Cost-effectiveness of a CYP2C19 genotype-guided strategy in acute myocardial infarction patients: Results from the POPular Genetics trial

POPular Genetics cost-effectiveness analysis

Daniel M.F. Claassens[1,2], M.D., *Pim W.M. van Dorst[3], MSc., *Gerrit J.A. Vos[1], M.D., Thomas O. Bergmeijer[1], M.D., Renicus S. Hermanides[2], M.D., Ph.D., Arnoud W.J. van 't Hof[4,5,6] M.D., Ph.D., Pim van der Harst[7,8], M.D., Ph.D., Emanuele Barbato[9,10], M.D., Ph.D., Carmine Morisco[9], M.D., Ph. D., Richard M. Tjon Joe Gin[11], M.D., Folkert W. Asselbergs[8,12,13], M.D., Ph.D., Arend Mosterd[14], M.D., Ph.D., Jean-Paul R. Herrman[15], M.D., Ph.D., Willem J.M. Dewilde[16,17], M.D., Ph.D., Maarten J. Postma[3,18,19], Ph.D., Vera H.M. Deneer[20,21], Pharm.D., Ph.D., Jurriën M. ten Berg[1,6], M.D., Ph.D. Cornelis Boersma[3,22], Pharm.D., Ph.D.,

* Both authors contributed equally to this work

1. Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands

2. Department of Cardiology, Isala Hospital, Zwolle, The Netherlands

3. Unit of Global Health, Department of Health Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

4. Department of Cardiology, University Medical Center Maastricht, Maastricht, The Netherlands

5. Department of Cardiology, Zuyderland Medical Center, Heerlen, The Netherlands

6. Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

7. Department of Cardiology, University Medical Center Groningen, Groningen, The Netherlands

8. Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

9. Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

10. Cardiovascular Research Center, Onze lieve Vrouwe Hospital, Aalst, Belgium

11. Department of Cardiology, Rijnstate Hospital, Arnhem, The Netherlands

12. Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom;

13. Health Data Research UK and Institute of Health Informatics, University College London, London, United Kingdom

14. Department of Cardiology, Meander Medical Center, Amersfoort, The Netherlands

15. Department of Cardiology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

16. Department of Cardiology, Amphia hospital, Breda, The Netherlands

17. Department of Cardiology, Imelda hospital, Bonheiden, Belgium.

18. Department of Pharmacy, University of Groningen, Groningen, The Netherlands

19. Department of Economics, Econometrics & Finance, University of Groningen, Faculty of Economics & Business, Groningen, The Netherlands

20. Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

21. Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands

22. Faculty of Management Sciences, Open University, Heerlen, The Netherlands

Address for correspondence:

Prof. Jurriën M. ten Berg, M.D., Ph.D.

Department of cardiology

St. Antonius Hospital

Koekoekslaan 1, 3435CM, Nieuwegein

The Netherlands

Email: jurtenberg@gmail.com

Tel: +31 88 320 13 82

Abstract:

Objective

The POPular Genetics trial demonstrated that a *CYP2C19* genotype-guided $P2Y_{12}$ inhibitor strategy reduced bleeding rates compared to standard treatment with ticagrelor or prasugrel, without increasing thrombotic event rates after primary percutaneous coronary intervention (PCI). In this analysis, we aimed to evaluate the cost-effectiveness of a genotype-guided strategy compared to standard treatment with ticagrelor or prasugrel.

Methods

A 1-year decision tree based on the POPular Genetics trial in combination with a lifelong Markov model was developed to compare costs and quality-adjusted life years (QALYs) between a genotype-guided and a standard $P2Y_{12}$ inhibitor strategy in myocardial infarction patients undergoing primary PCI. The cost-effectiveness analysis was conducted from a Dutch healthcare system perspective. Within-trial survival and utility data were combined with lifetime projections to evaluate lifetime costs-effectiveness for a cohort of 1000 patients. Costs and utilities were discounted at 4% and 1.5% respectively according to Dutch guidelines for health-economic studies. Besides deterministic and probabilistic sensitivity analyses, several scenario analyses (different time horizons, different discount rates, equal prices for $P2Y_{12}$ inhibitors and equal distribution of thrombotic events between the two strategies) were conducted.

Results

Base-case analysis with a hypothetical cohort of 1000 subjects, demonstrated 8.98 QALYs gained and €725,550.69 cost-savings for the genotype-guided strategy (dominant). The deterministic and probabilistic sensitivity analysis confirmed the robustness of the model and

the cost-effectiveness results. In scenario analyses, the genotype-guided strategy remained dominant.

Conclusion

In patients undergoing primary PCI, a *CYP2C19* genotype-guided strategy compared to standard treatment with ticagrelor or prasugrel resulted in QALYs gained and cost-savings.

Trial registration: Clinicaltrials.gov number: NCT01761786, Netherlands trial register number: NL2872

Key points:

- A *CYP2C19* genotype-guided de-escalation strategy is a reasonable alternative for standard $P2Y_{12}$ inhibitor therapy according to the latest European Society of Cardiology guideline for patients with acute coronary syndrome.
- A *CYP2C19* genotype-guided strategy compared to standard treatment with potent $P2Y_{12}$ inhibitors in patients with acute myocardial infarction results in cost-savings and improved quality of life.
- These results are based on the prevalence of *CYP2C19* loss-of-function alleles in European, mostly Dutch, patients and on Dutch healthcare costs.

