocardial infarction (7.3% vs 9.5%) -stroke (1.0% vs 1.0%) Key safety end point: -TIMI major bleeding (2.4% vs 1.8%)	KM curves (figure 1A) + tables (table 2 and 3)	**TRITON-TIMI 38** (41) *Comparison: prasugrel + aspirin vs clopidogrel + aspirin for 450 days.* *Population: ACS, undergoing PCI with stent implementation*
	-all cause death (2.3% vs 2.0%) -myocardial infarction (7.4% vs 3.7%) -stroke (0.9% vs 0.8%) -definite + probable stent thrombosis (2.9% vs 0.8%) -major bleeding (1.9% vs 2.6%)	KM curves (figure 2B, 2C, 2D, 3A and 4A)	**TL-PAS** (44) *Comparison: 12 months prasugrel + aspirin followed by 18 months placebo + aspirin vs 30 months prasugrel + aspirin.* *Population: ACS + stable angina, PCI with drug-eluting stent implementation*
	-all cause death (non-staged PCI) (3.1% vs 3.3%) -BARC 3 or 5 bleeding (non-staged PCI) (2.0% vs 2.4%)	KM curves (figure 2A and 2B) + table (figure 4)	**GLOBAL LEADERS** (45) *Comparison: 1 month ticagrelor + aspirin followed by 23 months ticagrelor vs 12 months ticagrelor + aspirin followed by 12 months aspirin. Sub study comparing staged PCI and non-staged PCI.* *Population: ACS and CCS, PCI with stent implementation*
	-all cause mortality (31% vs 11%)	KM curve (figure 4)	**SCAAR report** (42) *Comparison: mortality in clopidogrel vs ticagrelor + aspirin, 10-year/3.5-year observation.* *Population: ACS, primary PCI with stent implementation*

Table 2. Eligible studies for survival analysis. Grey area shows data up until 12 months. The purple area shows data over longer follow-up periods. The ''Data'' column sums up which relevant events were measured as occurrences over time and where those data were found in the studies referenced. The ''Source'' column mentions the study, the treatments compared in said study, indication for PCI and type of PCI performed.

There were two options for the long-term data on prasugrel: again, TRITON-TIMI 38, and the ''TAXUS Liberté Post Approval Study'' (TL-PAS).(44) TL-PAS was a multicenter, open-label study, reviewing two different DAPT durations after drug-eluting stent placement. One study arm received prasugrel for 12 months, followed by 18 months placebo. The other study arm received prasugrel for 30 months. The first arm was considered eligible for the overall survival estimates after prasugrel, since 12 months corresponds to the standard duration of DAPT and the extended treatment with a placebo allows for data observations after DAPT was finished. The demographic characteristics of patients of both TRITON-TIMI 38 and TL-PAS are greatly similar to those of the POPular Genetics population. TRITON-TIMI 38 has the disadvantage of the inclusion of elective PCI, TL-PAS comprises an akin disadvantage with the inclusion of stabile angina patients (next to ACS) and the implementation of only drug-eluting stents (the other studies usually show an equal division of drug-eluting and bare metal stents). Especially the use of drug-eluting stents could be one of the determinants of the clinical outcomes in TL-PAS. Despite the mentioned disadvantages, TL-PAS was preferred because TRITON-TIMI 38 published KM-curves that contain a cumulative primary efficacy end point which would have had required additional assumptions when estimating overall survival curves.

The estimation of overall survival rates after DAPT with ticagrelor as $P2Y_{12}$ inhibitor could be based on the SCAAR report or a sub study from GLOBAL LEADERS, a multicenter, open-label randomized controlled trial.(45) GLOBAL LEADERS compared 1 month of DAPT with ticagrelor followed by 23 months of ticagrelor monotherapy with the standard 12-month DAPT with ticagrelor. The data of the second arm could be used in this evaluation. Originally, the trial included both staged and non-staged PCI, but the sub study researched those two groups separately, which allows the application of the non-staged data to this economic evaluation. GLOBAL LEADERS however also included chronic coronary syndrome (CCS) patients. CCS consists of a multitude of clinical scenarios with different risks for future cardiovascular events,(46) which makes including this patient data undesirable. The CCS data are nevertheless expected to be largely excluded in the non-staged PCI data, because PCI in CCS patients is normally elective. The SCAAR report contains 3.5 years of observation data on long-term mortality after DAPT with ticagrelor. Both GLOBAL LEADERS and the SCAAR report both represent a slight mismatch with POPular Genetics in epidemiological data, since the average age of both populations is somewhat higher. The GLOBAL LEADERS population is more alike. Even though the GLOBAL LEADERS population was more consistent with that of POPular Genetics, the SCAAR data was preferred for the longer follow-up time and the survival rate being in line with all other studies, where GLOBAL LEADERS showed a divergently flat curved mortality rate. Next to that, the average age in the SCAAR report corresponded well what that of the cohort of this study.

The patient population of all studies consisted of a mix of patients who were undergoing their first (primary) PCI and patients who previously underwent one, reflecting a realistic case mix. Next to that, in all studies, the $P2Y_{12}$ inhibitor was always combined with aspirin, both medicines being part of DAPT. Aspirin treatment was therefore considered to equally affect all clinical outcomes.

3.2.2 Estimation of survival curves

Patient-level data from the trials was not available. With the published KM curves, pseudo individual patient-level data was created. The data of the images of all studies containing the relevant KM curves was extracted using the WebPlotDigitizer software (version 4.4). The images were individually uploaded to the software, after which reference points on the axes on the image were manually selected. Next, the relevant curve was indicated by manually marking that area of the image and indicating the color of the curve. The extraction was done automatically by the Averaging Window algorithm. The algorithm placed points on the relevant curve and translated it into pseudo individual patient-level data indicating corresponding points on the X-axis and Y-axis.

The mortality data represented by the KM graphs was translated into survival data by subtracting the mortality percentages from 100. Next, the survival data of the POPular Genetics, TL-PAS and SCAAR studies was normalized to bring all the variables to the same range. All time scales were converted to weeks. The extracted survival percentages of TL-PAS and SCAAR(ticagrelor) were linearly extrapolated to match the length of the SCAAR(clopidogrel) observations. The extrapolation was done linearly, using the trendline equation of the observed survival percentages.

The number at risk values were converted to the same scale by multiplying all population sizes with a factor that reduced the initial population size to the smallest initial population size. This way, the original rate at which the number at risk decreased throughout the study was preserved, but the KM graphs of the different studies became comparable. After that, the adjusted number at risk of the TL-PAS and SCAAR(ticagrelor) data was interpolated linearly to create the same time points at which number at risk is known for all studies, as the number at risk measurements originally took place at varying intervals. The interpolation resulted in a trendline equation that was used to extrapolate the TL-PAS and SCAAR(ticagrelor) to the timeframe of the SCAAR(clopidogrel) observations.

Lastly, both the survival percentages and the number at risk data were combined. The first 52 weeks of survival percentages and number at risk data consisted of the pseudo individual patient-level data from the POPular Genetics study. The data beyond 52 weeks up until 10 years consisted of the combination of the observed and extrapolated survival percentages of TL-PAS, SCAAR(ticagrelor) and SCAAR(clopidogrel) in the ratios presented in table 1, for both the PGx-guided and non-PGx-guided approach. The adjusted and extrapolated number at risk data was combined in the same way using the same ratios as well.

Several assumptions were made while combining survival data. First, it was assumed that interpolation of number at risk data could be done linearly. The assumption entails that between two observed numbers, the rate at which these numbers decreased was constant. Second, it was assumed that extrapolation could be done linearly. The rate at which the number at risk and the survival percentages were declining was assumed to be the rate at which these kept declining after the end of observation. Third, it was assumed that the ratio in which patients were on clopidogrel, prasugrel, and ticagrelor remained constant. These assumptions are discussed in the Discussion section in greater detail.

The underlying survival distribution was estimated using the method described by Hoyle and Henley.(47) In their ready-to-use Excel spreadsheet, the empirical survival probability $S(t)$, the number at risk $R(t)$, and the timepoints can be filled out. The spreadsheet can be used to estimate the number of censored patients and the number of patients with events within each time interval. The estimated number of events is defined as $D(t,\ t+1)$. The estimated number of censorships is defined as $C(t,\ t+1)$. The method assumes censoring is constant within each time interval. At a point halfway the time interval, both the number of events and the number of censorships are estimated at $S(t+0.5)$ using the survival probabilities at these time points. The exact same steps are followed for an estimation of events and censorships at $S(t+0.25)$ and $S(t+0.75)$. The spreadsheet was filled out to calculate the number of censorships and the number of deaths for the PGx-guided and non-PGx-guided arm separately.

The next step in the Hoyle and Henley method is fitting some parametric survival curves with a Weibull, exponential, lognormal and loglogistic distribution to the estimated number of events and censorships in each time interval.(47) The fitting was done in R (version 4.0.3), using the provided code in the Hoyle and Henley spreadsheet. The module Surv {survival} was operated. This module creates a survival object with the arguments ‘’time’’, ‘’event’’, ‘’time2’’, ‘’type’’, and ‘’origin’’.(48) The

underlying method of this module is that of maximum likelihood. The product of three terms results in likelihood $\hat{L}$:(35)

$$S(t_{max})^{R(t_{max})}$$

$$\prod_{t=0,\frac{1}{4},\frac{1}{2},\frac{3}{4},\ldots,t_{max-\frac{1}{4}}} \left[S(t) - S\left(t+\frac{1}{4}\right)\right]^{D\left(t,t+\frac{1}{4}\right)}$$

$$\prod_{t=0,\frac{1}{4},\frac{1}{2},\frac{3}{4},\ldots,t_{max-\frac{1}{4}}} S\left(t+\frac{1}{8}\right)^{C\left(t,t+\frac{1}{4}\right)}$$

The reason for the first term is that the last reported number at risk at the latest timepoint can be greater than zero, if maximum follow-up time was a bit longer beyond the timepoint. The second term expresses the assumption it is unknown when events occurred within the time interval (interval censorship). The third term expresses the assumption that censored events occurred in the middle of the time interval.(35)

The output of the R module consists of AIC values, intercept parameters, logscale parameters and Cholesky decompositions of the variance-covariance matrices of all distributions. The AIC, intercept and logscale parameters recorded from the output for the overall survival of the PGx-guided and non-PGx-guided arm are displayed in table 3.

	PG-X-guided			
	Exponential	Weibull	Lognormal	Loglogistic
AIC	2137.504	2130.377197	2396.385166	2268.156225
Intercept	7.1267	7.2237	6.4259	6.5061
Logscale		0.1091	0.4645	-0.2524
	Non-PGx-guided			
	Exponential	Weibull	Lognormal	Loglogistic
AIC	1332.813363	1321.537016	1518.827216	1434.345474
Intercept	6.9741	7.1415	6.1519	6.2037
Logscale		0.1379	0.4584	-0.2414

Table 3. R output values on survival data.

For both the PGx-guided and non-PGx-guided survival data, the Weibull distribution minimized the AIC, indicating that the Weibull curve is statistically the best fit. Visually, the Weibull distribution sufficiently fits as well. Compared to the observed data, the lognormal and loglogistic curves show a very rapid decrease in overall survival at the first years, while the observed data shows a much more gradual decrease. The Weibull curve therefore more accurately represents the observed mortality.

In Excel, the Weibull intercept and logscale values were used to created extrapolated survival curves. These curves were used to create a Markov trace that shows the number of patients in each health state at each cycle.

3.3 Model inputs – Quality of life estimates

A recent systematic review and meta-analysis of quality-of-life changes in ACS patients was used to identify relevant studies for the quality-of-life model inputs.(49) The authors of the systematic review selected 29 quantitative studies that describe the quality of life of ACS patients after PCI, coronary artery bypass grafting (CABG) and medical therapy. The selected studies were from 1999 until 2020. Using the same search strategy as described in the systematic review did not lead to finding any new studies from 2020 or 2021 that were not included by the authors. The systematic review revealed that just one study contained only Dutch ACS patients that underwent PCI. The Dutch cohort study is from 2010 and used the 36-Item Short Form Health Survey (SF-36) as measurement of the distribution of patients with poor or good health status at several time points after PCI.(50) The SF-36 has been the basis for the development of the generic SF-6D health-state measure. However, the SF-36 (unlike the SF-6D) cannot be used to compare the relative value of several composite health states as it only measures separate domains.(51) For this reason, the Dutch cohort study was considered not to form a sufficient basis for accurate QALY calculations in this economic evaluation.

As described in the theoretical framework, Dutch guidelines prefer the EQ-5D strongly over other health-related quality-of-life measures. Of the 29 studies selected for the systematic review, 7 used the EQ-5D.(49) From those studies, a randomized controlled trial with a mix of patients from Europe and North America was chosen to base utility estimates upon because the trial population consisted of a considerable number of Dutch patients and the researchers performed EQ-5D measurements at multiple points in time after PCI. The utility values are given in table 4. The values are assumed to be the same for both the PGx-Passport-guided and non-PGx-Passport-guided treatment strategy. Furthermore, the utility value measured at 12 months after primary PCI was assumed to represent the utility value after finalization of DAPT. Health-related quality of life is moreover influenced by new cardiovascular and other adverse events. The adverse event-related model inputs accounted for any decrease in quality of life caused by those events. The utility values were applied to each cycle (corrected for cycle duration) and multiplied by the number of patients alive. The death state was assumed to bring about a utility value of 0.

Cycle	Utility value	Standard error	Source
1-6	0.853	0.156	(52)
7-12	0.861	0.149	(52)
13 and beyond	0.855	0.155	(52)

Table 4. Utility values of the post-acute state after primary PCI.

3.4 Model inputs – Adverse events

For adverse events it was considered appropriate to work with varying incidence rates, since DAPT after primary PCI is prescribed for approximately one year and cardiovascular risk and bleeding risk are higher due to DAPT.(53) Therefore, incidence rates up until 1 year and incidence rates after 1 year were used in the model. For the incidence rates up until 1 year, the studies identified in a recent network meta-analysis comparing $P2Y_{12}$ inhibitors in ACS patients were analyzed.(54) The network meta-analysis included randomized clinical trials and observational studies comparing clopidogrel, prasugrel and/or ticagrelor on a background aspirin therapy. The 1-year probabilities of nonfatal

myocardial infarction (MI), nonfatal stroke, target-vessel revascularization, probable or definite stent thrombosis, major and minor bleeding (according to Thrombolysis in Myocardial Infarction (TIMI) criteria), and transient ischemic attack (TIA) were taken from the identified studies. Because some variety in the probabilities was observed, it was opted for to synthesize the data and to calculate the mean of varying incidences as a best guess. This approach aimed to account for interstudy variations. The average 1-year incidence rates are displayed in table 5.

Adverse event	Incidence clopidogrel (%)	Incidence prasugrel (%)	Incidence ticagrelor (%)	Source
Nonfatal MI	6.38	3.76	3.90	(41,55-59)
Nonfatal stroke	1.23	0.93	1.10	(41,55,56,59,60)
Target-vessel revascularization	5.23	4.43	4.50	(41,59,60)
Probable or definite stent thrombosis	2.08	1.36	1.68	(41,55,56,58-60)
Major bleeding	4.93	7.77	6.65	(41,55,56,60)
Minor bleeding	3.28	3.70	6.75	(41,55,59,60)
TIA	0.43	0.30	0.15	(55,59,60)

Table 5. Incidence rates in the first year post-PCI of adverse events per P2Y12 inhibitor.

Adverse event	Incidence genotype-guided clopidogrel (%)	Source
Nonfatal MI	0.21	(61)
Nonfatal stroke	0.75	(61,62)
Target-vessel revascularization	3.80	(62)
Probable or definite stent thrombosis	0.30	(62)
Major bleeding	3.70	(62)
Minor bleeding	3.70	(62)
TIA	0.43	Assumed

Table 6. Incidence rates in the first year post-PCI of adverse events in genotype-guided prescription of clopidogrel. Incidence of TIA was assumed the as in for regular clopidogrel prescription since no separate incidence rates were reported in the literature.

