ON THE ROAD TO
PERSONALIZED ANTIPLATELET THERAPY

Moving away from a one-size-fits-all approach

Wout W.A. van den Broek

Stellingen:

1. De variaties in het CYP2C19-gen zijn, voor nu, de enige relevante genetische variaties die routinematig getest zouden moeten worden bij het starten van trombocytenaggregatieremmers (dit proefschrift).

2. Een genotype-geleide P2Y12-inhibitor de-escalatie strategie is een veilige en kosteneffectieve manier om het bloedingsrisico van patiënten met een myocardinfarct te reduceren (dit proefschrift).

3. De optimale gepersonaliseerde behandeling met duale trombocytenaggregatieremmers gaat verder dan rekening houden met genetische aanleg alleen, en bevat ook het verkorten van de duur van duale behandeling op basis van het bloedingsrisico (dit proefschrift)

4. Algehele dekking van kosten van genetische testen door zorgverzekeraars, is essentieel voor een succesvolle implementatie van genotype-geleide medicamenteuze behandelingen in Nederland (dit proefschrift/valorisatie).

5. Het toepassen van een genotype-geleide strategie bij patiënten met stabiel coronairlijden is logisch en zou standaard zorg moeten worden.

6. Het pre-emptief testen van relevante *CYP*-polymorfismen zal de kwaliteit van de zorg verbeteren, en de lange termijn zorgkosten verminderen.

7. De huidige strikte privacywetgeving beschermt het individu, maar belemmert hoog kwalitatief populatie breed wetenschappelijk onderzoek.

8. Genotype-geleide antiplaatjestherapie is geassocieerd met verbeterde klinische uitkomsten en minder bijwerkingen voor de patiënt, en vormt een belangrijke stap richting duurzame en betaalbare cardiovasculaire zorg.

9. "The greatest scientific discovery was the discovery of ignorance", Yuval Noah Harari (Homo Sapiens).

10. "If people only talked about what they understood, Earth would be a very quiet place." — Albert Einstein.

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On The Road to Personalized Antiplatelet Therapy
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ON THE ROAD TO PERSONALIZED ANTIPLATELET THERAPY

Moving away from a one-size-fits-all approach

DISSERTATION

to obtain the degree of Doctor at Maastricht University,

on the authority of the Rector Magnificus, Prof. Dr. Pamela Habibović

in accordance with the decision of the Board of Deans,

to be defended in public on Friday 5 June 2026, at 13:00 hours

by

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CHAPTER 1

General Introduction and Thesis Outline

Coronary artery disease (CAD) poses a significant healthcare challenge, with over 60,000 patients admitted annually to Dutch hospitals due to an acute coronary syndrome (ACS), and approximately 40,000 undergoing percutaneous coronary intervention (PCI).[1,2] ACS is primarily caused by the obstruction of a coronary artery due to atherosclerotic plaque rupture or erosion and subsequent thrombus formation, leading to myocardial ischemia (**Figure 1**).[3] When an atherosclerotic plaque ruptures, it exposes the subendothelial matrix, triggering the activation of platelets and the coagulation cascade.[4] Platelet activation initiates a complex signalling process, leading to shape change, degranulation, and the release of secondary agonists such as adenosine diphosphate (ADP) and thromboxane A2, which further amplify platelet aggregation and promote the formation of a stable platelet plug.[5] In ACS, the thrombus that forms is typically rich in platelets, distinguishing it from conditions such as deep vein thrombosis or pulmonary embolism, where fibrin predominates.[6] This underscores the critical role of platelets in the pathophysiology of ACS and highlights the importance of targeting platelet activation to prevent further ischemic events.[7] As a result, the majority of patients are treated with dual antiplatelet therapy (DAPT), combining aspirin and a P2Y12-receptor inhibitor to reduce the risk of recurrent thrombotic complications.[8] Aspirin inhibits thromboxane A2-mediated platelet aggregation, while a P2Y12-receptor inhibitor prevents ADP-mediated platelet activation.[7,8]