Declarations

Funding

This work was supported by ZonMw, a Dutch government agency, as part of its efficiency research program (project 171102022). Spartan Bioscience (Nepean, Ottawa) provided the Spartan RX system and the reagents used free of charge.

Disclosures

Dr. Asselbergs reports grants from the University College London Hospitals National Institute for Health Research Biomedical Research Centre. Dr. van 't Hof reports institutional grants from Medtronic, AstraZeneca and Sanofi and personal fees from AstraZeneca and AMGEN; Dr. Barbato reports personal fees from Boston scientific, Abbott Vascular and GE; Dr. Ten Berg reports institutional grants from AstraZeneca and ZonMw and personal fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, the Medicines Company, Accumetrics, Boehringer-Ingelheim, Bayer, BMS, Pfizer and Ferrer; Dr. Postma reports institutional grants from AstraZeneca, GSK, Pfizer and Amgen and personal fees from AstraZeneca, Daiichi Sankyo, Boehringer-Ingelheim, Bayer, BMS, Pfizer, GSK and Roche. All other authors have nothing to disclose.

Availability of data and material

Data will be made available upon reasonable request

Code availability

Analyses were performed using R version 3.6 or later and Excel

Author's contribution

Conceptualization: TO Bergmeijer, JM ten Berg, VHM Deneer; Methodology: DMF Claassens, WM van Dorst, C Boersma; Formal analysis and investigation: DMF Claassens, WM van Dorst, TO Bergmeijer, GJA Vos; Writing - original draft preparation: DMF Claassens, WM van Dorst; Writing - review and editing: GJA Vos, TO Bergmeijer, RS Hermanides, AWJ van 't Hof, P van der Harst, E Barbato, C Morisco, RM Tjon Joe Gin, FW Asselbergs, A Mosterd, JPR Herrman, WJM Dewilde, MJ Postma; Funding acquisition: VHM Deneer; Resources: RS Hermanides, AWJ van 't Hof, P van der Harst, E Barbato, C Morisco, RM Tjon Joe Gin, FW Asselbergs, A Mosterd, JPR Herrman, WJM Dewilde; Supervision: VHM Deneer, JM ten Berg, C. Boersma, MJ Postma

Ethics approval

An institutional review board at each site approved the trial.

Consent to participate

All patients provided informed consent to participate in the trial.

Consent to participate

Not applicable

1 Introduction

Patients with myocardial infarction (MI) and patients undergoing percutaneous coronary intervention (PCI) are treated with dual antiplatelet therapy consisting of aspirin and a $P2Y_{12}$ inhibitor. Guidelines favour ticagrelor and prasugrel over clopidogrel in MI patients due to a reduction in thrombotic events [1,2]. One of the reasons for the reduced effectiveness of clopidogrel compared to the other $P2Y_{12}$ inhibitors is that clopidogrel has to be converted into its active metabolite. The most important enzyme in this process is the CYP 450 2C19 enzyme. This enzyme is encoded by the *CYP2C19* gene, of which more than 30 different alleles have been identified [3]. Some of these alleles encode for an enzyme that is not functional. The *CYP2C19**2 and *3 alleles are the most common loss-of-function alleles and almost 1/3 of the people in western populations carry one or two of these alleles [4]. Several studies demonstrated that these patients have an increased risk of developing major adverse cardiac events [5]. This has prompted the Food and Drug administration (FDA) to add a boxed warning for clopidogrel, describing that the drug might not be effective in patients carrying two loss-of-function alleles [6]. Nevertheless, clopidogrel is still the most frequently prescribed $P2Y_{12}$ inhibitor, either due to fear of bleeding complications or other side effects when using the stronger $P2Y_{12}$ inhibitors or for economic reasons (e.g. lower costs of treatment) [7-9].

The Patient Outcomes after primary PCI (POPular) Genetics trial showed in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI, that a CYP2C19 genotype-guided $P2Y_{12}$ inhibitor strategy was non-inferior for a net clinical benefit outcome while reducing bleeding outcomes as compared to standard treatment with ticagrelor and prasugrel [10]. Since genetic testing is associated with higher costs, while clopidogrel has a lower price than the other $P2Y_{12}$ inhibitors, the objective of this study was to assess cost-

effectiveness of the genotype-guided strategy compared to a standard treatment strategy with ticagrelor or prasugrel, within the context of the Dutch healthcare system.