To differentiate between the PGx-guided and non-PGx-guided treatment arm, separate incidences for adverse events during DAPT with genotype-guided clopidogrel were retrieved from literature. It is known that patients with genetic LOF CYP2C19*2 and *3 variants are at higher risk for adverse events on clopidogrel. The incidence rates in table 5 were retrieved from studies that did not conduct any sort of genotyping, resulting in a presumably mixed population consisting of patients with and without allele variants influencing drug response to clopidogrel. The authors of a study on the clinical utility of CYP2C19 genotyping to guide DAPT in ACS patient undergoing PCI have provided an overview of multiple observational trials on this subject.(63) These observational trials have reported the incidences of adverse events in genotype-guided DAPT groups. The incidences of adverse events in patients on clopidogrel without LOF CYP2C19*2 and *3 variants were derived from these trials and displayed in table 6. Because genetic makeup does not influence drug response to prasugrel and ticagrelor, no separate adverse event incidence rates were considered necessary for the PGx-guided approach.

As for the long-term incidences beyond 1 year after primary PCI, a literature search was performed, selecting several studies that monitored the prevalence of adverse events after finalization of DAPT. Incidence rates were selected from studies focusing on ACS patients undergoing PCI as much as possible. No long-term information on bleeding risk and occurrence of TIA was available for ACS patients undergoing PCI in particular. Major and minor bleeding risk on aspirin monotherapy was assumed to sufficiently represent bleeding risk after DAPT, especially because ACS patients are prescribed lifelong aspirin treatment. Long-term TIA incidence was taken from a study on lacunar infarct patients on DAPT. The occurrence of adverse events was assumed to be non-dependent on the $P2Y_{12}$ inhibitor previously taken, therefore the incidences are the same for both treatment arms. See table 7.

Adverse event	Yearly incidence (%)	Range	Source
Nonfatal MI	1.3	(1.0 - 1.6)	(64)
Nonfatal stroke	0.7		(65)
Target-vessel revascularization	0.209		(64)
Probable or definite stent thrombosis	0.25	(0.04 - 0.75)	(66)
Major bleeding	1.7	(1.4 - 1.9)	(67)
Minor bleeding	1.8	(1.5 - 2.0)	(67)
TIA	0.57		(68)

Table 7. Long-term incidence of adverse events. All rates represent yearly risk. Not all sources provided ranges.

The disutilities of the mentioned adverse events were derived from several studies. Disutilities for target-vessel revascularization and stent thrombosis could be derived from studies on ACS patients undergoing PCI. The disutilities of experiencing the other adverse events were derived from studies on atrial fibrillation (AF) patients. Even though base case utility of AF patients is expected to differ from base case utility of ACS patients, only net disutilities were taken from studies (calculated by subtracting utility after the adverse event from the base case utility), which is assumed to correct sufficiently for the differing base case utility values. In table 8 the disutility values, the reported standard error or range, and duration of the disutilities are displayed. A distinction was made between acute disutilities and chronic disutilities. Most adverse events that are prevalent in ACS patients are characterized by a sudden onset, requiring direct medical intervention. Some events are however expected to permanently affect quality of life afterwards, resulting in a lifelong reduction of utility.(66) Chronic disutilities are displayed in table 9. The chronic disutilities were all derived from studies on ACS patients undergoing PCI. Acute and chronic disutilities were applied as a one-off each year in the model (the acute disutilities starting from the first year, the chronic disutilities starting from the second year). The disutilities were multiplied with the number of patients alive at the start of each year, which can have led to a slight overestimation of total disutility.

The QALYs lost due to adverse events were subtracted from the QALYs accrued, leading to a given number of total QALYs per cycle in the Markov trace.

Adverse event	Disutility	Standard error or (range)	Duration	Range of duration	Source
Nonfatal MI	-0.096	0.0156	3 months		(69)
Nonfatal stroke	-0.59	(-0.295, -0.885)	3 months		(69)
Target-vessel revascularization	-0.06		14 days	(7, 21)	(64)
Probable or definite stent thrombosis	-0.07	(-0.01, -0.135)	4 days		(66)
Major bleeding	-0.198	(-0.008, -0.498)	2 weeks		(70)
Minor bleeding	-0.198	(-0.008, -0.498)	2 days		(70)
TIA	-0.131	(-0.066, -0.197)	1 day		(69)

Table 8. Acute disutilities caused by adverse events.

Adverse event	Disutility	Standard error or (range)	Duration	Source
Nonfatal MI, first year	-0.1055	(-0.0791, -0.1319)	1 year	(71)
Nonfatal MI, subsequent years	-0.1000	(-0.0750, -0.1250)	Lifetime	(71)
Nonfatal stroke	-0.3100	-0.0205	Lifetime	(69)

Table 9. Chronic disutilities caused by adverse events.

3.5 Model inputs – Costs

Dutch guidelines on treatment of ACS patients after primary PCI have been consulted to determine cost categories. Cost categories consisted of healthcare costs (PGx-Passport, medication, post-acute treatment, follow-up, adverse events, unrelated disease in life-years gained), costs of patients and family (travelling, informal care), and costs in other sectors (productivity costs).

3.5.1 Pharmacogenetic Passport costs

As mentioned in the Introduction, the PGx-Passport based on DPWG guidelines currently covers 58 variant alleles located in 14 pharmacogenes relating to 49 frequently prescribed drugs.(9) The PGx-Passport proposed by the DPWG currently contains 9 variant alleles of the CYP2C19 gene, including the alleles interacting with clopidogrel. The Dutch Association for Clinical Chemistry and Laboratory Medicine (Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde, NVKC) provides a database with information on which laboratories in the Netherlands perform genotyping, and of which pharmacogenes.(72) Two laboratories provide tests for all pharmacogenes of the PGx-Passport: Erasmus MC and Gelre Apeldoorn. Both laboratories already provide a limited version of the PGx-Passport, both for a slightly different panel of genes. For the genes not included in these passports, only singular gene testing prices were available. Both laboratories charge a one-time order tariff. It was assumed the price of a PGx-Passport consisted of the sum of the limited passport, the singular genotyping of remaining genes, and the order tariff, see table 10. The purple cells indicate the genes that are included in the limited passport price.

Gene	Price at Erasmus MC (€)	Price at Gelre Apeldoorn (€)
CYP2B6	82.5	
CYP2C9		
CYP2C19		
CYP2D6		
CYP3A5		
DPYD	82.5	186.38
F5	127.33	66.35
HLA-A	82.5	66.35
HLA-B	82.5	66.35
NUDT15	82.5	66.35
SLCO1B1	82.5	66.35
TPMT	82.5	66.35
UGT1A1	82.5	66.35
VKORC1		
Order tariff	6.56	11.67
Limited passport price	600	699
Total	1393.89	1361.50

Table 10. Prices of panel-based and singular genotyping at two Dutch laboratories.

There were several options for incorporating the price of the PGx-Passport into the model. The assumption was made that in principle the price of the entire passport could be attributed to the healthcare costs of the PGx-guided arm. The average of the Erasmus MC and Gelre Apeldoorn price was used as a cost input. However, it is arguable that the passport can be used multiple times a lifetime, so that part of the cost of the passport should be counted here. For this reason, a scenario analysis was performed for different ways to calculate the costs, which is discussed in the sensitivity analysis section. It was assumed all patients in the PGx-guided arm had a PGx-Passport, which is why these costs were multiplied with the starting size of the cohort (1,000).

3.5.2 Medication costs

In the post-acute phase of ACS, oral maintenance drugs are prescribed long term. DAPT consisting of a $P2Y_{12}$ inhibitor and aspirin is indicated during the first 12 months after the PCI. Patients taking a combination of a $P2Y_{12}$ inhibitor and aspirin are at risk for gastric damage, therefore, medication to protect the stomach lining is indicated.(73) The proton pump inhibitor (PPI) omeprazole is preferred according to Dutch guidelines. If clopidogrel is used as a $P2Y_{12}$ inhibitor however, the PPI pantoprazole is indicated.(73,74) Omeprazole and pantoprazole are no longer indicated when the DAPT is finalized. Other standard maintenance drugs after a PCI are a statin, a cardio selective lipophilic beta blocker and an angiotensin converting enzyme (ACE) inhibitor.(15) These drugs are taken during DAPT and are continued afterwards as well. Maintenance drugs are taken life long as a form of cardiovascular risk management.(75) The drugs assumed in table 11 are all recommended by Dutch guidelines for older ACS patients in the post-acute phase after PCI. Average daily costs were derived from the ''Farmacotherapeutisch Kompas'', which provides an overview of costs per drug. If multiple reimbursed drugs were available at varying costs, the average was calculated. The lowest and highest cost are mentioned as well.

Medication	Drug assumed	Dosage (mg/day)	Average daily cost (lowest-highest) (€)	Source
$P2Y_{12}$ inhibitor	Clopidogrel	1 x 75	0.55 (0.09-1.38)	Farmacotherapeutisch Kompas
	Prasugrel	1 x 5	1.23	
	Ticagrelor	2 x 90	2.40 (2.31-2.49)	
PPI	Omeprazole	1 x 20	0.35 (0.05-0.55)	
	Pantoprazole	1 x 20	0.14 (0.04-0.23)	
Acetylsalicylic acid	Aspirin	1 x 80	0.06	
Statin	Simvastatin	1 x 40	0.15 (0.05-0.25)	
Cardio selective lipophilic beta blocker	Metoprolol	1 x 100 – 200	0.21 (0.09-0.42)	
ACE inhibitor	Lisinopril	1 x 2.5 – 5	0.28 (0.05-0.51)	

Table 11. Medication costs.

The costs for medication are to a large extent identical for the PGx-guided and non-PGx-guided group, except for the ratio in which clopidogrel, prasugrel and ticagrelor are prescribed, thus the ratio of patients that receives omeprazole or pantoprazole differs as well. The ratios for both groups are displayed in table 12. Medication costs were applied in each cycle and half-cycle corrected.

Drug	Proportion in PGx-guided approach (%)	Proportion in non-PGx-guided approach (%)
Clopidogrel	60.6	7
Prasugrel	1	2.3
Ticagrelor	36.1	90.5
Omeprazole	39.4	93
Pantoprazole	60.6	7

Table 12. Proportions of $P2Y_{12}$ inhibitor and PPI drugs in population.

3.5.3 Post-acute treatment costs

For patients that underwent a PCI, participation in a multidisciplinary cardiac rehabilitation program for 3 to 6 months is indicated. Cardiac rehabilitation contributes to psychosocial recovery by reducing mental health issues, improving social support and modification of risk factors.(15) Phases of cardiac rehabilitation are the clinical phase, rehabilitation phase and post-rehabilitation phase.(15) The clinical phase starts directly after the acute phase in the hospital.(76) It was therefore assumed all patients undergo this phase, opposed to the second and third phase.

A report on the uptake of the cardiac rehabilitation program after the clinical phase in the Netherlands provides a detailed description of the participants and the modules they take within the program.(77) Between 2012 and 2016, 50.7% of patients that underwent PCI participated in one or more modules of the cardiac rehabilitation program. Approximately 36% of the participating patients took up a physical fitness module, whereas 31% participated in a combined fitness and relaxation module. About 20% picked a combination of all available modules: fitness, relaxation, and lifestyle. A small portion of 10% took up a fitness and lifestyle module.(77) It was assumed that these percentages for total uptake and modules followed applied to the cohort of this economic evaluation as well. All patients that have

taken part in the rehabilitation phase are monitored at 6 and 12 months after the program in the third phase. Monitoring is done through outpatient clinic visits or remote consultations.(78)

Costs of the phases and (combined) modules were derived from the most recent Dutch Diagnosis Treatment Combinations (DTC's) reported by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit, NZa). The costs of some modules depend on the number of sessions. For those modules, the average price was taken. Each DTC covers the whole range of services that is part of the treatment. See table 13. The post-acute treatment costs were assumed to entirely occur in the first year. A half-cycle corrected cost per cycle was applied.

Cardiac rehab phase	**Specifications**	**Average cost (year) (€)**	**Assumed proportion of population (%)**	**Source**
Clinical phase		5190 (2017)	100	DTC reported by NZa
Rehabilitation phase	Intake	575 (2020)	50.7	
	Fitness module	990 (2020)	18.3	
	Fitness + relaxation module	1400 (2020)	15.7	
	Fitness + relaxation + lifestyle module	1895 (2020)	10.1	
	Fitness + lifestyle module	1750 (2020)	5	
Post-rehabilitation phase		330 (2020)	50.7	

Table 13. Cardiac rehabilitation costs.

3.5.4 Follow-up costs

ACS patients should visit the general practitioner (GP) at least once a year for check-ups.(15) During these check-ups, the GP checks for any symptoms indicating angina pectoris or heart failure. The GP also should pay attention to psychosocial well-being, lifestyle, and adherence to medication. Physical checkups consist of palpation of the pulse, measurement of blood pressure and determination of the body weight. Some laboratory tests are indicated as well: the lipid spectrum, the glucose level, the serum creatinine level and the albumin creatinine ratio in the urine should be examined.(75)

Dutch reports show that 65% of follow-ups of patients with cardiovascular disease exclusively takes place within the primary care setting. About 25% of patients remain under control of a cardiologist in the secondary care setting. Some patients do not attend any follow-up visits at all. The patients in primary and secondary care setting most often remain under control of the GP or cardiologist for the rest of their life.(79) It was assumed these percentages apply to the cohort of this economic evaluation as well. It was assumed follow-ups were lifelong.

The cost of a standard GP consult was derived from the Dutch costing tool for economic evaluations.(80) Diagnostic testing in primary care is not regulated by DTC, instead the price is determined by contracts between healthcare provider and health insurer in the free segment. A tariff list of the provider ''Diagnostiek voor U'' was consulted for an estimation of the lab test prices. It was assumed the tariff list was an accurate representation of the lab costs. The costs of ACS follow-up and

diagnostics were derived from the applicable DTC. See table 14. Follow-up costs were applied in all cycles and were half-cycle corrected.

Follow-up	Average cost (year) (€)	Assumed proportion of population (%)	Source
Standard GP consult	33 (2014)	65	(80)
Lab – lipid spectrum	12.24 (2021)	65	Tariff list Diagnostiek voor U
Lab – glucose	5.19 (2021)	65	
Lab – serum creatine	6.97 (2021)	65	
Lab – albumin creatine	5.37 (2021)	65	
Cardiologist consult + diagnostics	430 (2020)	25	DTC reported by NZa

Table 14. Follow-up costs.

3.5.5 Adverse events costs

Costs for adverse events were derived from DTC's. For MI, DTC's depend on the number of day treatments and/or nursing days. Based on DTC information, approximately 66% of patients stay longer for 6 days or more. Approximately 34% of patients stay 5 days maximum.

Stroke is treated either conservatively (71%) or with thrombolysis (29%).(81) There are different DTC's per treatment strategy. Length of stay and any clinical neurophysiological examinations determine the applicable DTC as well. DTC information shows that 70% of patients undergoing conservative treatment stay for a short period at the hospital, 30% stays for a long period. Of the patients undergoing thrombolysis, 73% stays for a short period and 27% stays for a long period. It was assumed clinical neurophysiological examinations were performed on half of the patients. After discharge of the hospital, 9.8% of patients reside temporarily at a rehabilitation center.(82) Again, DTC's are dependent on length of stay. DTC information shows 39% stays for a short period, 61% stays for a long period.

Target-vessel revascularization costs depend on the location of the revascularization (aorta or artery) and the number of stents. The average of the applicable DTC's was taken as a best guess.