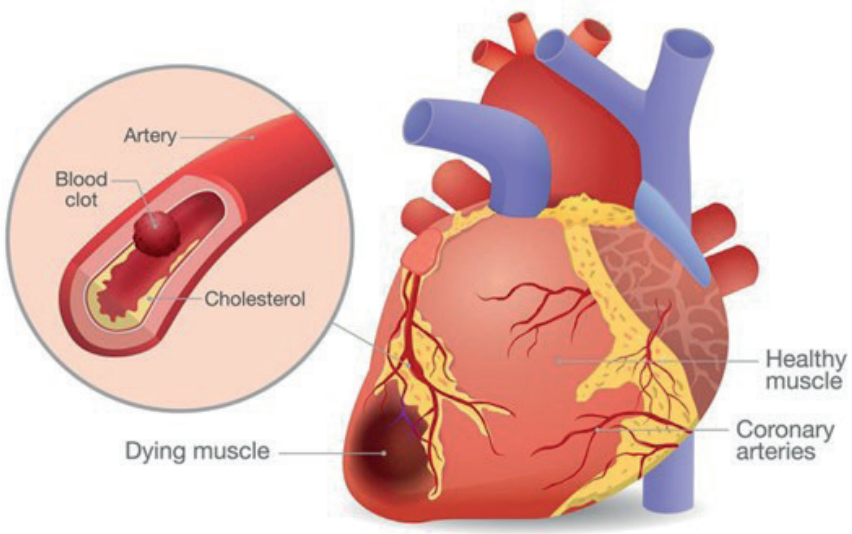

Figure 1. Pathophysiology of an acute coronary syndrome.
From CSL – Anatomy of a Heart Attack, by Nate Scharping | 05 Jul 2022

Historical Perspective on DAPT

The evolution of DAPT in cardiovascular care has been driven by key clinical trials that shaped current practice. The ISIS-2 trial, conducted in 1988, was the first to demonstrate the efficacy of aspirin in reducing cardiovascular events compared to placebo in patients with suspected myocardial infarction

(MI), establishing it as the foundation of secondary prevention in patients with cardiovascular disease.[9] Clopidogrel later emerged as an alternative to aspirin in patients with cardiovascular disease, with the CAPRIE trial showing that clopidogrel was superior in reducing the risk of cardiovascular events.[10] In 1996, ticlopidine plus aspirin (then called "combined antiplatelet therapy") showed superiority over the use of anticoagulation plus aspirin in patients treated with a coronary stent, marking the start of the DAPT era.[11] The 2001 CURE trial further established the benefits of DAPT in ACS, combining clopidogrel with aspirin, demonstrating that this combination was more effective than aspirin alone in preventing recurrent ischemic events.[12] Six years later, for the first time, it was recommended to add clopidogrel on top of aspirin for all non-ST-elevation ACS patients in the European Society of Cardiology (ESC) guidelines.[13] In subsequent years, newer P2Y12-receptor inhibitors—prasugrel and ticagrelor—were introduced, offering enhanced potency in inhibiting platelet activity. The TRITON and PLATO trials demonstrated that both prasugrel and ticagrelor, when combined with aspirin, were superior to clopidogrel in reducing ischemic events.[14,15] Consequently, the 2011 ESC guidelines for patients with non-ST-segment elevation acute coronary syndrome recommended ticagrelor or prasugrel over clopidogrel, establishing these agents as the standard treatment for ACS patients, a practice that continues today.[16]

This evolution in treatment, though beneficial, also introduced a new challenge: the enhanced potency of these agents is associated with a higher risk of major bleeding. Despite the significant 22% reduction in all-cause mortality observed in ticagrelor-treated patients, the PLATO trial reported a significant 19% relative increase in non-CABG-related major bleeding and a significant rise in fatal intracranial bleeding events.[13] Similarly, the TRITON study showed a significant 32% increase in major bleeding with prasugrel compared to clopidogrel, without a benefit in all-cause mortality.[14] These findings underscore the need for a careful balance between reducing ischemic risk and minimizing the potential for bleeding complications in patients receiving DAPT. While the ischemic benefits of ticagrelor and prasugrel compared to clopidogrel are well-documented, it is crucial to recognize that these advantages may be significantly overstated due to the pharmacogenetic effects of clopidogrel-related polymorphisms.[17,18]

Pharmacogenetics and Drug Metabolism

Pharmacogenetics is the study of how genetic variations affect individual responses to drugs, particularly by influencing a drug's pharmacokinetics or pharmacodynamics. These variations often impact the activity of cytochrome P450 (CYP450) enzymes, which are key mediators in the metabolism of many drugs, and include processes like oxidation, reduction, and hydrolysis.[19] These enzymes either activate a drug by converting it into its active metabolite or deactivate it. The **1* allele represents the fully functional genotype, corresponding to the normal metabolizer (NM) phenotype, and serves as the reference point for identifying other genetic variants.[20] Individuals with one (heterozygous) or two (homozygous) loss-of-function (LOF) alleles, resulting in reduced or absent enzyme activity, are classified as intermediate (IMs) or poor metabolizers (PMs), respectively. In contrast, rapid metabolizers (RMs), with one **1* allele and one gain-of-function allele, and ultra-rapid metabolizers (UMs), with two gain-of-function alleles, display elevated enzyme activity, accelerating drug metabolism.[20,21] This can lead to faster conversion of drugs to either active or inactive metabolites, potentially impacting drug efficacy and safety.