2 Methods

2.1 Study design

Details on the methods and results of the POPular Genetics trial have been reported previously [10,11]. In brief, POPular Genetics was an open label randomized, multicentre trial with 2,488 STEMI patients undergoing primary PCI. It compared a standard treatment with the $P2Y_{12}$ inhibitors ticagrelor (90mg twice daily) or prasugrel (5 or 10mg once daily based on the summary of product characteristics approved by the European Medicines Agency (EMA)) with a *CYP2C19* genotype-guided strategy, where patients without *CYP2C19**2 or *3 loss-of-function alleles were prescribed clopidogrel (75mg once daily), and ticagrelor or prasugrel (dosage identical to standard treatment) if they were carrier of such a loss-of-function allele. All patients also received guideline recommended aspirin. Treatment and follow-up duration were 12 months. At 1, 6 and 12 months all patients received a questionnaire by either mail or email. This questionnaire contained the EQ-5D-5L, which was used to calculate health utilities. The cost-effectiveness analysis was pre-specified as part of the trial protocol. The trial was approved by the appropriate ethics committees and national authorities. All patients provided informed consent.

2.2 Model overview

The current analysis was designed to calculate the cost-effectiveness of a *CYP2C19* genotype-guided strategy for STEMI patients undergoing primary PCI. A two-part decision-analytic model was developed, comprising of a 1-year decision tree to determine the initial distribution of the cohort over the Markov states (Figure 1A) and a Markov model to simulate life-long

costs and effects (Figure 1B). In the 1-year decision tree, all patients could experience a minor or major bleeding independent of experiencing any of the other events. At the end of the 1-year decision tree period, patients would enter the respective Markov states depending on the experienced event (e.g. event-free recurrent MI, recurrent stroke or death). The Markov-model structure is identical to previously published trials investigating antiplatelet therapy in similar populations [12], clinically validated and adjusted to allow for recurrence of stroke and MI. Four disease transient states were included reflecting the lifetime progression of individuals after STEMI, including MI, post-MI, stroke and post-stroke. Additionally, the model comprised two absorbing states, defined as cardiovascular (CV) death and non-CV death. A cohort of 1000 hypothetical subjects was used, to simulate the progression through the different disease states. Subjects could switch between disease states or remain in the same disease state, based on transition probabilities. In the base case analysis, a lifetime horizon was used with a cut-off at the age of 100.

2.3 Model assumptions

One of the assumptions underpinning the model was that patients in both groups were treated with aspirin monotherapy after the 1-year trial period was finished. Therefore, no difference in bleeding rates was expected in the Markov model. Furthermore, bleeding usually decreases quality of life for only a short period. Hence, bleeding was not included as a separate health state in the Markov model. It was assumed that patients could not develop multiple events during the 1-year trial, which was in line with the Platelet Inhibition and Patient Outcomes (PLATO) trial cost-effectiveness analysis [12]. In addition, the assumption was made that recurrent stroke or MI could only happen with a minimum interval of 1 year.

2.4 Population

The intention-to-treat population from the POPular Genetics trial was used for the current decision-analytic model (Table 1). The mean age of the trial population was 61 years old, 15% was 75 years and older, 25% was female and 10% had a prior history of coronary artery disease). In line with the mean age of the patients in the POPular Genetics trial cohort, all individuals were at the age of 61 at the start of the decision tree.

2.5 Model input parameters

2.5.1 Transition probabilities

All model inputs are presented in Table 2. Probabilities for all patients in the 1-year decision tree were based on the results from the POPular Genetics trial[10]. At the end of the decision tree, patients were allocated to their respective health state in the long-term Markov model. Starting from the second year, a Markov state-transition model with yearly cycles was used to simulate disease progression of patients over their lifetime. In each health state, patients could experience an MI, stroke or death in any year. Patients in the 'Post-MI' and 'Post-stroke' health states had a higher risk of subsequent events than patients in the 'No-event' health state. The transition probabilities of experiencing subsequent events were derived by multiplying the baseline probabilities by the relative risk factors (Table 2) [12]. For mortality, an age specific mortality rate was used based on the Dutch population lifetables. It was not possible to transition from 'post-stroke' to 'post-MI', since the MI health state had a lower risk and was less costly than the stroke health state.

2.5.2 Costs

Cost-effectiveness was estimated from the healthcare perspective, so only medical costs were included. Costs were inflated to 2020 using the consumer price index inflation from the Dutch Central Bureau of Statistics (Table 2). Costs were based on the Dutch healthcare system and

obtained from literature or Dutch governmental agencies. Cost categories were treatment costs (genetic test and different antiplatelet drugs) and costs associated with the different events: minor bleeding, major bleeding, nonfatal MI, nonfatal stroke, post-MI, post-stroke and death. The cost associated with the use of aspirin and other medication was excluded from the analysis, since it was assumed to affect both treatments strategies equally. Costs were discounted using an annual rate of 4% in accordance with existing guidelines for conducting health-economic evaluations [23].

2.5.3 Health utilities

Health utilities, measured in quality-adjusted life years (QALYs), were dependent on the events experienced by patients (Table 2). Health utility estimates were either derived from the POPular Genetics trial (using the EQ-5D-5L questionnaire) or, in case data was not available from the trial, utility estimates were derived from literature focused on the Dutch healthcare system with similar populations. Based on previously published literature, bleeding let to a temporary disutility for the duration of the event during the first year following treatment. QALYs were discounted using an annual rate of 1.5% in accordance with Dutch guidelines for conducting health-economic evaluations [23].

2.5.4 Outcomes

The outcome measures to compare the two strategies in this study were costs, QALYs and the incremental cost-effectiveness ratios (ICERs) presented as cost per QALY gained.