The applicable DTC for major bleeding depends on the number of days spent in the hospital afterwards and the exact location of the bleeding. For short-term stay (5 days maximum) and long-term stay (6 days or more), the mean of applicable DTC's was taken.

TIA is commonly treated on a day treatment at an outpatient clinic. DTC's depend on the extent of the examination. The proportion of patients receiving standard, comprehensive, and very comprehensive treatment was derived from DTC information.

The costs of target-vessel revascularization, stent thrombosis and minor bleeding were derived from the applicable DTC without any further distinction or specification. See table 15.

A study on resource utilization of ACS patients that underwent PCI shows that on average, patients that experience new clinical events visit the GP 7 additional times, the office cardiologist 3 additional times, and the hospital 1 additional time.(83) It was therefore assumed all patients that experienced an adverse event paid additional visits to these healthcare providers. See table 16. Since it was unknown when adverse events occurred and only yearly incidences were found in the literature, the costs related to these events were applied as a yearly one-off cost-item.

Adverse event	Specifications	Average cost (year) (€)	Proportion of patients that experienced adverse event (%)	Source
Nonfatal MI	Short stay	1980 (2020)	34	DTC reported by the NZa
	Long stay	6105 (2020)	66	
Nonfatal stroke	Conservative treatment + short stay	2840 (2020)	49.7	
	Conservative treatment + long stay	7330 (2020)	21.3	
	Thrombolysis + short stay	3592 (2020)	21.17	
	Thrombolysis + long stay	8147 (2020)	7.83	
	Short rehab stay	6405 (2020)	3.822	
	Long rehab stay	12170 (2020)	5.978	
Target-vessel revascularization		3721 (2015)	100	
Probable or definite stent thrombosis		3600 (2020)	100	
Major bleeding	Short stay	2415 (2020)	54	
	Long stay	8320 (2020)	46	
Minor bleeding		965 (2020)	100	
TIA	Standard	985 (2020)	16	
	Comprehensive	1210 (2020)	79	
	Very comprehensive	1400 (2020)	5	

Table 15. Adverse event costs.

Resource utilization after adverse events	Volume (range)	Average cost (year) (€)	Source
Standard GP consult	7 (3, 11)	33 (2014)	(80)
Cardiologist	3 (1, 4)	170 (2020)	DTC reported by NZa
Outpatient visit	1 (0, 2)	91 (2014)	(80)

Table 16. Resource utilization related to adverse events.

3.5.6 Indirect medical costs related to life years gained

The societal perspective required considering the costs related to life years gained. Only the costs of unrelated diseases (i.e., costs of all diseases except the disease targeted by the intervention) were considered to avoid counting costs twice. To estimate costs related to life years gained, the Practical Application to Include future Disease costs (PAID) 3.0 tool was used.(28,84) The survival curves of both arms were uploaded into the tool, and the number of individuals alive at the start of the calculations, the proportion of the population being male, the age and the cost discount rate were filled out. PAID considers increasing age and the high costs in the year prior to death. PAID multiplied the average

healthcare costs per person with the number of life years gained to estimate the total discounted costs of the entire population, see table 17.

Indirect medical costs	PGx-guided arm (€)	Non-PGx-guided arm (€)	Source
Costs of unrelated diseases in life years gained	57,134,448	56,696,015	(84)

Table 17. Indirect medical costs.

Since the PAID tool already accounted for cohort size and discount rate, the costs of life years gained were applied as a one-off item without multiplying it with number of patients alive.

3.5.7 Travel costs

The travel distance per relevant transport type of Dutch ACS patients in particular is unknown. Therefore, averages were used as recommended by Dutch economic evaluation guidelines.(28) The Dutch costing tool for economic evaluations provides average distances.(80) Guidelines recommend assuming a kilometer price equal to that of travel by car/public transport (the most common modes of transport) when the exact numbers are missing, which was the case for this evaluation.(28) Kilometer prices were derived from the costing tool as well.

The frequency estimates of hospital and GP visits were based on the healthcare usage estimates. During post-acute treatment, patients following the rehabilitation program were assumed to travel 1 time to the hospital for the intake, 5 times for the module and 2 times for the post-rehabilitation check-up. During follow-ups, patients who attend those were assumed to travel once to the GP or hospital each year. In case of an adverse event, patients were assumed to travel once to the hospital for initial treatment, 7 times to the GP and 4 additional times to the hospital for check-ups. Pharmacist guidelines prescribe that with chronic medicine use, a drug supply of maximum 3 months can be delivered to the patient at a time.(85) It was therefore assumed a patient goes 4 times a year to the pharmacy. The distance was multiplied by 2 to calculate the kilometers travelled per visit for the outward and return journey. Next to that, parking costs of 3 euro per hospital visit were calculated. It was assumed 75% of patient come by car and are faced with parking costs. See table 18. Travel costs were applied in every cycle and half-cycle corrected.

Provider	Average distance (km)between household and…	Average cost per km (€)	Frequency
Hospital	7.0	0.19 (2014)	Dependent on healthcare usage
GP	1.1		Dependent on healthcare usage
Pharmacy	1.3		4 times/year

Table 18. Travelling costs.

3.5.8 Informal care costs

Informal care costs were calculated for the initial ACS event, and the adverse events which were assumed to have a permanent effect on quality of life (recurrent MI and stroke). The volume of informal care was derived from a cross-sectional study on informal care and patient productivity loss following ACS and stroke in Europe.(86) The study collected data through the Productivity Cost Questionnaire (iPCQ) as developed by the Institute for Medical Technology Assessment. The study assessed total costs of informal care occurring in the first year after the event. Total volume was calculated by dividing the total cost by the hourly wage used by the authors. The costing manual recommends valuing informal care based on replacement costs for domestic care (using the proxy good method). The price per hour was derived from the costing tool. It was assumed that informal care for ACS and MI are the same. It was furthermore assumed that informal care costs for the adverse events occur each year for a lifetime. See table 19. Informal care costs were applied in every cycle and half-cycle corrected.

Reason for informal care	Average hours of informal care per week	Price per hour (year) (€)	Source
ACS	1.6	14 (2014)	(86)
Recurrent MI	1.6		
Stroke	1.85		

Table 19. Informal care costs.

3.5.9 Productivity losses

Productivity costs were calculated for the initial ACS event, and the adverse events which were assumed to have a permanent effect on quality of life (recurrent MI and stroke). Of people aged 65-74 in the Netherlands, 19.1% of men and 8.8% of women have a paid job. These employment rates were assumed to apply to the cohort of this economic evaluation. It was assumed productivity losses did no longer occur after the population reached the age of 75. Productivity losses were calculated using the friction cost method (multiplying lost working days with the number of hours in a working day and the productivity costs per hour). No productivity losses exceeded the friction period of 85 days; therefore, productivity losses did not need to be reduced. The cross-sectional study mentioned in the previous paragraph provided data on the number of lost working days due to presenteeism and absenteeism, see table 20.(86) Productivity losses due to ACS were applied to the whole population, productivity losses due to recurrent MI and stroke were applied to the patients experiencing these adverse events. The 3:1 male-female ratio of the population was reckoned with, using sex-specific productivity costs.(80) See table 21. Productivity costs were applied in every cycle and half-cycle corrected.

	Average number of working days lost due to…			Source
Productivity loss	ACS	MI	Stroke	(86)
Absenteeism	53.0	53.0	47.1	
Presenteeism	6.3	6.3	8.8	

Table 20. Absenteeism and presenteeism.

Productivity input	Cost (year) (€) / number	Source
Productivity costs per hour (men)	37.90 (2014)	(80)
Productivity costs per hour (women)	31.60 (2014)	
Number of hours per working day	8	Assumed

Table 21. Productivity costs.

3.6 Model inputs – Index rates and discount rates

Cost prices of several units were not determined based on data of the same calendar year. For this reason, some prices were corrected for inflation between years to 2020/2021 prices. The year to which prices relate were stated in all tables containing cost inputs. The consumer price indices of the Dutch Central Bureau of Statistics were used, see table 22.

From	To	Percentage	Factor	From	To	Percentage	Factor
2014	2015	0.6	1.006	2014	2020	8.1	1.081
2015	2016	0.3	1.003	2015	2020	7.5	1.075
2016	2017	1.4	1.014	2016	2020	7.2	1.072
2017	2018	1.7	1.017	2017	2020	5.7	1.057
2018	2019	2.6	1.026	2018	2020	3.9	1.039
2019	2020	1.3	1.013	2019	2020	1.3	1.013

Table 22. Price indices.

Dutch guidelines assume a standard discount rate of 4% for costs and 1.5% for effects, which were applied to the total QALYs and total costs in this evaluation as well.

3.7 Set-up of sensitivity analyses

A PSA, a univariate one-way analysis, and a scenario analysis were performed.

3.7.1 Probabilistic sensitivity analysis

The PSA was carried out using a Monte Carlo simulation that calculated 1,000 ICURs, each time with different parameter values. A distribution was chosen for each input parameter to accommodate the variations of the PSA. A beta distribution was assumed for all presumably binomially distributed parameters with a value between 0 and 1. This was the case for all utility values, and binominal proportions like the probability of experiencing an adverse event, and the proportion of patients attending rehabilitation or follow-up consults. When data was assumed to be multinomial (i.e., data that can be divided into a number of categories), a Dirichlet distribution was assumed. A Dirichlet distribution was assumed for the proportions in which the $P2Y_{12}$ inhibitors were prescribed, the ratio male-female in the cohort, the proportion of patients following a given rehabilitation module, and the proportions of the cohort undergoing a certain treatment for the same adverse event. The Dirichlet distribution is the multivariate generalization of the beta distribution, with the number of categories in the multinomial distribution determining the parameters.(26) Lastly, a gamma distribution was assumed for all costs and numbers that had the logical constraint they could not become negative (numbers of hours lost due to absenteeism or presenteeism, number of hours spent on informal care).

The alpha and beta were calculated using $\alpha = \hat{\mu} \cdot \left(\frac{\hat{\mu}(1-\hat{\mu})}{s^2} - 1\right)$ and $\beta = (1-\hat{\mu}) \cdot \left(\frac{\hat{\mu}(1-\hat{\mu})}{s^2} - 1\right)$ for the beta distribution. The formulas $\alpha = \frac{\hat{\mu}^2}{s}$ and $\beta = \frac{s^2}{\hat{\mu}}$ were used for the gamma distribution. The $\hat{\mu}$ consisted of the deterministic parameter value. The s was either derived from literature if reported or estimated to be 5%-20% of the deterministic parameter value. As for disutilities and incidences related to adverse events, 5% of the mean was assumed when a small range was observed in the literature, 20% was assumed if the range in the literature was rather broad. Duration of adverse events was assumed to have a standard error of 20% of the mean. Because all costs were assumed to be relatively uncertain, a standard error of 20% of the mean was assumed. Lastly, independent probabilities from which the underlying data was assumed to be binomially distributed were assumed to have a standard error of 5% of the mean.

The Excel functions GAMMA.INV and BETA.INV were operated to calculate the probabilistic parameter values of the parameters that were assumed to follow a beta or gamma distribution. The arguments of these functions were a pseudo-random number, the alpha, and the beta. The pseudo-random number was drawn by the RAND function from an interval of 0-1 with a uniform distribution. The alpha acts as the shape parameter to the distribution, the beta acts as the scale parameter. Samples from the parameters which were assumed to follow a Dirichlet distribution were drawn differently. First, the GAMMA.INV function with three arguments was operated: a pseudo-random number drawn by the RAND function, a parameter consisting of the deterministic value multiplied by 1,000, and 1. The GAMMA.INV was operated for each category that was part of the multinomial relation. To calculate the probabilistic parameter values, the output of the GAMMA.INV function of that parameters was divided by the sum of outputs of the GAMMA.INV of all parameters within the multinomial relation.

The parameters of the Weibull distribution (intercept and logscale) that were used for the extrapolation of the survival curves were also varied in the PSA. It was assumed the intercept and the logscale were correlated and followed a bivariate normal distribution. The Cholesky decomposition from variance-covariance matrices mentioned earlier was used to draw random number from the bivariate distribution. Random values were drawn by multiplying the Cholesky matrix with a vector (consisting of random draws between 0-1). The vector was added with the mean intercept and the mean logscale.

3.7.2 Univariate one-way sensitivity analysis

Each parameter (except for the multinomially distributed parameters) was varied individually using a high and low input value, while keeping the other parameters the same. This way, the impact of each parameter on the ICUR could be investigated. Low and high values were derived from literature as much as possible. If studies had not reported any range, the parameter was varied by one standard error. The increments between low and high value were ranked from largest to smallest to create a tornado diagram.

3.7.3 Scenario analysis

The base case assumption was made that the costs of the PGx-Passport were equal to the sum of the existing limited PGx-Passport and the single gene testing prices of the other genes. It is however not unthinkable that a PGx-Passport will become less costly if producing it becomes standardized for a given panel of genes. Next to that, if the PGx-Passport is used multiple times a lifetime, average costs per treatment will decline. A few scenarios were modelled to explore the impact on the ICUR. In one scenario, the PGx-Passport was assumed to cost the same as the current limited passport. Other scenarios were a price equal to genotyping of the CYP2C19 gene, the base case price divided by the

numbers of genes in the panel, and the base case price divided by the number of diseases the proposed PGx-Passport can be used for to guide treatment strategies.

3.8 Model validation

To validate the developed model, the TECHnical VERification (TECH-VER) tool was utilized.(87) As prerequisite, this tool recommends identification of relevant calculations and assessment of the justifications of methods used. Assessing and justifying method choices has been performed throughout the modelling process. Next, the verification tests of TECH-VER were conducted on the following domains: input calculations, event-state calculations, result calculations, uncertainty analysis calculations and overall checks. Using the TECH-VER black-box tests, the model was reviewed on each of these domains to check whether the calculations were in line with a priori expectations. The description of the test, the way the test was conducted, the expected and actual result of the tests were documented. An overview is available in the Appendix. A few black-box tests were left out, since several elements were not relevant for this economic evaluation (e.g., no use was made of odds ratios, hazard ratios, or relative risks, and no progression-free state was implemented). All black-box tests were passed, and no errors were encountered. No white-box tests were deemed necessary to detect any root causes, since no errors were uncovered.

4. Results

4.1 Deterministic results

ACS patients of 65 years old undergoing primary PCI have, after PGx-Passport-guided antiplatelet treatment for a year, a quality-adjusted life expectancy of 12.7 QALYs (15.5 undiscounted QALYs). In the standard treatment group without any PGx-guidance, patients have a quality-adjusted life expectancy of 12 QALYs (14.6 undiscounted QALYs). The PGx-guided arm accrues more QALYs than the non-PGx-guided arm (17.3 versus 16.6) due to slightly better overall survival rates and loses less QALYs because of adverse events (1.8 versus 2) due to lower incidences of MI, stroke, target-vessel revascularization, stent thrombosis, major and minor bleeding, and TIA in the first year during DAPT. The lower number of QALYs lost in the PGx-guided treatment arm can mainly be attributed to two factors. First, genotype-guided use of clopidogrel leads to lower risks than clopidogrel use without any genotyping. This goes especially for the probability of MI and stroke. Moreover, MI and stroke were assumed to have a lifelong impact on quality of life. Therefore, the incidences of MI and stroke in the first year after PCI affect the total disutilities accrued relatively heavily. Of the disutilities, the loss of 1.76 and 1.94 QALYs is to be attributed to *chronic* disutilities in the PGx-guided and non-PGx-guided arm, respectively. Second, the probability of stent thrombosis or bleeding is relatively high on ticagrelor. Ticagrelor makes up a large proportion (91%) of DAPT in the non-PGx-guided arm, leading to more disutilities due to these adverse events.

On average, the costs for PGx-Passport-guided treatment are € 77,249 per patient over a lifetime. The costs of standard treatment are € 75,768. It varies per cost category whether the intervention or the comparator incurs more costs. Table 23 provides an overview of total costs per person per cost category for both the intervention and the comparator, and the increment of those costs.