2.5.5 Sensitivity and scenario analysis

The base-case analysis was based on the model inputs as shown in Table 2. To accommodate for the model uncertainty, univariate deterministic sensitivity analyses and probabilistic

sensitivity analyses were conducted. For the sensitivity analyses, the estimated range of each parameter was based on the 95% CI in the studies. If 95% CI was not available, ranges were calculated with a standard error of the mean of 25%. For univariate deterministic sensitivity analyses, each of the parameters was varied one by one over the 95% CI, to examine the influence of individual parameters on the ICER. In the probabilistic sensitivity analysis, a Monte Carlo simulation was performed (1000 iterations) by varying the parameters simultaneously over their 95% CI. The cost, probability and utility parameter distributions were varied with a Gamma-, Pert and Beta distribution, respectively. Outcomes of the sensitivity analysis are presented in a tornado-diagram and a cost-effectiveness plane. Four additional scenarios were conducted to capture the effect of the time horizon (1, 5, 10 and 25 years in the Markov model (scenario 1), adjustment of the discount rates to both costs and utilities at 4% (scenario 2), equal drug prices for all three drugs at €0.05/day, to mimic the availability of generic variants in the future (scenario 3) and equal distribution of the cohort over 'post-MI', 'post-stroke' and 'death' (both CV death and non-CV death) at the start of the Markov-model for both strategies to account for the uncertainty that a genotype-guided strategy does not result in numerically less stroke and MI as seen in the POPular Genetics trial (scenario 4).

3 Results

3.1 Base-case analysis

For a cohort of 1000 patients undergoing primary PCI based on the POPular Genetics trial, the genotype-guided strategy resulted in a gain in QALYs of 8.98 while saving €725,550.69 (0.009 QALYs gained and €725.56 saved per patient) (Table 3). Cost-saving results for the genotype-guided strategy indicate that this strategy dominates current standard treatment without genotyping. In Figure 2, results of the univariate deterministic sensitivity analysis are

displayed in a tornado diagram. The results demonstrate that when varying the different model inputs over their confidence intervals, the genotype-guided strategy remains cost-saving. Results of the 1000 iterations of the probabilistic sensitivity analysis were plotted on a cost-effectiveness plane (Figure 3). The genotype-guided strategy was cost-saving in each iteration of the Monte Carlo simulation, while it increased QALYs in almost all iterations.

3.2 Scenario analyses

In Table 3 results are presented for the varying time horizons (scenario 1), adjustment in discount rates (scenario 2), equal prices for all $P2Y_{12}$ inhibitors (scenario 3) and an equal distribution of patients amongst health states between the two strategies (scenario 4). In all different scenarios, the genotype-guided strategy remained cost saving and improved QALYs.

4 Discussion

In this prospectively designed cost-effectiveness analysis, based on the POPular Genetics trial data, a *CYP2C19* genotype-guided strategy was associated with an increase in QALYs and was cost-saving (dominant) as compared to standard treatment with ticagrelor or prasugrel in STEMI patients undergoing primary PCI. The robustness of this finding was confirmed by various additional sensitivity and scenario analyses. In the Netherlands, the willingness to pay threshold varies between €20.000 to €80.000 depending on the intervention, while the willingness to pay threshold in other European countries varies as well, but is generally of the same magnitude [24]. Our results are well below the lower end of this range.

In the United States, a guideline on health economic analyses was published by the American College of Cardiology (ACC)/American Heart Association (AHA) [25]. According to this

guideline, our findings suggest a high value of a genotype-guided strategy as compared to a standard treatment strategy with ticagrelor or prasugrel, since it improved QALYs while reducing costs.

The cost-effective results showing that the genotype-based strategy is dominant were primarily driven by two differences in the first year. The first determining variable is the price for generic clopidogrel which is lower (€0.05/day) compared to the patented ticagrelor and prasugrel (€2.18/day and €1.65/day, respectively) [15-17]. The difference in costs between clopidogrel and the other $P2Y_{12}$ inhibitors reflects the potential additional cost of performing a genetic test that was estimated to be €150.00 for a point-of-care test. Since both ticagrelor and prasugrel are expected to have generic variants available in the next few years, which will likely cause a drop in prices, a scenario analysis was conducted in which the daily costs of ticagrelor and prasugrel were identical to clopidogrel costs (€0.05/day). Following this scenario-analysis, the genotype-guided strategy remained cost-saving, with similar QALYs gained compared to the base-case analysis. Therefore, it can be realistically assumed that extra costs associated with performing genetic testing will not change the results. The availability of generic ticagrelor and prasugrel will lower prices in the future, but it is uncertain to what extent. The scenario analysis performed is therefore on the conservative end of the spectrum.

The second important factor driving the results of the current analysis is the distribution of the patients at the onset of the Markov model. Based on the results from the POPular Genetics trial, patients in the genotype-guided arm were in a more favourable health-state than patients in the standard treatment arm when they entered the Markov model, due to a lower incidence of stroke and MI in the genotype-guided cohort as compared to the standard treatment cohort. To account for the uncertainty that a genotype-guided strategy actually leads to numerically

less stroke and less MI, as seen in the POPular Genetics trial, a scenario analysis was conducted in which there was no difference amongst the distribution of patients in the different health states when entering the Markov model between the two strategies. In this scenario analysis, the genotype-guided strategy remained cost saving while only a small difference in QALYs gained remained. This was expected, since the difference in QALYs is now only caused by a difference in minor bleeding events between both groups, which have a relatively low impact on long-term health utilities. These results demonstrate that the cost-savings and long-term benefits are based on the differences in the first year after genotype-guided treatment.

In the POPular Genetics trial, more than 95% of the included patients was Caucasian, while only a small proportion of patients was of Asian, Latin American or African descent [10]. The prevalence of *CYP2C19* loss-of-function alleles does not differ much between Africans, Americans and Europeans, but is a lot higher in Asian populations [4]. A higher prevalence of loss-of-function alleles means more people will remain on ticagrelor or prasugrel, which will negatively affect the results of the cost-effectiveness analysis in these countries. In addition, it is uncertain how this affects outcomes of the trial. On the other hand, in countries with a similar prevalence of loss-of-function alleles, one would expect similar clinical outcomes as in our trial and similar results of a cost-effectiveness analysis. However, we should be aware that healthcare costs can differ significantly between countries.

4.1 Comparison with other studies

Several health economic analyses concerning a genotype-guided $P2Y_{12}$ inhibitor strategy have been published in the past [14, 26-29]. These analyses used extrapolated data from for instance the PLATO or Trial to Assess Improvement in Therapeutic Outcomes by Optimizing

Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON TIMI) 38 trial to build their decision tree, but they did not have data from a trial specifically investigating a genotype-guided strategy. A study by Lala *et al*., who based most of their model input parameters on the TRITON TIMI 38, found similar results as presented within the current study [14]. They found a genotype-guided strategy to be cost-saving, and an increase in QALYs compared to both a standard treatment with prasugrel and a standard treatment with clopidogrel. Our results are also in accordance with the cost-effectiveness analysis by Wang *et al*., which used data from the PLATO trial and found a genotype-guided strategy to be cost-saving and with improving QALYs as compared to standard treatment with ticagrelor [26]. In addition, they also concluded that compared to a standard treatment with clopidogrel, a genotype-guided strategy improved QALYs at an ICER of $2560. A cost-effectiveness analysis by Limdi *et al*. investigated whether universal ticagrelor treatment or genotype-guided de-escalation was cost-effective in acute coronary syndrome patients undergoing PCI as compared to universal clopidogrel treatment based on real-world data [27]. While both strategies increased QALYs compared to universal clopidogrel treatment, only genotype-guided de-escalation was cost-effective at an ICER of $42,365. Similar as to our results, results from both Wang *et al.* and Limdi *et al*. are below the 'high value' limit of $50.000/QALY as set by the ACC/AHA guideline [25].

In contrast to our results, two studies by Sorich *et al.* and Crespin *et al.*, both based on results from the PLATO trial, found that ticagrelor treatment was cost-effective as compared to a genotype-guided strategy. This means higher costs with additional QALYs gained [28,29]. The fact that ticagrelor compared to the genotype-guided strategy resulted in QALYs gained, already explains the major difference between the results of Crespin *et al.* and Sorich *et al.* compared to the results of this study [28,29]. In addition, some important considerations with

respect to the findings of Crespin *et al.* and Sorich *et al.* should be taken into account [28,29]. Crespin *et al.* noted that ticagrelor would no longer be cost-effective if the hazard ratio for mortality between ticagrelor and clopidogrel is higher than 0.93 [29], which was the case in the POPular Genetics trial (HR 1.00) [10]. In the study by Sorich *et al.*, the cost of ticagrelor was only 3 times the cost of clopidogrel while the Dutch tariffs indicate a 43.6 times higher cost of ticagrelor compared to clopidogrel [28]. Sorich *et al.* reported that this small price difference between clopidogrel and ticagrelor was one of the reasons as to why ticagrelor treatment was cost-effective compared to a genotype-guided strategy in their study (ICER of ticagrelor versus a genotype-guided strategy: AUS$ 22,821). Furthermore, researchers indicated that when the hazard ratio between ticagrelor and clopidogrel would exceed 0.95, as it does in our study, the ICER would increase to over AUS$ 50,000 making the cost-effectiveness of ticagrelor compared to a genotype-guided strategy highly questionable.

While the previously mentioned studies used data from the PLATO and TRITON TIMI 38 trial to build their study model, the respective study groups themselves also wrote health economic analyses. The health economic analysis of the PLATO trial, which compared ticagrelor to clopidogrel, noted, like Crespin *et al.*, that most of the QALYs gained in the ticagrelor arm of their analysis were derived from the mortality benefit from ticagrelor as compared to clopidogrel [12]. Most benefit in the TRITON TIMI 38 health economic analysis was derived from a reduction in MI in the prasugrel arm as compared to the clopidogrel arm [30]. In the POPular Genetics trial, no numerical benefit in both MI and mortality were seen in the standard treatment arm as compared to the genotype-guided arm [10]. Besides the much lower costs of clopidogrel treatment compared to the other $P2Y_{12}$ inhibitors and some savings on bleeding events, this is one of the most important reasons as to why there was no benefit for ticagrelor and prasugrel in our analysis.