Costs of…	PGx-guided (€)	Non-PGx-guided (€)	Increment (€)
PGx-Passport	1,378	0	1,378
Medication	5,680	5,828	-149
Post-acute treatment	7,088	7,053	36
Follow-up	3,024	2,878	146
Adverse events	6,822	6,819	3
Life years gained	57,134	56,696	438
Travel	105	101	3
Informal care	1,813	1,814	-1
Productivity losses	480	536	-57

Table 23. Costs of intervention and comparator strategy and increments.

The largest increment emanates from the costs of the PGx-Passport, since only the PGx-guided arm incurs those costs. The medication costs of the standard treatment arm being slightly higher than those of the PGx-arm can be explained by the fact that in the first year, a large proportion of patients is prescribed ticagrelor (which is more expensive than clopidogrel) and omeprazole (which is more expensive than pantoprazole). After the first year, prescribed drugs are identical for both arms and thus costs are nearly identical as well. The post-acute treatment costs are fairly similar, which can be attributed to the treatment being the same for both arms, the only difference being the number of

patients alive to undergo post-acute treatment. The difference of follow-up costs can be attributed towards the number of patients being alive, since follow-up treatment is the same for both arms. Despite adverse event incidences and costs differ during the first year after PCI during DAPT, incidences of new adverse events were assumed to be the same long-term for both arms, resulting in very comparable adverse event costs. Costs for unrelated disease during life years gained are higher in the PGx-guided arm since the overall survival rate drops slower for those patients. The travel costs are again quite similar, which can be explained by the costs in the first year resulting partly from regular post-acute treatment and follow-up consults (which were assumed to be the same for both arms) and in the subsequent years resulting entirely from adverse event hospitalization and regular follow-up visits (which were again assumed to be the same for both arms). The similarity between the informal care costs of both arms has a comparable explanation. In the first year after primary PCI, informal care was assumed to be the same for ACS patients independently from the type of antiplatelet strategy they are in. In subsequent years, informal care costs are related to recurrent MI and stroke, which were assumed to occur at the same incidences in both arms in the long-term. Productivity losses differ primarily because of the slightly higher incidence of MI and stroke in the first year within the standard treatment arm, resulting in more patients losing hours due to presenteeism and absenteeism.

The mentioned costs and effects result in a deterministic ICUR of € 2,342 per QALY or € 1,526 per life year gained, see table 24.

Treatment	Costs (€)	QALY	LY
PGx-Passport-guided	77,249	12.67	20.16
Non-PGx-Passport-guided	75,768	12.04	19.18
Increment	1,481	0.63	0.97
ICUR		**Incremental costs/QALY (€)**	**Incremental costs/LY (€)**
		2,342	1,526

Table 24. Deterministic results: Incremental costs, QALYs, LYs and ICURs.

4.2 Sensitivity analysis results

4.2.1 Probabilistic sensitivity analysis results

First, a PSA was performed. The result of the analysis is displayed in Figure 3. The x-axis represents incremental QALYs, and the y-axis represents incremental costs. The dots are the result of 1,000 Monte Carlo simulations, producing 1,000 estimated combinations of additional costs and additional effects of each simulation. Dots are located in all 4 quadrants of the scatter plot, with most of them in the north-east quadrant and the south-east quadrant. The north-east quadrant indicates that according to a part of the simulated ICURs, the PGx-Passport-guided strategy is more effective, but also incurs more costs than the standard treatment. The south-east quadrant implies that some of the estimates show that the intervention is more effective and less costly than the comparator. The dots in the north-west quadrant represent more costs and less effects, and the dots in the south-west quadrant represent less costs and less effects. If an intervention yields more effects and generates less costs than the comparator, the intervention is by definition acceptable. The opposite goes for an intervention that yields more costs and less effects. Whether an intervention is acceptable in the north-west or south-east quadrant depends on the willingness to pay for a QALY.

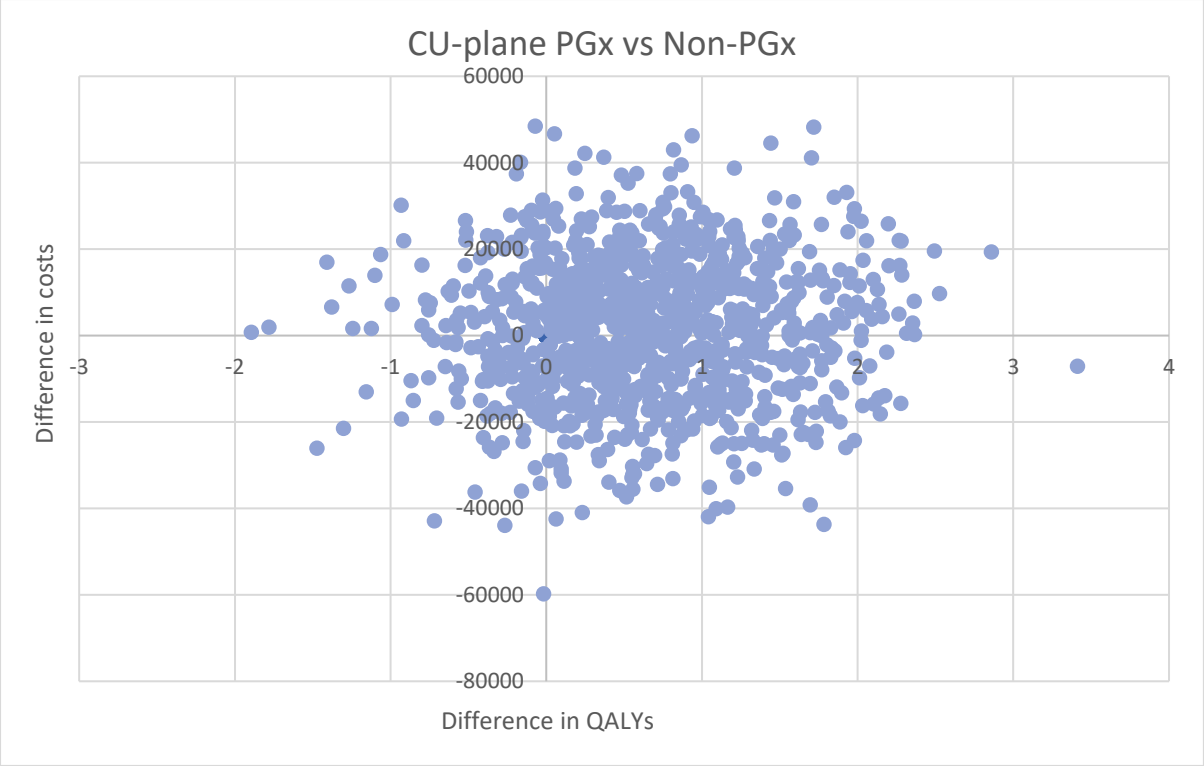

Figure 3. Probabilistic sensitivity analysis: CU-plane of PGx-guided treatment versus non-PGx-guided treatment.

The burden of disease is the determinant of the applicable cost-utility threshold in the Netherlands: the higher the burden, the higher the threshold. The threshold consists of an amount of € 20,000, € 50,000 or € 80,000 per QALY. According to the Disease Burden Calculator (iDBC) tool, the applicable threshold for this economic evaluation is € 20,000 per QALY based on the remaining QALYs with standard treatment (14.61), the QALYs without disease corrected for age and sex (16.15), the absolute shortfall (1.54) and the proportional shortfall (0.1).(88) The absolute shortfall indicates the lost QALYs in the target population under standard treatment. The proportional shortfall indicates the lost part of the normal quality adjusted life expectancy in the target population without the new treatment. The method of the iDBC tool considers the uncertainty about cost-effectiveness and severity of disease. The tool shows that there is no uncertainty about the severity-based cost-utility threshold in this population.

In Figure 4 the CEAC is displayed. The curve indicates what percentage of ICURs from the simulation is acceptable given various willingness-to-pay thresholds. The starting point of the curve represents the percentage of ICURs indicating that the intervention is cost-saving (i.e., below the x-axis in the CU-plane). The curve starts at 0.46, which means that 46% of the simulated ICURs indicates the PGx-Passport-guided strategy is cost-saving. For a threshold of € 20,000, there is a 70% chance that the PGx-Passport-guided strategy is cost-effective and thus a 30% chance that it is not cost-effective. The higher the theoretical willingness to pay, the higher the chance that the intervention is cost-effective. For this intervention, no threshold can provide 100% certainty that the intervention is cost-effective. The reason for this is that the limit of the curve is determined by the percentage of ICURs indicating that the intervention is more effective than the comparator (i.e., simulations on the right side of the y-axis). Some degree of uncertainty is always involved in the decision of policy makers whether or not to reimburse the PGx Passport.

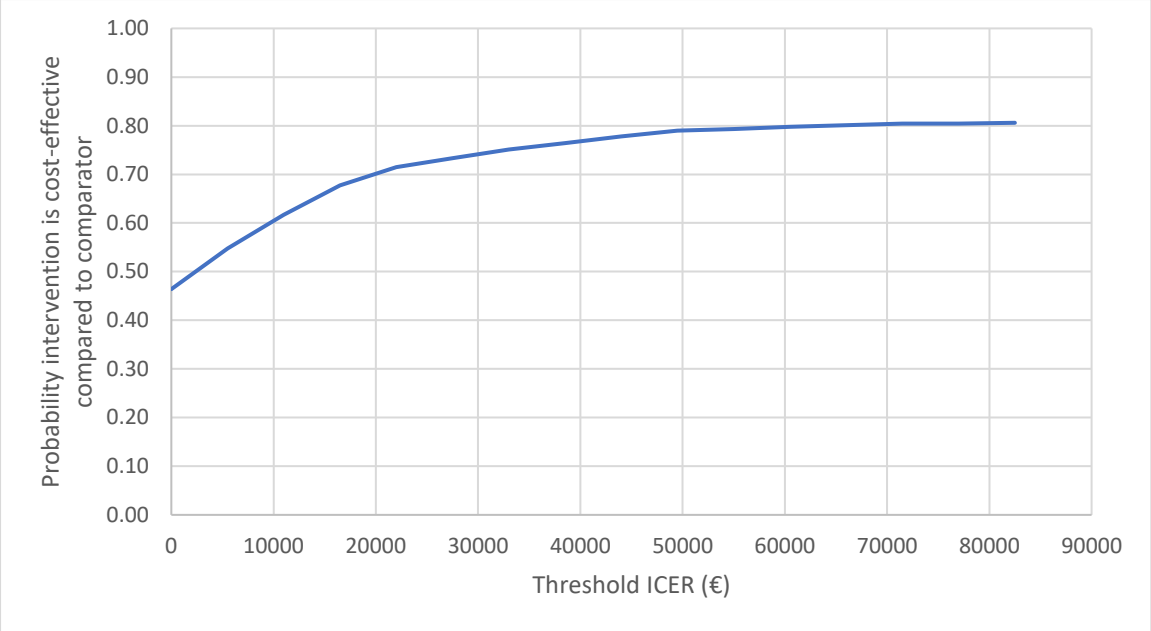

Figure 4. Probabilistic sensitivity analysis: CEAC.

4.2.2 One-way analysis results

To further explore the source of uncertainty, a one-way univariate deterministic sensitivity analysis was performed to identify which variations of parameters affect the ICUR the most. In Figure 5, a tornado diagram displays the parameter variations with the largest to smallest effect on the ICUR. The values on the bars show the difference between the deterministic ICUR of € 2,342 and the ICUR that results from the low and high input values. The bars on the left side of the middle axis show how much lower the ICUR became, the bars on the right side of the middle axis show much higher the ICUR became. The dark blue color indicates the low input values, the light blue color indicates the high input values. The variation in costs associated with unrelated disease in the life years gained in both arms has by far the largest impact on the deterministic ICUR. To show the impact of the subsequent 25 input parameters in greater detail, a second tornado diagram was created without the life-years-gained cost inputs. See Figure 6.

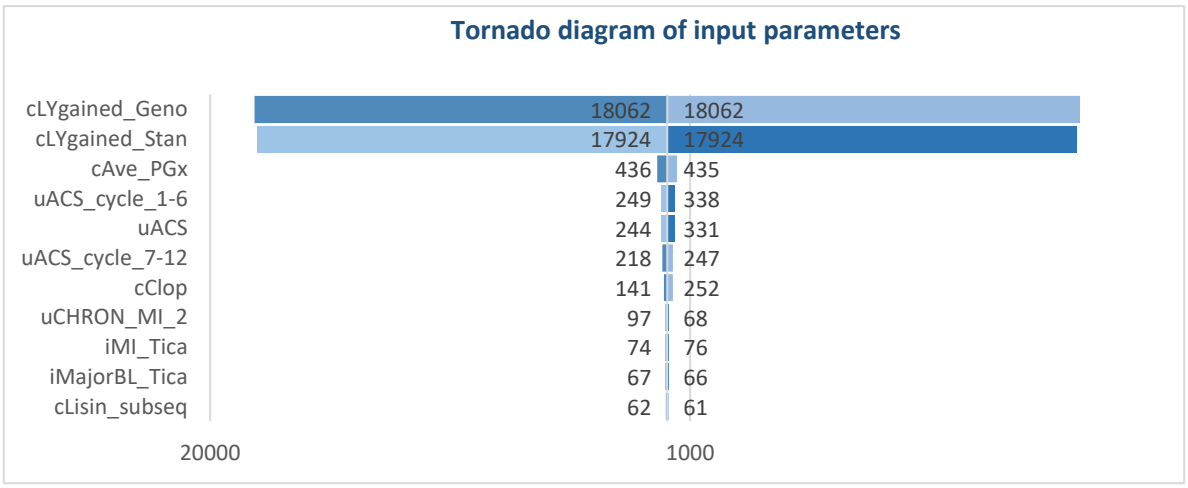

Figure 5. Tornado diagram of deterministic sensitivity analysis.

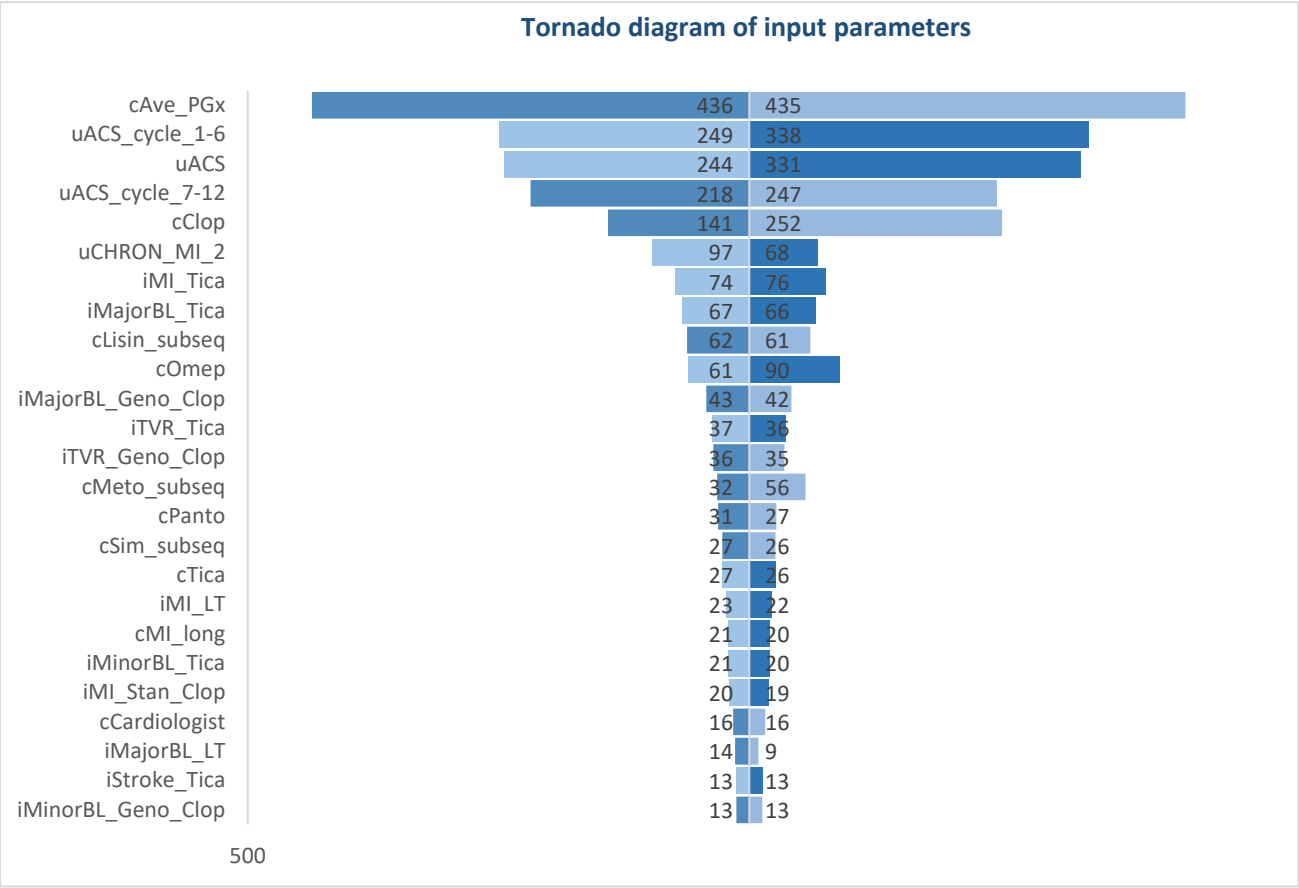

Figure 6. Tornado diagram of deterministic sensitivity analysis, zoomed in.