4.2 Limitations

Our results should be interpreted in light of the following limitations. This cost-effectiveness analysis was based on data from STEMI patients undergoing primary PCI. Therefore, it is unknown if these results also apply to patients with another form of acute coronary syndrome and patients not undergoing PCI. In addition, a majority of the patients in the POPular Genetics trial were treated with ticagrelor. Since the recently published Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial found that the use of prasugrel might be beneficial over the use of ticagrelor [31], both costs and event rates might be affected if more patients are treated with prasugrel instead of ticagrelor. This applies to both the standard treatment and genotype-guided groups, since 1/3 of patients in the genotyping group are still treated with ticagrelor or prasugrel. Concerning the health-economic analysis, the analysis is based on a healthcare perspective instead of a societal perspective which is sometimes preferred. However, using a societal perspective would mean further assumptions regarding costs that had to be made. Besides, the only difference in our model was present in the first year during the decision tree, hence adding the same costs to both arms (treatment and control) was expected not to add additional value to the model nor affect the result of the analysis.

5 Conclusion

In STEMI patients undergoing primary PCI, a *CYP2C19* genotype-guided strategy compared to standard treatment with ticagrelor or prasugrel resulted in QALYs gained and cost-savings.

References

1. Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016; 68: 1082-115.

2. Ibanez B, James S, Agewall S, 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). Eur Heart J 2018; 39: 119-77.

3. Scott SA, Sangkuhl K, Shuldiner AR, et al. PharmGKB summary: very important pharmacogene information for cytochrome P450, family 2, subfamily C, polypeptide 19. Pharmacogenetics and genomics. 2012; 22: 159–65

4. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. Clinical pharmacology and therapeutics. 2013; 94: 317–23

5. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010; 304: 1821-30

6. Holmes DR, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM, ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the

American College of Cardiology foundation task force on clinical export consensus documents and the American Heart Association endorsed by the Society of Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol 2010; 56: 321-41

7. Motovska Z, Hlinomaz O, Kala P, et al. 1-year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. JACC 2018; 71: 371-81

8. Gimbel ME, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet 2020; 395: 1374-81

9. Zettler ME, Peterson ED, McCoy LA, et al. Switching of adenosine diphosphate receptor inhibitor after hospital discharge among myocardial infarction patients: insights from the treatment with adenosine diphosphate receptor inhibitors: Longitudinal assessment of treatment patterns and events after acute coronary syndrome (TRANSLATE-ACS) observational study. Am Heart J. 2017; 183: 62-8

10. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. N Engl J Med 2019; 381: 1621-31

11. Bergmeijer TO, Janssen PWA, Schipper JC, et al. CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients-Rationale

and design of the patient outcome after primary PCI (POPular) Genetics study. Am Heart J 2014; 168: 16-22.e.1

12. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. Eur Heart J 2012; 34: 220-28

13. Central Bureau for Statistics. Lifetables. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/83482NED/table?ts=1603871419734. Accessed 15 Oct 2020.

14. Lala A, Berger JS, Sharma G, Hochman JS, Braithwaite RS, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: a cost-effectiveness analysis. J Thromb Haemost 2013; 11: 81–91

15. Zorginstituut Nederland. GIPdatabank: Vergoeding per DDD 2015-2019 voor ATC-subgroep B01AC04 : Clopidogrel. https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=vg&spec=vg_ddd&item=B01AC04. Accessed 15 Oct 2020.

16. Zorginstituut Nederland. GIPdatabank: Vergoeding per DDD 2015-2019 voor ATC-subgroep B01AC24 : Ticagrelor. https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=vg&spec=vg_ddd&item=B01AC24. Accessed 15 Oct 2020.

17. Zorginstituut Nederland. GIPdatabank: Vergoeding per DDD 2015-2019 voor ATC-subgroep B01AC22 : Prasugrel. https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&geg=vg&spec=vg_ddd&item=B01AC22. Accessed 15 Oct 2020.

18. Jacobs MS, De Jong LA, Postma MJ, Tieleman RG, Van Hulst M. Health economic evaluation of rivaroxaban in elective cardioversion of atrial fibrillation. Eur J Health Econ 2018; 19: 957-65

19. ten Cate-Hoek AJ, Toll DB, Buller HR, et al. Cost-effectiveness of ruling out deep venous thrombosis in primary care versus care as usual. J Thromb Haemost 2009; 7: 2042–9

20. Stevanovic J, Pompen M, Le HH, Rozenbaum MH, Tieleman RG, Postma MJ. Economic Evaluation of Apixaban for the Prevention of Stroke in Non-Valvular Atrial Fibrillation in the Netherlands. PLoS One 2014; 9: e103974

21. De Jong LA, Groeneveld J, Stefanovic J, et al. Cost-effectiveness of apixaban compared to other anticoagulants in patients with atrial fibrillation in the real-world and trial settings. PloS one, 2019; 14.9: e0222658.

22. Van Eeden M, Van Heugten C, Van Mastrigt GAPG, Van Mierlo M, Visser-Meily JMA, Evers SMAA. The burden of stroke in the Netherlands: estimating quality of life and costs for 1 year poststroke. BMJ open 2015; 5: e008220

23. Ijzerman MJ, Al MJ, De Boer A, et al. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Zorginstituut Ned. 2016; 1–38. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-

voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg. Accessed 15 Oct 2020.

24. Ligtenberg G, Staal PC, Goettsch WG, Knies S. Kosteneffectiviteit in de zorg, op weg naar een genuanceerd en geaccepteerd gebruik van kosteneffectiviteitsgegevens in de zorg. College voor Zorgverzekeringen 2013; 1-41. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/rapport/2013/09/30/kosteneffectiviteit-in-de-zorg/Kosteneffectiviteit+in+de+zorg.pdf. Accessed 15 Oct 2020.

25. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: 2304–22.

26. 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; 18: 113-20

27. Limdi NA, Cavallari LH, Lee CR, et al. Cost-effectiveness of CYP2C19-guided antiplatelet therapy in patients with acute coronary syndrome and percutaneous coronary intervention informed by real-world data. Pharmacogenomics J 2020; 20: 724-35

28. 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; 14: 2013-21

29. 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; 14: 483-91

30. Mahoney EM, Wang K, Arnold SV, et al. Cost-effectiveness of prasugrel versus clopidogrel in patients with acute coronary syndromes and planned percutaneous coronary intervention: results from the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction TRITON-TIMI 38. Circulation 2010; 121: 71-79

31. Schüpke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019; 381: 1524-34

Figure 1. Cost-effectiveness model

Figure 1. Model structure. Figure 1A: 1-year decision tree based on the POPular Genetics trial. Figure 1B: Long-term Markov model.

MI: myocardial infarction.

Figure 2. Deterministic sensitivity analysis

Figure 2. One-way sensitivity analysis of a genotype-guided strategy versus standard treatment with ticagrelor or prasugrel. Horizontal bars indicate the range of cost-savings obtained when setting each individual variable at its maximum and minimum confidence interval. Since all results remain cost saving, the direction of the bar makes no difference.

CV: cardiovascular, MI: myocardial infarction, NF: non-fatal

Figure 3. Probabilistic sensitivity analysis

Figure 3. Results of the probabilistic sensitivity analysis on the cost-effectiveness plane. The scatterplot depicts results of the Monte Carlo analysis (1000 iterations) when all model inputs are randomly varied between their confidence intervals. The black line depicts the willingness to pay €20,000/QALY. A genotype-guided strategy is cost-effective if it falls below the black line.

QALY: quality-adjusted life year

Table 1. POPular Genetics trial population baseline characteristics

Characteristics	**Genotype-guided (N=1242)**	**Standard treatment (N=1246)**
Mean age - yr	61.9±11.1	61.4±11.5
Age ≥75 years – no. (%)	188 (15.1)	175 (14.0)
Female sex – no. (%)	317 (25.5)	309 (24.8)
Mean body-mass index[a]	27.5±6.67	27.0±4.27
Creatinine clearance <60ml/minute at baseline[b] -– no. (%)	121 (9.8)	109 (8.8)
Medical history -– no. (%)		
Current smoker	562 (45.8)	565 (45.8)
Diabetes Mellitus	150 (12.1)	138 (11.1)
Arterial hypertension	521 (42.0)	511 (41.0)
Hyperlipidemia	260 (20.9)	255 (20.5)
History of coronary artery disease	133 (10.7)	118 (9.5)
Peripheral arterial disease	39 (3.1)	34 (2.7)
History of bleeding	30 (2.4)	23 (1.9)
Angiographic and procedural characteristics		
Number of diseased coronary vessels ≥50% – no. (%)		
1	634 (51.2)	675 (54.2)
2	417 (33.7)	376 (30.2)
3	188 (15.1)	194 (15.6)
Ostial lesion – no. (%)	76 (6.4)	65 (5.5)
Bifurcation lesion – no. (%)	214 (18.1)	239 (20.2)

Stent type – no. (%)		
Bare metal stent	60 (4.8)	50 (4.0)
Bioresorbable vascular scaffold	9 (0.7)	16 (1.3)
Drug eluting stent	1167 (94.0)	1174 (94.2)
Plain old balloon angioplasty	17 (1.4)	23 (1.9)
Total stent length - mm	27.0±14.8	28.0±15.3
Medication at discharge – no. (%)		
Aspirin	1211 (97.7)	1208 (97.4)
ADP receptor antagonist	1237 (99.8)	1237 (99.8)
Clopidogrel	688 (55.5)	91 (7.3)
Prasugrel	15 (1.2)	27 (2.2)
Ticagrelor	534 (43.1)	1119 (90.2)
(Novel) oral anticoagulation	14 (1.1)	9 (0.7)

Table 1. Baseline characteristics of the POPular Genetics trial population. Plus-minus values are means±SD. There were no significant differences between the groups except with respect to body-mass index (P=0.05).

a: The body-mass index is the weight in kilograms divided by the square of the height in meters.

b: The creatinine clearance was calculated using the CKD-EPI formula.