Other cost categories with a relatively large impact on the ICUR are the price of the PGx-Passport, the utility values of ACS, the price of clopidogrel, and the chronic disutility of MI. Furthermore, some of the smaller impacts are observed due to some specific variables related to ticagrelor and PGx-guided clopidogrel.

The great impact of the variation in costs associated with unrelated disease in the life years gained can be explained by the fact that those costs were implemented in the model as a one-off cost in the first cycle. The size of this one-off cost input for the PGx-guided arm and the non-PGx-guided arm did not differ to a great extent. Furthermore, the costs associated with unrelated disease in the life years gained make up a significant portion of the total costs per arm. Taken together, these factors explain that when varying this one-off by a given percentage in a univariate analysis, the total costs per arm are greatly influenced and the ICUR reacts strongly to the variation. The costs of the PGx-Passport were applied in the first cycle in the PGx-guided arm only, and the base case assumption of the PGx-Passport being € 1,377 imposes a relatively high cost per patient. Therefore, the variation of the costs of the PGx-Passport also has a relatively large impact on the total costs of the PGx-guided arm, and therefore on the incremental costs.

The impact of the variation of utility values of ACS after primary PCI can be explained by the large portion of the total effects that is determined by these values. Variation of the utility values is therefore expected to affect the total effects. Even though the utility values for both arms are the same, the incremental effects can be explained by the different mortality rates that influence the number of patients alive each cycle.

Finally, the smaller impacts on the ICUR that emanate from variations in variables related to ticagrelor and PGx-guided clopidogrel can be explained by the proportions of $P2Y_{12}$ inhibitors that were assumed for both arms. Ticagrelor was assumed to be prescribed the most in the standard treatment arm, clopidogrel was assumed to make up the largest proportion of $P2Y_{12}$ inhibitors in the PGx-Passport-guided arm. Therefore, it is plausible that variations in adverse event incidences and costs related to these two drugs impact the ICUR.

A tornado diagram displaying all variables that impact the ICUR can be found in the Appendix.

4.2.3 Scenario analysis results

As mentioned in the Methods section, a scenario analysis was performed representing the different ways PGx-Passport costs can be attributed to the intervention. The ICURs for different price scenarios are presented in table 25. The lower the price of the PGx-Passport, the lower the costs per QALY or life year. Lowering the price of the PGx-Passport substantially impacts the ICUR, which seems logical since the deterministic analysis shows that the PGx-Passport creates the largest disaggregated cost increment when comparing the intervention and the comparator, and the one-way analysis reveals that variation in this price is one of the most impactful parameters in this study.

Scenario – Costs of PGx-Passport are equal to…	Costs (€)	Incremental costs/QALY (€)	Incremental costs/LY (€)
Average limited passport price	650	1,191	776
Average price of CYP2C19 genotyping	74.43	282	183
Total price divided by number of pharmacogenes	98.41	319	208
Total price divided by number of diseases	28.12	208	136

Table 25. Scenario analysis on different attributions of the PGx-Passport costs.

5. Discussion

5.1 Related works

Assuming a willingness-to-pay threshold of € 20,000 per QALY, the deterministic ICER indicates that the PGx-Passport guided strategy for ACS patients undergoing primary PCI is cost-effective. The sensitivity analysis shows a 70% chance of the PGx-guided strategy being cost-effective. A related works search was performed based on the search protocol of a recent systematic review on economic evaluations of CYP2C19 genotype-guided antiplatelet therapy compared to universal use of antiplatelets in ACS patients.(89) Using similar search terms on Pubmed and Embase, 8 economic evaluations ranging from 2011 to 2020 were extracted. Papers were only selected for this Discussion if some type of genotyping was compared to at least universal ticagrelor and/or prasugrel and if there was a Markov model used. All available economic evaluations are from the United States (US) and China, except for one Australian evaluation of Sorich et al.(90) There are 3 studies that found that universal antiplatelet therapy was cost-effective compared to genotype-guided strategies: Crespin et al, Kazi et al, and Sorich et al.(90-92) The other 5 studies concluded that a genotype-guided strategy was cost-effective: Jiang et al 2016, Jiang et al 2017, Lala et al, Wang et al, and Dong et al.(93-97)

First, the studies that found that universal antiplatelet therapy is cost-effective or that genotype-guided therapies are not cost-effective will be discussed. The studies have in common that none of them used the concept of the PGx-Passport. The studies assumed reactive point-of-care (i.e., a quick test as soon as it becomes clear the patient will be prescribed a $P2Y_{12}$ inhibitor) genotyping of a single gene (CYP2C19). The costs of genotyping were estimated 200-235 US dollars (2011) and 46.55 Australian dollars (2011). Crespin et al tested universal ticagrelor versus genotyping with ticagrelor or clopidogrel. At $10,059 per QALY and a threshold of $50,000, it was concluded universal ticagrelor use was cost-effective.(91) Kazi et al assessed 5 strategies: universal use of clopidogrel, prasugrel, and ticagrelor, and two variations of genotyping. At a threshold of $50,000, they concluded that genotyping was not cost-effective with $107,050 per QALY.(92) Sorich et al assessed 3 strategies: universal clopidogrel, universal ticagrelor, and genotyping with ticagrelor or clopidogrel. The Australian government does not set a strict standard, but $30,000-$50,000 per QALY is usually considered cost-effective. At $23,000 per QALY, universal ticagrelor was found to be cost-effective.(90)

The biggest differences between these studies and this economic evaluation are the chosen intervention and comparator, the cost categories used, the adverse events that were assessed, the assumptions made regarding survival rates, and the discount rates.

All studies included a limited number of cost categories, using a healthcare or third-party payer perspective. The studies all included the costs of $P2Y_{12}$ inhibitors, adverse events, and genotyping. Kazi et al only assessed costs of acute care.(92) Sorich et al applied an average yearly cost related to ACS.(90) The adverse events included differ per study. Crespin et al included MI, bleeding and dyspnea.(91) Kazi et al included MI, target-vessel revascularization, stent thrombosis and bleeding.(92) Sorich et al only included MI and stroke.(90) Moreover, Kazi et al worked with an age-adjusted base case utility. Crespin et al and Sorich et al based their survival estimates on data and hazard ratios derived from the ''PLATelet inhibition and patient Outcomes'' (PLATO) trial, Kazi et al based the survival rates on US Medicare claims data. Crespin et al report that the PLATO survival data was used for 1 year, after that, mortality rates were assumed to be identical for both arms (with a 5-

year time horizon). Sorich et al extrapolated the PLATO survival data to a 40-year time horizon, without reporting further details on the extrapolation. All studies have discounted costs and effects at the same discount rate (3% for the US studies, 5% for the Australian study). Noteworthy is that both US studies report that the outcome of the evaluation is sensitive to the price of ticagrelor. At the time of those assessments, ticagrelor was still a patented drug in the US, and therefore incurred relatively high monthly costs.(91,92)

It is difficult to say which factor exactly explains the difference between the results of the studies and this evaluation. The most likely explanation is that it is a combination of included costs and disutilities, other survival data underlying the number of people alive in different cycles of the Markov trace, and other choices made, such as which antiplatelet therapies are used in the genotype-guided arm. The high price of ticagrelor might partly explain the differences as well. The one-way analysis showed that the ICUR of this evaluation is sensitive to costs for life years gained and the costs of the PGx-Passport. These cost categories are not included at all in the studies discussed, which hinders further comparison. A limitation of the economic evaluations that used the PLATO data, is that the sub study on pharmacogenetics was not powered to detect pharmacogenetic interaction.(98) However, it might be the case no other specific data on genotype-guided DAPT was available at the time.

Most of the studies that found that genotype-guided therapies are cost-effective or cost-saving, did not use the concept of the PGx-Passport, but assumed single-gene testing instead. The exception is the study of Dong et al.(97) Dong et al reviewed the cost-effectiveness of both single-gene and multi-gene testing compared to no genotyping. The multi-gene testing included CYP2C19, SLCO1B1, CYP2C9 and VKORC1, closely resembling the gene panel of the limited PGx-Passport that is already available in the Netherlands. The assumed costs of genotyping in these studies were 200-500 US dollars. Jiang et al (2016) concluded that genotyping was cost-saving compared to standard treatment with prasugrel and ticagrelor, saving $76,296 per QALY.(93) According to their sensitivity analysis, the genotype-guided strategy was cost-saving in 83% of the simulations. Jiang et al (2017) concluded that genotyping was cost-saving as well, saving $42,632 per QALY and genotyping being cost-saving in almost 90% of the simulations.(94) Lala et al found that genotyping was cost-saving as well, saving $2,219,615 per QALY compared to universal prasugrel prescription.(95) The chance of genotyping being cost-effective was 75% according to the PSA. Finally, Wang et al and Dong et al found that genotype-guided strategies were cost-effective.(96,97) The study of Wang et al resulted in an ICUR of $2,560 per QALY at a threshold of $42,425. The study of Dong et al resulted in an ICUR of $3,780 per QALY at a threshold of $100,000. In the PSA, 80% of the simulations resulted in genotyping being cost-effective.

Again, the biggest differences between these studies and this economic evaluation are the cost categories used, the adverse events that were assessed, the assumptions made regarding survival rates, and the discount rates.

Jiang et al (2016), Jiang et al (2017), and Wang et al opted for a healthcare provider perspective.(93,94,96) Lala et al and Dong et al used a US payer and Medicare perspective.(95,97) All studies included the costs of $P2Y_{12}$ inhibitors, adverse events, and genotyping. Lala et al included next to these categories inpatient and outpatients costs related to adverse events, and pharmaceutical costs.(95) They explicitly excluded general ACS costs, for the reason that all patients incur these costs. Wang et al included follow-up costs and pharmaceutical costs.(96) Dong et al included the costs of statin and warfarin drug therapy.(97) Jiang et al (2016) and Jiang et al (2017) are the only studies that included some form of long-term costs, namely the costs of stroke patients.(93,94) Jiang et al (2016), Jiang et al (2017), and Wang et al included MI, stroke, stent thrombosis, and bleeding as adverse events.(93,94,96) Dong et al included MI, stroke, and major bleeding.(97) Additionally, Dong et al

included myalgia and myopathy related to statin and thrombotic events related to warfarin. Lala et al included MI, stroke, major bleeding, and TIA.(95) The treatment strategies in Lala et al diverge from all other related works assessed: the authors assume DAPT for 10 years (instead of the usual 1 year) and did not include ticagrelor in any arm (even though it is the most frequently prescribed alternative for clopidogrel). This might explain the unusual large costs saved per QALY according to this study.

Jiang et al (2016) and Jiang et al (2017) derived event rates from the TRITON-TIMI trial and Asian meta-analyses.(93,94) Lala et al derived event rates from the US Food and Drug Administration.(95) Wang et al reported that all model inputs and key assumptions were from the Lala et al study, an Asian sub study of PLATO and some Asian clinical trials.(96) Dong et al based their survival rates on Medicare claims.(97) All studies discounted costs and effects at a rate of 3%. Jiang et al (2016), Wang et al, and Dong et al reported the parameters that are most influential on the outcome. For Jiang et al, variation of transition probabilities, the costs of PCI and the base case utility affected the ICUR the most. The ICUR of Wang et al was influenced most heavily by the hazard ratios of MI and stroke (between clopidogrel and ticagrelor). Lastly, the ICUR in the Dong et al study was most sensitive to the costs of multi-gene testing.

Again, it is difficult to determine which factor exactly explains the differences between the ICURs of these studies and this evaluation. All studies used a non-societal perspective, thus including different cost categories. Even the healthcare costs assessed usually do not involve long-term reiterative costs, thereby possible underestimating costs incurred on the long-term. The studies also included a narrower range of adverse events than used in this evaluation (except for Dong et al). Next to that, it is clear Lala et al made assumptions that diverge a lot from those made in this economic evaluation. The two most recent studies of Wang et al and Dong et al presented an ICUR that is quite comparable to the ICUR of this evaluation ($2,560 and $3,780 versus € 2,342), though the parameters used are dissimilar.

A schematic overview of all related works can be found in the Appendix.

5.2 Assumptions

5.2.1 Assumptions regarding survival estimates

One assumption regarding the selected cohort that might raise some questions concerning representativeness of the clinical trials chosen for the survival estimates, is the choice for a starting age of 65. The mean age of the POPular Genetics cohort was 61.9 and 61.4, the mean age in TL-PAS was 59.2 and in SCAAR 67.3.(40,42,44) The impact of age on the effectiveness of DAPT is not undisputed. In the PLATO trial for example, no heterogeneity in treatment response by age was observed in a cohort with a mean age of 62 and 15% of patients being 75 or older.(99) Another observational trial nevertheless reports a reduced effectiveness of clopidogrel and ticagrelor among elderly patients of 70 and older.(100) If treatment response decreases by age, it might be the case that using the KM curves of POPular Genetics and TL-PAS has resulted in too optimistic survival curves for a cohort of 65 years old. This could have resulted in an overestimation of (quality-adjusted) life expectancy. It is expected that the effect on the ICUR is limited, since the same survival data have been used for both arms.

While combining the studies' survival data, it was assumed that the number at risk could be interpolated linearly, and the data of TL-PAS and the SCAAR data on ticagrelor could be extrapolated linearly. Using the method of Hoyle and Henley, the comparable assumption was implicitly made that

censoring was constant within each time interval. These assumptions were necessary to make, since all studies only report this information for a (very) limited number of time points and no data is available to inform interpolation choices. The number at risk and number of censors could therefore have been over- or underestimated between the observed time points. The observed mortality data of the long-term data studies appeared to be very close to a linear curve, which suggests the linear extrapolation did not result in highly unrealistic survival estimates. Since observed and extrapolated data were combined, the fitting of the parametric curves has been affected by data that was not derived from empirical research. Ideally, parameters are estimated from the original patient-level data. It was furthermore assumed the patient survival follows a Weibull distribution. Of all parametric distributions fitted, the Weibull resulted in the thickest tail of the survival curve. Cost-effectiveness is driven by mean survival, and mean survival is strongly influenced by the tail of the survival curve.(47) The choice for the Weibull distribution therefore might have led to an overestimation of survival curves and an overestimation of the ICUR. The long tail of the survival curve was the main reason for the time horizon of 40 years, to exclude a portion of patients that lives extremely long according to the extrapolated curve. The long survival of some of the patients according to the extrapolation can be explained by the fact that the chosen studies probably just failed to capture the naturally rapidly declining survival at a later age. The choice for this time horizon is expected not to significantly affect the ICUR. Since DAPT after primary PCI has a duration of one year, the incidences of new clinical events are the highest in the first year, the cost categories to which the ICUR is most sensitive are applied as a one-off, and productivity costs are assumed to be non-existent after 10 years, it is believed the chosen time horizon captures the most important costs and effects.