Table 2. Model input parameters

Parameters	**Base-case value**	**Range**	**Distribution**	**Source**
Probabilities (decision tree)				
Genotype-guided strategy				
Minor bleeding	0.0765	NA	NA	Trial
Major bleeding	0.0225	NA	NA	Trial
Myocardial infarction	0.0153	NA	NA	Trial
Stroke	0.0064	NA	NA	Trial
Non-CV Death	0.0080	NA	NA	Trial
CV death	0.0070	NA	NA	Trial
Standard treatment				
Minor bleeding	0.1051	NA	NA	Trial
Major bleeding	0.0233	NA	NA	Trial
Myocardial infarction	0.0209	NA	NA	Trial
Stroke	0.0088	NA	NA	Trial
Non-CV death	0.0070	NA	NA	Trial
CV death	0.0080	NA	NA	Trial
Probabilities (Markov model)[a]				
Annual risk from ' No-event' to ' MI'	0.019	0.01-0.05	PERT	12
Annual risk from ' No-event' to ' Stroke'	0.003	0.001-0.02	PERT	12
Annual risk from ' No-event' to 'Non-CV death'	Age specific mortality rate		PERT	13

Increased risk of a subsequent event after having an event	2	1-4	PERT	14
Increased risk of death in 'No-event'	2	1.5-2.5	PERT	12
Increased risk of death in 'Non-fatal MI'	6	4.5-7.5	PERT	12
Increased risk of death in 'post MI'	3	2.25-3.75	PERT	12
Increased risk of death in 'Non-fatal stroke'	7.43	5.57-9.29	PERT	12
Increased risk of death in 'post stroke'	3	2.25-3.75	PERT	12
Costs (euro's)[b]				
Genotyping	150.00	76.50-223.50	Gamma	Trial
1 year clopidogrel treatment	18.25	9.31-27.19	Gamma	15
1 year ticagrelor treatment	795.70	405.81-1,158.59	Gamma	16
1 year prasugrel treatment	602.25	307.15-897.35	Gamma	17
Minor bleeding	310.76	189.02-433.57	Gamma	18
Major bleeding	5,422.78	2,765.62-8,079.95	Gamma	19
Myocardial infarction	5,550.95	2,830.99-8,270.99	Gamma	20
Post-MI	2,536.81	2,367.22-2,667.82	Gamma	21
Stroke	28,233.36	18,378.83-38,806.05	Gamma	21
Post-stroke	11,551.15	7,724.37-14,596.40	Gamma	21
CV death	3,223.09	1,842.21-4,982.85	Gamma	21

Utilities[c]				
No event	0.88	0.87-0.89	Beta	Trial
Myocardial infarction	0.80	0.71-0.90	Beta	Trial
Post-MI	0.81	0.72-0.90	Beta	Trial
Stroke	0.59	0.30-0.88	Beta	21
Post-stroke	0.74	0.71-0.77	Beta	22
Death	0	NA	Beta	
Minor bleeding (disutility 2 days)	0.06	0.03-0.09	Beta	20
Major bleeding (disutility 14 days)	0.14	0.07-0.21	Beta	20

Table 2. Cost-effectiveness model input parameters. CI: confidence interval, CV: cardiovascular, NA: not applicable, MI: myocardial infarction

a: Range indicating min/max as provided by paper. If min/max was unavailable, ranges where calculated with 25% of the base-case value.

b: Range is based on 95% CI. If 95% CI was unavailable, ranges were calculated with standard error of 25% of the mean

c: Range is based on 95% CI

Table 3. Lifetime cost-effectiveness results for base-case and scenario analyses

	Cost genotype-guided (€)	**Cost standard treatment (€)**	**ΔCost (€)**	**QALYs genotype-guided**	**QALYs standard treatment**	**ΔQALY**	**ICER[a] (€/QALY)**
Base-case							
Lifetime, discounted costs at 4%, QALYs at 1.5%	10,650,062	11,375,613	-725,551	11394.59	11385.60	8.98	NA
Scenario analyses							
1 year	1,080,346	1,442,899	-362.553	1702.92	1701.47	1.45	NA
5 years	2,874,516	3,370,275	-495.759	4709.45	4705.54	3.91	NA
10 years	5,577,006	6,187,410	-610.404	7671.43	7665.21	6.23	NA
25 years	10,471,360	11,194,994	-723,634	11314.19	11305.27	8.93	NA
Undiscounted	16,695,121	17,580,561	-885,440	12929.05	12918.72	10.33	NA
Costs & utilities discounted at 4%	10,650,062	11,375,613	-725,551	9443.80	9436.30	7.50	NA

Identical prices for $P2Y_{12}$ inhibitors	10,347,722	10,658,977	-311,255	11394.59	11385.60	8.98	NA
No difference in health states at the start of the Markov model	11,098,092	11,375,613	-277,521	11385.61	11385.60	0.01	NA

Table 3. Cost-effectiveness analysis outcomes of the base-case and sensitivy analyses based on the POPular Genetics trial.

a: When a genotype-guided strategy resulted in cost-savings, the ICER could not be calculated.

ICER: incremental cost-effectiveness ratio, NA: not applicable, QALY: quality-adjusted life years