The choice to extract survival data from certain studies and to combine this data, has the consequence that the difference in survival between the PGx-guided and non-PGx-guided arm is solely driven by the differences in survival observed in POPular Genetics, and for the long-term survival, the proportions in which clopidogrel, prasugrel and ticagrelor were assumed to be prescribed. The limitation of this economic evaluation is that the ICUR is only valid for these proportions of antiplatelet agents. However, the proportions were varied in the PSA, which suggests some variation in these parameters still allows for a high chance of cost-effectiveness. Generalizations of the results to largely diverging genotype-guided treatment strategies are limited.

5.2.2 Assumptions regarding utility values

The utilities of living with ACS post-PCI, and the disutilities caused by adverse events have been derived from studies that utilized the EQ-5D as method of measurement. As mentioned in the Theoretical Framework, the EQ-5D is a generic questionnaire applied in indirect valuation. In TTO valuation tasks, a health profile is described with an X number of life years in health state Q. The respondent is asked how many years of full health they would equally prefer to the health profile described. The general consensus in behavioral economics research is that different elicitation methods yield systematically different results, caused by several biases.(101) TTO is biased through three factors: utility curvature, loss aversion, and scale compatibility.(102)

The expected utility hypothesis is an approach to determine the expected economic utility of a decision in the event of uncertain outcomes. Determination of expected utility is established by estimating the probability of each possible outcome and valuing each of the outcomes. The expected utility hypothesis is applied in the field of decision theory and the validity of the hypothesis is one of the assumptions underlying the QALY model.(103) However, violations of the expected utility

hypothesis lead to biases in TTO (and in other elicitation methods as well). The first violation is utility curvature.

To discuss this bias, first, a distinction needs to be made between QALY models. The general QALY model assumes that the utility of an X number of life years in health state Q is calculated by multiplying the utility of the health state with the utility of the life duration:

$$U(Q,T) = H(Q) \cdot L(T)$$

U is the total utility of health profile *Q*,*T*; *H*(*Q*) is the utility *H* of health state *Q*; *L*(*T*) is utility *L* of life duration (*T*).(104)

The linear QALY model assumes risk neutrality with respect to life duration. Risk neutrality entails that the behavior of an economic agent is neither risk-averse nor risk-seeking. If the mathematical expectation is the same for two games of chance, they are equivalent to the agent. Translated to risk neutrality with respect to life duration this means, if an agent is confronted with two health profiles with equal expected utility, the agent will be indifferent towards these two health profiles. *L*(*T*) is therefore assumed to be linear, i.e., all life years have the same utility as the number of life years.(105) The linear QALY model assumes the utility of X life years in health state Q is calculated by multiplying the utility of the health state with life duration:

$$U(Q,T) = H(Q) \cdot T$$

The difference between these QALY models has consequences for the valuation of a TTO result. Say, a TTO task resulted in the following indifference: $(T_1, FH) \sim (T_2, Q)$. FH means full health, which gets the maximum utility value of 1. Furthermore, T_2 is expected to be larger than T_1, since a participant is expected to be willing to give up some life years to return to full health from health state Q. Under the general QALY model, the value of health state Q in this TTO indifference is calculated like this:

$$\begin{gathered}(T_1, FH) \sim (T_2, Q) \\ L(T_1) \cdot H(FH) = L(T_2) \cdot H(Q) \\ L(T_1) = L(T_2) \cdot H(Q) \\ H(Q) = \frac{L(T_2)}{L(T_1)}\end{gathered}$$

To determine *H*(*Q*), both the years of indifference and the utility function need to be known. That is why in practice it is assumed the linear QALY model holds.(102) Under the linear QALY model, the value of *H*(*Q*) in the same TTO indifference is calculated like this:

$$\begin{gathered}(T_1, FH) \sim (T_2, Q) \\ T_1 \cdot H(FH) = T_2 \cdot H(Q) \\ T_1 = T_2 \cdot H(Q) \\ H(Q) = \frac{T_2}{T_1}\end{gathered}$$

Under the linear QALY model, the utility function is linear. Empirical research however has shown that the utility curvature of life duration is in fact concave.(106) A concave utility function implies that $L(T_2)$ is larger than T_2. Since the numerator of the equation of *H*(*Q*) is estimated too low, the value of health state Q will be estimated too low as well. Therefore, utility curvature leads to a downward bias in TTO.(102)

Loss aversion is another violation of the expected utility hypothesis. Loss aversion is the tendency that people prefer to avoid losses more than obtaining gains of the same size. In TTO tasks, loss aversion

can be amplified when a given T is (subconsciously) taken as a reference point. When for example the following task is presented: $(10, FH) \sim (\ldots, Q)$, a person that is not loss averse might be expected to fill in '7', whereas a loss averse person in practice fills out a higher number of life years. Instead of a value of 7/10 = 0.7 of health state Q, a value of e.g., 8/10 = 0.8 might be found. Thus, loss aversion leads to an upward bias in TTO.(102)

The last violation of the expected utility hypothesis that affects TTO, is scale compatibility. Scale compatibility entails that when filling out a valuation task, the unit in which the person needs to respond gains extra focus, leading to higher elicited choices. In TTO tasks, the response scale is life duration. The focus on duration causes people being less willing to give up years, leading to an upward bias.(102)

All in all, TTO is biased downwards by utility curvature and upwards by loss aversion and scale compatibility. In general, TTO is deemed to be more consistent with individual preferences than SG, which is driven by upward bias forces only.(107) However, because empirical research suggests utility curvature is limited, it is assumed TTO suffers from an upward bias overall.(27,107)

In this economic evaluation, the utility values of ACS after primary PCI that were elicited through EQ-5D questionnaires are therefore expected to be biased upwards. The real values might be somewhat lower. The one-way sensitivity analysis has shown that the ICUR is relatively sensitive to changes in the ACS utility values. A lower utility in cycle 1-6 and in the subsequent cycles beyond cycle 12 leads to a higher ICUR. A lower utility in cycle 7-12 leads to a lower ICUR. Taken together, it is expected that the ICUR is slightly underestimated because of the elicitation of utility values through TTO. As for the disutilities, it is more difficult to reason what the effect of the TTO measure is on the ICUR. In all studies from which disutilities were derived, disutility was calculated by subtracting the utility after an adverse event from the base case utility. Therefore, even when TTO biases caused both base case utility and utility after adverse events to be overestimated, the increment might be quite similar compared to the 'correct' lower utility estimates. It is thus expected that the EQ-5D estimates of disutility have a minimal effect on the ICUR.

The last point of discussion concerning the utility values is transferability. To which extent can the results of the studies from which these values were derived, be adopted and applied to the Dutch setting? All studies reported their quality-of-life questionnaires were valued with an American value set. It is known that the same health states receive different scores in different countries.(24) Empirical research suggests that the difference between the EQ-5D value sets are considerable.(108) Even though transferring utilities from one country to another without any adjustment is questionable, there were no alternatives available at the time of this evaluation. It is recommended that further research on utility values of Dutch ACS patients using Dutch value sets is carried out for future health technology assessment.

5.2.3 Assumptions regarding costs

The key assumption made regarding cost parameters, is that DTCs are an accurate reflection of real inpatient and outpatient costs. All post-acute care and adverse event management costs, and some follow-up costs were taken from DTCs. A (possibly outdated) Dutch micro-costing study suggests DTCs were a fairly truthful reflection of real costs.(81) A more recent study suggests there might be discrepancies between DTC values and true costs at times.(109) One way or the other, it is not expected that costs derived from DTCs have had a large impact on the ICUR, since the costs mentioned are the same for both arms. Next to that, the one-way sensitivity analysis has demonstrated the ICUR

is robust against variations in costs. The cost category derived from DTCs with the largest impact was the follow-up cost at the cardiologists' office, which only changed the ICUR by € 16.00.

5.3 Recommendations

Based on the results of this study, it has become clear Dutch policy makers have relatively large certainty that PGx-Passport-guided antiplatelet therapy in ACS patients undergoing primary PCI with stent placement is cost-effective, or even cost-saving. Reimbursement of the PGx-Passport for this patient group would therefore be recommended. This recommendation cannot be generalized to ACS patients of younger age, patients undergoing elective PCI or differentiate between different stent subgroups. Reimbursement is expected to enhance clinical implementation of standardized genotyping, thereby contributing to improved personalized medicine and PCC in the Netherlands. If given the current uncertainty surrounding cost-effectiveness further evidence would be required before a reimbursement decision is taken, additional research on the costs and implementation of the PGx-Passport would be recommended. Of course, the concept of the PGx-Passport is that it covers a wide range of variant alleles and is applicable in multiple treatment strategies, possibly various times per patient. This evaluation was limited to only 1 of the 49 actionable drugs that are included in the passport. Research on how many times a person on average will be prescribed an actionable drug could be informative to determine which portion of the total PGx-Passport costs needs to be attributed to a treatment in economic evaluations, and whether the PGx-Passport should be reimbursed for a variety of patient groups (or even for everyone). Further research should furthermore cover questions such as whether extending or reducing the panel of pharmacogenes affects the ICUR, and whether there is an optimal gene panel in terms of cost-effectiveness.

Some more general recommendations can be made as well. First, long-term observational studies in the Netherlands could reduce the extent to which economic evaluation results are driven by assumed or extrapolated data, which could reduce uncertainty margins for the policy maker. Second, either more research on the utilities of Dutch (ACS) patients could be initiated, or researchers could be encouraged to report 'raw' TTO scores in supplementary material or appendices to enhance broader application of research efforts. Using different country value sets, results of quality-of-life elicitations could be employed in several contexts, preventing applicability being bound by nationality.

Finally, from a medical point of view, it is advisable to utilize pharmacogenetic information in antiplatelet-prescribing decisions, since literature reviews revealed that incidence of clinical events is reduced significantly when interindividual variability in CYP2C19 production is reckoned with.

5.4 Conclusions

The results suggest that aligning treatment strategies with information from the PGx-Passport is potentially cost-effective and can optimize DAPT for Dutch ACS patient undergoing primary PCI. This was the case when the PGx-Passport-guided treatment was compared with standard treatment (largely consisting of ticagrelor prescription), at a time horizon of 40 years if the threshold is € 20,000 per QALY gained.

References

(1) Zandbelt LC, Smets EMA, Oort FJ, Godfried MH, de Haes, Hanneke C. J. M. Medical specialists' patient-centered communication and patient-reported outcomes. Med Care 2007 -04;45(4):330-339.

(2) Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: Definitions and applications to improve outcomes. Journal of the American Academy of Nurse Practitioners 2008;20(12):600-607.

(3) Coulmont M, Roy C, Dumas L. Does the Planetree patient-centered approach to care pay off?: a cost-benefit analysis. Health Care Manag (Frederick) 2013 Jan-Mar;32(1):87-95.

(4) Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. Fertil Steril 2018 -06;109(6):952-963.

(5) Weinshilboum R. Inheritance and Drug Response. New England Journal of Medicine 2003 February 6,;348(6):529-537.

(6) European Medicines Agency. ICH Topic E15 Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. 2007 November(EMEA/CHMP/ICH/437986/2006).

(7) Zhu Y, Moriarty JP, Swanson KM, Takahashi PY, Bielinski SJ, Weinshilboum R, et al. A model-based cost-effectiveness analysis of pharmacogenomic panel testing in cardiovascular disease management: preemptive, reactive, or none? Genet Med 2021 -03;23(3):461-470.

(8) Van Driest SL, Shi Y, Bowton EA, Schildcrout JS, Peterson JF, Pulley J, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clin Pharmacol Ther 2014 -04;95(4):423-431.

(9) van der Wouden, Cathelijne H., van Rhenen MH, Jama WOM, Ingelman-Sundberg M, Lauschke VM, Konta L, et al. Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing. Clin Pharmacol Ther 2019 -10;106(4):866-873.

(10) van der Wouden, C. H., Cambon-Thomsen A, Cecchin E, Cheung KC, Dávila-Fajardo CL, Deneer VH, et al. Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium. Clin Pharmacol Ther 2017 -03;101(3):341-358.

(11) Abbasi J. Getting Pharmacogenomics Into the Clinic. JAMA 2016 -10-18;316(15):1533-1535.

(12) Farmacotherapeutisch Kompas. Geneesmiddelenoverzicht P2Y12-remmers. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/groepsteksten/p2y12_remmers. Accessed 18 May, 2021.

(13) Collet J, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting

without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal 2021 April 7,;42(14):1289-1367.

(14) Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal 2018 January 7,;39(2):119-177.

(15) Rutten F, Bakx C, Bruins Slot M, Van Casteren B, Derks C, Rambharose R, et al. NHG-STANDAARD M80 Versie 2.1 Acuut coronair syndroom. Available at: https://richtlijnen.nhg.org/standaarden/acuut-coronair-syndroom#volledige-tekst-controles. Accessed 18 May, 2021.

(16) Snijders R, Smit V. Cardiologie en vasculaire geneeskunde. 2nd ed. Rotterdam: Synopsis BV; 2019.

(17) Danse P, Derks L, Timmermans M. NHR Rapportage 2020. 2021.

(18) Nederlandse Vereniging voor Cardiologie. Richtlijnen. Available at: https://www.nvvc.nl/Kwaliteit/richtlijnen. Accessed 18 May, 2021.

(19) Farmacotherapeutisch Kompas. Behandeling van een NSTEMI/IAP ACS. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/coronairlijden?anchor=coronairlijden_behandeling_van_een_nstemi_iap_acs. Accessed 18 May, 2021.

(20) Bergmeijer TO, Reny J, Pakyz RE, Gong L, Lewis JP, Kim E, et al. Genome-wide and candidate gene approaches of clopidogrel efficacy using pharmacodynamic and clinical end points—Rationale and design of the International Clopidogrel Pharmacogenomics Consortium (ICPC). Am Heart J 2018;198:152-159.

(21) Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. Lancet 2010 -10-16;376(9749):1312-1319.

(22) Fanari Z, Weiss S, Weintraub WS. Cost Effectiveness of Antiplatelet and Antithrombotic Therapy in the Setting of Acute Coronary Syndrome: Current Perspective and Literature Review. Am J Cardiovasc Drugs 2015 -12;15(6):415-427.

(23) Farmacotherapeutisch Kompas. Preparaatteksten - Clopidogrel. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/clopidogrel#kosten. Accessed 18 May, 2021.

(24) Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

(25) Commissie richtlijnherziening. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Zorginstituut Nederland 2016.

(26) Briggs A, Claxton K, Schulpher M. Decision Modelling for Health Economic Evaluation. 1st ed. New York: Oxford University Press; 2006.

(27) Lipman SA, Brouwer WBF, Attema AE. What is it going to be, TTO or SG? A direct test of the validity of health state valuation. Health Econ 2020 -11;29(11):1475-1481.

(28) Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding:Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Zorginstituut Nederland 2016.

(29) Koopmanschap MA, van Exel, N. Job A, Bernard van den Berg, Brouwer WBF. An Overview of Methods and Applications to Value Informal Care in Economic Evaluations of Healthcare. Pharmacoeconomics 2008;26(4):269-280.

(30) Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995 -06;14(2):171-189.

(31) Pol Mvd, Irvine A. Time Preferences for Health. ; 2018.

(32) Attema A, Brouwer W, Claxton K. Discounting in economic evaluations. PharmacoEconomics 2018 May 19,;36(7):745-758.

(33) Roberts M, Russell LB, Paltiel AD, Chambers M, McEwan P, Krahn M. Conceptualizing a Model: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-2. Value in Health 2012;15(6):804-811.

(34) Williams C, Lewsey JD, Mackay DF, Briggs AH. Estimation of Survival Probabilities for Use in Cost-effectiveness Analyses: A Comparison of a Multi-state Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling. Med Decis Making 2017 -05;37(4):427-439.

(35) Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC medical research methodology 2011 Oct 10,;11(1):139.

(36) Jackson CH, Sharples LD, Thompson SG. Survival models in health economic evaluations: balancing fit and parsimony to improve prediction. Int J Biostat 2010;6(1):Article 34.

(37) Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. Health Economics 2004;13(5):405-415.

(38) Nederlands Huisartsen Genootschap. NHG-STANDAARD M84 Versie 4.0 Cardiovasculair risicomanagement. 2019; Available at: https://richtlijnen.nhg.org/standaarden/cardiovasculair-risicomanagement. Accessed 18/05/, 2021.

(39) Bouma M, Rutten FH, Wiersma T, Burges JS. Herziene NHG-standaard 'Acuut coronair syndroom. 2012 Feb, 20,;157(A6006).

(40) Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof, Arnoud W. J., van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. New England Journal of Medicine 2019 October 24,;381(17):1621-1631.

(41) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine 2007 November 15,;357(20):2001-2015.

(42) Sebastian Völz, Petur Petursson, Jacob Odenstedt, Dan Ioanes MD, Inger Haraldsson, Oskar Angerås, et al. Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry. Journal of the American Heart Association 2020 July 21,;9(14):e015990.

(43) Elective Percutaneous Coronary Intervention (PCI) Program Reports, 2019.

(44) Garratt KN, Weaver WD, Jenkins RG, Pow TK, Mauri L, Kereiakes DJ, et al. Prasugrel plus aspirin beyond 12 months is associated with improved outcomes after TAXUS Liberté paclitaxel-eluting coronary stent placement. Circulation 2015 -01-06;131(1):62-73.

(45) Kawashima H, Tomaniak M, Ono M, Wang R, Hara H, Gao C, et al. Safety and Efficacy of 1-Month Dual Antiplatelet Therapy (Ticagrelor + Aspirin) Followed by 23-Month Ticagrelor Monotherapy in Patients Undergoing Staged Percutaneous Coronary Intervention (A Sub-Study from GLOBAL LEADERS). American Journal of Cardiology 2021 /01/01;138:1-10.

(46) Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal 2020 January 14,;41(3):407-477.

(47) Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC medical research methodology 2011 Oct 10,;11(1):139.

(48) Create a Survival Object. Available at: https://stat.ethz.ch/R-manual/R-patched/library/survival/html/Surv.html. Accessed May 24, 2021.

(49) Kaambwa B, Gesesew HA, Horsfall M, Chew D. Quality of Life Changes in Acute Coronary Syndromes Patients: A Systematic Review and Meta-Analysis. IJERPH 2020 -09-21;17(18).

(50) Schenkeveld L, Pedersen SS, van Nierop, Josephine W. I., Lenzen MJ, de Jaegere, Peter P. T., Serruys PW, et al. Health-related quality of life and long-term mortality in patients treated with percutaneous coronary intervention. Am Heart J 2010;159(3):471-476.

(51) Jonker MF. Estimating Dutch SF-6D Health State Weights. Nederlandse Organisatie voor Wetenschappelijk Onderzoek 2013.

(52) Cohen DJ, Van Hout B, Serruys PW, Mohr FW, Macaya C, den Heijer P, et al. Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery. N Engl J Med 2011 -03-17;364(11):1016-1026.

(53) Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-Effectiveness of Genotype-Guided and Dual Antiplatelet Therapies in Acute Coronary Syndrome. Annals of Internal Medicine 2014 -02-18.

(54) Baldetti L, Melillo F, Moroni F, Gallone G, Pagnesi M, Venuti A, et al. Meta-Analysis Comparing P2Y12 Inhibitors in Acute Coronary Syndrome. Am J Cardiol 2020;125(12):1815-1822.

(55) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045-1057.

(56) Schüpke S, Neumann F, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381(16):1524-1534.

(57) Krishnamurthy A, Keeble C, Anderson M, Somers K, Burton-Wood N, Harland C, et al. Real-world comparison of clopidogrel, prasugrel and ticagrelor in patients undergoing primary percutaneous coronary intervention. Open heart 2019;6(1):e000951.

(58) De Filippo O, Cortese M, Raposeiras-Roubin S, Abu-Assi E, Kinnaird T, Ariza-Solé A, et al. Real-world data of prasugrel vs. ticagrelor in acute myocardial infarction: results from the RENAMI registry. American Journal of Cardiovascular Drugs 2019;19(4):381-391.

(59) Welsh RC, Sidhu RS, Cairns JA, Lavi S, Kedev S, Moreno R, et al. Outcomes among clopidogrel, prasugrel, and ticagrelor in ST-elevation myocardial infarction patients who underwent primary percutaneous coronary intervention from the TOTAL trial. Can J Cardiol 2019;35(10):1377-1385.

(60) Klingenberg R, Heg D, Räber L, Carballo D, Nanchen D, Gencer B, et al. Safety profile of prasugrel and clopidogrel in patients with acute coronary syndromes in Switzerland. Heart 2015;101(11):854-863.

(61) Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, et al. Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes: The PHARMCLO Trial. J Am Coll Cardiol 2018;71(17):1869-1877.

(62) Sánchez-Ramos J, Dávila-Fajardo CL, Toledo Frías P, Díaz Villamarín X, Martínez-González LJ, Martínez Huertas S, et al. Results of genotype-guided antiplatelet therapy in patients who undergone percutaneous coronary intervention with stent. Int J Cardiol 2016;225:289-295.

(63) Klein MD, Williams AK, Lee CR, Stouffer GA. Clinical Utility of CYP2C19 Genotyping to Guide Antiplatelet Therapy in Patients With an Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention. Arteriosclerosis, Thrombosis, and Vascular Biology 2019 April 1,;39(4):647-652.

(64) Garg P, Cohen DJ, Gaziano T, Mauri L. Balancing the risks of restenosis and stent thrombosis in bare-metal versus drug-eluting stents: results of a decision analytic model. J Am Coll Cardiol 2008 -05-13;51(19):1844-1853.

(65) Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, et al. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme Acute Coronary Syndromes.

(66) Garg P, Galper BZ, Cohen DJ, Yeh RW, Mauri L. Balancing the risks of bleeding and stent thrombosis: a decision analytic model to compare durations of dual antiplatelet therapy after drug-eluting stents. Am Heart J 2015 -02;169(2):222-233.e5.

(67) Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: Meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. American Journal of Hematology 2004;75(1):40-47.

(68) The SPS3 Investigators. Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke. New England Journal of Medicine 2012 August 30,;367(9):817-825.

(69) López-López JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359.

(70) Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med 2011 -01-04;154(1):1-11.

(71) EUROpean Treatment & Reduction of Acute Coronary Syndromes cost analysis The EUROTRACS Project Consumers, Health, Agriculture and Food Executive Agency Agreement number 2012 12 07 Deliverable N. D07-00 Title: Cost-effectiveness analysis of acute coronary syndrome (ACS) procedures that lower in-hospital fatality in patients older than 34 years. 2015 -07.

(72) Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde. NVKC Wie Doet Wat Database 3.0. 2021; Available at: https://www.nvkc.nl/professional/wie-doet-wat-database-30?searchtext=genotypering&btnZoek=Zoek%21&action=search. Accessed May 29, 2021.

(73) De Jongh E, De Wit NJ, Numans ME, Smeink P, Van der Weele, G M, Wesseler GH. NHG-Behandelrichtlijn Preventie van maagcomplicaties door geneesmiddelgebruik. March 2021 2021 March.

(74) Zorginstituut Nederland. Farmacotherapeutisch Kompas - Maagbescherming. Available at: https://www.farmacotherapeutischkompas.nl/bladeren/indicatieteksten/maagbescherming. Accessed 27 May, 2021.

(75) Nederlands Huisartsen Genootschap. NHG-Standaard Cardiovasculair risicomanagement (M84). 2019 June.

(76) NVVC. NVVC praktijkrichtlijn hartrevalidatie . 2011 March.

(77) De Vries H, Van den Broek I, Van Dis I, Van Engen-Verheul MM, Janssen VR, Kemps H, et al. Kenmerken van deelnemers aan hartrevalidatie-programma's. Hartstichting 2017:199-233.

(78) Neeleman-van der Steen, C. W. M, Heniks HJM, Bertram R, Graus J, Herwaarden Fv, Jongert T, et al. Handelen volgens de KNGF-richtlijn Hartrevalidatie: Een prospectieve cohortstudie. Nederlands Tijdschrift voor Fysiotherapie 2008;118:2-11.

(79) Klomp M, Romeijnders A, De Braal E, Rutten G, Meulepas M. TRANSPARANTE KETENZORG RAPPORTAGE 2017 ZORGGROEPEN DIABETES MELLITUS, VRM, COPD EN ASTMA. Ineen 2018 June,:21-23.

(80) Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare. 2015.

(81) Tan SS, Oostenbrink JB, Rutten F. Costs and prices of healthcare services in the Netherlands: a micro costing approach based on case-vignettes. 2006 -10.

(82) Van Eeden M, Van Heugten C, Van Mastrigt, G A P G, Van Mierlo M, Visser-Meily JMA, S, et al. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke.

(83) Bakhai A, Ferrieres J, Iniguez A, Sartral M, Belger M, Schmitt C, et al. Clinical Outcomes, Resource Use, and Costs at 1 Year in Patients with Acute Coronary Syndrome Undergoing PCI: Results from the Multinational APTOR Registry. Journal of Interventional Cardiology 2012;25(1):19-27.

(84) van Baal PH, Wong A, Slobbe LJ, Polder JJ, Brouwer WB, de Wit GA. Standardizing the inclusion of indirect medical costs in economic evaluations. Pharmacoeconomics 2011;29(3):175-87.

(85) KNMP. KNMP-Richtlijn Ter Hand Stellen. Apothekersorganisatie KNMP 2018 Dec,:3-36.

(86) Kotseva K, Gerlier L, Sidelnikov E, Kutikova L, Lamotte M, Amarenco P, et al. Patient and caregiver productivity loss and indirect costs associated with cardiovascular events in Europe. European Journal of Preventive Cardiology 2019 July 1,;26(11):1150-1157.

(87) Büyükkaramikli NC, Rutten-van Mölken, Maureen P. M. H., Severens JL, Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics 2019 -11;37(11):1391-1408.

(88) Versteegh MM, Ramos IC, Buyukkaramikli NC, et al. Severity-Adjusted Probability of Being Cost Effective. PharmacoEconomics 2019 May 27,;37:1155–1163.

(89) AlMukdad S, Elewa H, Al-Badriyeh D. Economic Evaluations of CYP2C19 Genotype-Guided Antiplatelet Therapy Compared to the Universal Use of Antiplatelets in Patients With Acute Coronary Syndrome: A Systematic Review. J Cardiovasc Pharmacol Ther 2020 -05;25(3):201-211.

(90) Sorich MJ, Horowitz JD, Sorich W, Wiese MD, Pekarsky B, Karnon JD. Cost-effectiveness of using CYP2C19 genotype to guide selection of clopidogrel or ticagrelor in Australia. Pharmacogenomics 2013 -12;14(16):2013-2021.

(91) Crespin DJ, Federspiel JJ, Biddle AK, Jonas DE, Rossi JS. Ticagrelor versus genotype-driven antiplatelet therapy for secondary prevention after acute coronary syndrome: a cost-effectiveness analysis. Value Health 2011 -06;14(4):483-491.

(92) Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, et al. Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med 2014 -02-18;160(4):221-232.

(93) Jiang M, You JH. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics 2016 -05;17(7):701-713.

(94) Jiang M, You JHS. CYP2C19 LOF and GOF-Guided Antiplatelet Therapy in Patients with Acute Coronary Syndrome: A Cost-Effectiveness Analysis. Cardiovasc Drugs Ther 2017 -02;31(1):39-49.

(95) Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. J Thromb Haemost 2013 -01;11(1):81-91.

(96) Wang Y, Yan BP, Liew D, Lee VWY. Cost-effectiveness of cytochrome P450 2C19 *2 genotype-guided selection of clopidogrel or ticagrelor in Chinese patients with acute coronary syndrome. Pharmacogenomics J 2018 -01;18(1):113-120.

(97) Dong OM, Wheeler SB, Cruden G, Lee CR, Voora D, Dusetzina SB, et al. Cost-Effectiveness of Multigene Pharmacogenetic Testing in Patients With Acute Coronary Syndrome After Percutaneous Coronary Intervention. Value in health 2020 Jan;23(1):61-73.

(98) Hulot J, Collet J, Montalescot G. Genetic substudy of the PLATO trial. Lancet 2011 -02-19;377(9766):637, author reply 637-638.

(99) Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009 -09-10;361(11):1045-1057.

(100) Verdoia M, Pergolini P, Rolla R, Nardin M, Schaffer A, Barbieri L, et al. Advanced age and high-residual platelet reactivity in patients receiving dual antiplatelet therapy with clopidogrel or ticagrelor. Journal of Thrombosis and Haemostasis 2016;14(1):57-64.

(101) Bleichrodt H, Johannesson M. Standard gamble, time trade-off and rating scale: experimental results on the ranking properties of QALYs. J Health Econ 1997 -04;16(2):155-175.

(102) Bleichrodt H. A new explanation for the difference between time trade-off utilities and standard gamble utilities. Health Econ 2002 -07;11(5):447-456.

(103) Cohen BJ. Is expected utility theory normative for medical decision making? Med Decis Making 1996 Jan-Mar;16(1):1-6.

(104) Miyamoto JM, Wakker PP, Bleichrodt H, Peters HJM. The Zero-Condition: A Simplifying Assumption in QALY Measurement and Multiattribute Utility. Management Science 1998;44(6):839-849.

(105) Pliskin JS, Shepard DS, Weinstein MC. Utility Functions for Life Years and Health Status. Operations Research 1980;28(1):206-224.

(106) Kaplow L. Concavity of utility, concavity of welfare, and redistribution of income. Int Tax Public Finance 2010;17(1):25-42.

(107) van Osch, Sylvie M. C., Wakker PP, van den Hout, Wilbert B., Stiggelbout AM. Correcting biases in standard gamble and time tradeoff utilities. Med Decis Making 2004 Sep-Oct;24(5):511-517.

(108) Knies S, Evers, Silvia M. A. A., Candel, Math J. J. M., Severens JL, Ament, André J. H. A. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics 2009;27(9):767-779.

(109) Krabbe-Alkemade, Y. J. F. M., Groot, T. L. C. M., Lindeboom M. Competition in the Dutch hospital sector: an analysis of health care volume and cost. Eur J Health Econ 2017 -03;18(2):139-153.

Appendix

Test description	Method of conducting the test	Expected result	Result
Pre-analysis calculations			
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Price of PGx-Passport +1,000. Checks on Parameters sheet, Markov trace sheet and Analysis sheet.	Yes	Yes
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	The AIC and intercept value of the exponential distribution were copied to the Weibull values, and the logscale value was changed to 0.	Yes	Yes, the formulae of the Weibull distribution generated the exact same values as obtained from the exponential distribution.
Event-state calculations			
Calculate the sum of the number of patients at each health state	Check was built-in, which added number of patients in the stable disease state and in the death state.	Should add up to the cohort size	Added up to cohort size of 1,000.
Check if all probabilities and number of patients in a state are greater than or equal to 0	Markov trace was checked for any negative number of patients in a cycle. Parameters	Yes	Yes

	sheet was checked for negative probabilities.		
Check if all probabilities are smaller than or equal to 1	All probabilities on Parameters sheet were checked.	Yes	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	Number of patients in death state in Markov trace was checked.	Should be larger	Was larger.
Set all utilities to 1	All utilities on the Parameters sheet were set to 1. On the Markov trace sheets, life years accrued and QALY accumulated were compared.	The QALYs accumulated at a given time would be the same as the life-years accumulated at that time	Were indeed the same.
Set all utilities to 0	All utilities on the Parameters sheet were set to 1. On the Markov trace sheets, the total QALYs accumulated were checked.	No utilities will be accumulated in the model	Total QALYs equal to 0.
Decrease all state utilities simultaneously (but keep event-based utility decrements constant	0.1 was subtracted from all utilities on the Parameters sheet. Analysis sheet was	Lower utilities will be accumulated each time	For both arms, total QALYs accumulated was decreased with 2 QALYs.

	checked for total QALYs accrued.		
Set all costs to 0	Costs set to 0 on Parameters sheet.	No costs will be accumulated in the model at any time	No costs accumulated.
Put mortality rates to 0	Intercept and logscale of chosen Weibull distribution were set to 100 and 1, respectively.	Patients never die	Patients never died.
Put mortality rate at extremely high	Intercept and logscale of chosen Weibull distribution were set to 1 and 0, respectively.	Patients die in the first few cycles	All patients were dead by cycle 8.
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	On the Parameters sheet, all utilities and parameters relating to adverse events were set to PGx-guided arm values.	Same life-years and QALYs should be accumulated for all treatment at any time	Same life years and QALYs were accumulated.
In addition to the inputs above, set cost-related model inputs for all treatment options equal	On the Parameters sheet, all costs were set to non-PGx-guided arm values.	Same costs, life-years, and QALYs should be accumulated for all treatment at any time	Same costs, life years and QALYs were accumulated.
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	Model inputs were reversed for both arms.	Accumulated life-years and QALYs in the model at any time should also be reversed	Accumulated life years and QALYs were reversed on Analysis sheet.
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	No life tables were available with a starting age of 65. CBS	At any given age, the percentage alive should be lower or equal in comparison with the general population estimate	The life years accrued are 20.16 and 19.18 for the PGx and non-PGx-guided

	statistics show that life expectancy of a 65-year-old is 20.52.		arm. This is lower than the general population estimate.
Check if the QALY estimate at any cycle is in line with general population utility estimates	No QALE life tables were available. A study on QALE has shown the QALE of a 65-year-old in the Netherlands is 14.94.	At any given age, the utility assigned in the model should be lower or equal in comparison with the general population utility estimate	The QALYs accrued are 12.67 and 12.04 for the PGx-guided and non-PGx-guided arm. This is lower than the population estimate.
Set the inflation rate for the previous year higher	Index factors were increased with 1.	The costs (which are based on a reference from previous years) assigned at each time will be higher	All increases led to higher total costs for both arms (for example: change in factor of 2015 led to 77,249 -> 77,472 in PGx-arm).
Increase the treatment acquisition cost	Costs of PGx-Passport were increased with 1,000.	Costs accumulated at a given time will increase during the period when the treatment is administered	Costs accumulated in first cycle increased, which is indeed the cycle where these costs are incurred.
Results calculations			
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Incremental life years and QALYs checked on Analysis sheet, compared with results of POPular Genetics.	If a treatment is more effective, it generally results in positive incremental LYs and QALYs in comparison with the less-effective treatments	The incremental life years and QALYs are quite small, but positive. Results in line with expectations based on the POPular Genetics trial.
Check the incremental cost results. Are they in line with the treatment costs?	Incremental costs were checked on Analysis sheet.	If a treatment is more expensive, and if it does not have much effect on other costs, it generally results in positive incremental costs	Incremental costs are positive, but not large. In line with the fact that the PGx-

			Passport causes the biggest incremental cost.
Total life years greater than the total QALYs	Life years and QALYs were compared on Analysis sheet.	Yes	Yes
Undiscounted results greater than the discounted results	Total discounted and undiscounted costs and QALYs were compared.	Yes	Yes. E.g., for the PGx-arm: 83,524 > 77,249 (costs), 15.49 > 12.67 (QALYs).
Divide undiscounted total QALYs by undiscounted life years	Undiscounted QALYs were divided by undiscounted life years.	This value should be within the outer ranges (maximum and minimum) of all the utility value inputs	Yes. E.g., for PGx-arm: 15.48/20.14 = 0.769, which is within the outer ranges of 0 and 1.
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Origin of results was reviewed.	Yes	Yes
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Time horizon was changed to 20 years.	Yes	Yes. E.g., for the PGx-arm: total costs were 75,650, total life years were 13.47 and total QALYs were 9.73.
Is the reporting and contextualization of the incremental results correct?	Results section of thesis was reviewed.	The use of terms such as 'dominant'/'dominated'/'extended ly dominated'/'cost effective'. etc.. should be in line with the results In the incremental analysis table involving multiple treatments, ICERs should be calculated against the next non-dominated treatment	Yes. ICUR was correctly named cost-effective, and only two treatments were compared.
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	The subtotals of the Markov trace results were reviewed.	Yes	Yes

Check the discounted value of costs/QALYs after 2 years	Calculations were performed.	Discounted value = undiscounted/(1 + r)2	Yes
Set discount rates to 0	Discount rates were set to 0 on Parameters sheet.	The discounted and undiscounted results should be the same	Discounted and undiscounted results were the same.
Set mortality rate to 0	Intercept and logscale of chosen Weibull distribution were set to 100 and 1, respectively.	The undiscounted total life-years per patient should be equal to the length of the time horizon	Undiscounted total life years was 40, time horizon is 40 years indeed.
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements	Costs + disutility were set to 0 first, AE incidence was set 0 next.	The results would be the same as the results when the AE rate is set to 0	Yes
Divide total undiscounted treatment acquisition costs by the average duration on treatment	Price of the PGx-Passport was divided by 1 (since it was assumed it can be applied within 1 day).	This should be similar to treatment-related unit acquisition costs	Yes
Set discount rates to a higher value	Both discount rates were set to 8%.	Total discounted results should decrease	Total discounted costs and QALYs decreased. E.g., for the PGx-arm: 77,249 -> 74,322 and 12.67 -> 6.79.
Set discount rates of costs/effects to an extremely high value	Discount rates were set to 50%. Total discounted costs and QALYs were compared with totals of the first 10 cycles.	Total discounted results should be more or less the same as the discounted results accrued in the first cycles	Yes
Put adverse event/discontinuation	Adverse events rates	Less costs and higher QALYS/LYs when adverse event rates are 0,	Yes

rates to 0 and then to an extremely high level	were put to 0 and 0.9.	higher costs and lower QALYS/LYs when AE rates are extreme	
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	Adverse event incidences of the PGx-guided arm on clopidogrel were halved.	Approximately twice the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	QALY increment: 0.66; LY increment: 0.97. This is not twice the incremental effect. This can be explained by the fact that 3 drugs are prescribed in both treatment arms, only proportions differ. Only 1 of the 3 drugs shows pharmacogenetic variation, which means if the PGx-Passport could generate half of current AEs on clopidogrel, the difference is not huge.
Do the same for a scenario in which the difference in efficacy and safety is halved	Adverse event incidences of the PGx-guided arm on clopidogrel were doubled.	Approximately halve of the incremental effect results of the base case. If this is not the case, report and explain the underlying reason/mechanism	QALY increment: 0.59; LY increment: 0.97. Mechanism is the same as explained in previous row.
Uncertainty analysis calculations			
Are all necessary parameters subject to uncertainty included in the OWSA?	Parameters included in the one-way sensitivity analysis were reviewed.	Yes	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves	Parameters included in the one-way sensitivity analysis were reviewed.	No	No

with multiple parameters)			
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Upper and lower values included in the one-way sensitivity analysis were reviewed.	Yes	Partly, some lower and upper bounds were derived from literature.
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Tornado diagram was reviewed.	Yes	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ≥ mean ≥ lower bound)	All parameters were checked.	Yes	Yes
Standard error and not standard deviation used in sampling	All standard error inputs were checked.	Yes	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Distributions for costs and resource use were reviewed.	Yes	Yes
Beta for utilities and proportions/probabilities	Distributions for utilities and proportions were reviewed.	Yes	Yes
Dirichlet for multinomial	Multinomial data distributions were reviewed.	Yes	Yes
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Survival curve variations	Yes	Yes

	were reviewed.		
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	PSA output was reviewed.	No (in general)	No. Mean costs and QALYs are 78,088 and 12.82 (PGx) and 76,922 and 12.18 (non-PGx), which is very close to the deterministic results.
If you take new PSA runs from the Microsoft Excel model do you get similar results?	PSA was run again.	Yes	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	CEAC and CE scatter plot were compared.	Yes	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	PSA cloud was reviewed.	No	No, only quite some uncertainty.
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Scenario analysis on PGx-Passport price was reviewed.	Yes	Yes (more optimistic scenarios were explored, but base case assumption was quite a pessimistic option already).
Are the scenario analysis results plausible and in line with a priori expectations?	Scenario analysis on PGx-Passport price was reviewed.	Yes	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Two PSA results were compared.	Should be very low (very high) if different (same) random streams are used for different arms	Very high
Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	Choices made in sensitivity analysis were reviewed.	No	No

Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	PSA iterations were checked + scenarios and correspondin g outcomes were checked.	Yes	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Parameter sheet and Markov trace sheets were checked precisely.	Yes	Yes

Table A1. TECH-VER black-box tests: test description, method of conducting the test, expected result and result were reported. All black-box tests were passed by the model.

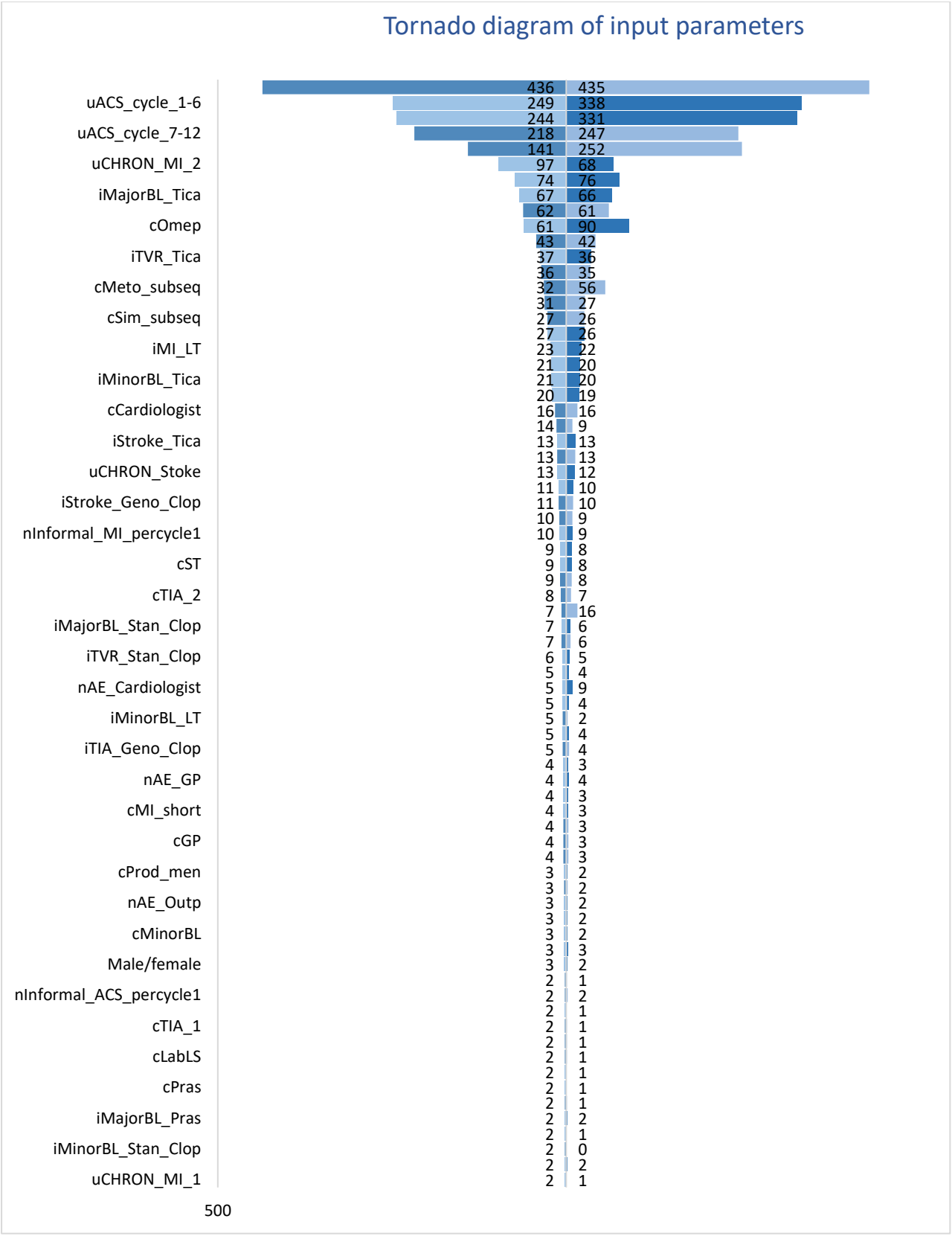

Figure A1. Extended version of the tornado diagram, showing the impact of variations of parameters. Parameters without any impact were excluded from this diagram.

First author, year	Country	Interventions compared	Time horizon	Economic evaluation perspective	ICUR (threshold)
Crespin, 2011	US	Universal ticagrelor, genotyping with clopidogrel and ticagrelor	5 years	US third-party payer	$10,059 ($50,000)
Kazi, 2014	US	Universal clopidogrel, universal ticagrelor, universal prasugrel, genotyping with prasugrel and ticagrelor (2 varieties)	Lifetime	US healthcare provider	$107,050 ($50,000)
Sorich, 2013	Australia	Universal clopidogrel, universal ticagrelor, genotyping with clopidogrel and ticagrelor	Lifetime	Australian healthcare system	$23,000 ($30,000-$50,000)
Jiang, 2016	China	Universal clopidogrel, universal prasugrel and ticagrelor, genotyping (2 varieties)	30 years	US healthcare provider	-$76,296 ($50,000)
Jiang, 2017	China	Universal clopidogrel, universal prasugrel and ticagrelor, genotyping	30 years	US healthcare provider	-$42,632 ($50,000)
Wang, 2018	China	Universal clopidogrel, universal ticagrelor, genotyping with clopidogrel and ticagrelor	25 years	Asian healthcare provider	$2,560 ($42,425)
Lala, 2013	US	Universal clopidogrel, universal prasugrel, genotyping with clopidogrel and prasugrel	10 years	US payer	-$2,219,615 ($100,000)
Dong, 2020	US	No genotyping, single-gene testing, multi-gene testing	Lifetime	Medicare	$3,780 ($100,000)

Articles have been extracted from Pubmed and Embase, based on search terms from the systematic review from AlMukdad et al (2019). Papers were only selected if all patients of the cohort underwent PCI, if some type of genotyping was compared to universal ticagrelor and/or prasugrel and if there was a Markov model used. In the case that more than two comparators were used in the study, the ICUR reported is the one of the genotype-guided treatment versus the comparator that resembled the comparator of this evaluation the most (usually, this was universal ticagrelor). The purple cells indicate the studies that concluded that genotype-guided antiplatelet selection is not cost-effective, the grey cells indicate the studies that concluded that genotype-guided antiplatelet selection is cost-effective or cost-saving.

Table A2. Schematic overview of related works.