Pharmacogenetics and Antiplatelet Therapy

Aspirin (acetylsalicylic acid) is metabolized by various enzymes, including UDP-glucuronosyltransferase 1A6, CYP2C9, and N-acetyl transferase 2, but no clinically significant associations between genetic polymorphisms and aspirin's platelet reactivity or clinical outcomes have been established.[22,23] In contrast, ticagrelor is a direct-acting drug, whereas clopidogrel and prasugrel, both thienopyridines, are prodrugs that require conversion by cytochrome P450 enzymes to their active metabolites.[24] Ticagrelor's metabolism involves CYP3A4/5, but no relevant genetic interactions with these enzymes have been identified (Figure 2).[25] For prasugrel, its metabolism is primarily mediated by CYP3A4 and CYP2B6, with minor contributions from CYP2C9 and CYP2C19.[26] Polymorphisms in these enzymes have not been shown to cause significant pharmacokinetic or pharmacodynamic variations in prasugrel, nor have they been linked to increased cardiovascular risk in treated patients.[27,28]

Clopidogrel, however, presents a different pharmacogenetic profile. Significant inter-individual variability exists in clopidogrel's pharmacokinetics and pharmacodynamics, with approximately 30% of patients exhibiting inadequate responses to the drug.[29] The metabolism of clopidogrel involves several CYP enzymes (CYP2C19, CYP3A4/5, CYP1A2, CYP2B6, CYP2C9), with CYP2C19 being the principal contributor in both steps of its biotransformation into the active metabolite (**Figure 2**).[30] Although some studies have linked genetic variations in the *CYP2C9* gene to an increased risk of stent thrombosis, their impact on clinical outcomes remains unclear.[31,32] However, the impact of *CYP2C19* LOF-alleles on clinical outcomes has been studied extensively. Carriers of *CYP2C19* LOF-alleles have reduced enzyme activity, leading to impaired drug activation and lower levels of the active metabolite.[18,26,28,33] As a result, these patients face an elevated risk of thrombotic events, including stent thrombosis.[18,27,31,34] This may also apply to patients undergoing PCI treated with oral anticoagulation (e.g., due to atrial fibrillation). In these patients, combination therapy with clopidogrel (i.e., known as dual antithrombotic therapy [DAT]) is recommended. However, there is lack of evidence regarding the impact of *CYP2C19* polymorphisms in these patients.

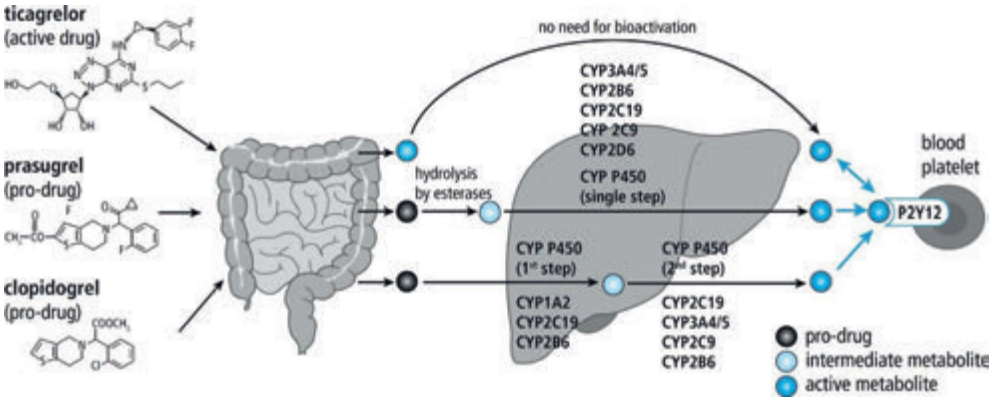

Figure 2. Bioactivation processes of P2Y12 receptor antagonists.
With permission of Sage Publications, Weeks et al, 2015;20(4):370-377.

Genotype de-escalation

In Europe and the United States, ticagrelor and prasugrel are the preferred P2Y12-receptor inhibitors due to their potent antiplatelet effects; however, this comes at the cost of an increased risk of bleeding. These bleeding events occur mainly in the first months after PCI and are associated with an increase in morbidity and reduced quality of life, underscoring the importance of minimizing bleeding risk without compromising efficacy when prescribing DAPT.[35–37] Some studies have even found that recurrent major bleeding events carry a mortality risk comparable to myocardial infarction.[38,39] Conversely, recent advancements have led to improved cardiovascular outcomes and a reduction in ischemic complications. These improvements stem from enhanced secondary prevention strategies, advancements in interventional techniques, and the development of new drug-eluting stents featuring thinner struts and biocompatible coatings.[40] As a result, the risk of stent thrombosis and associated ischemic complications following PCI has significantly decreased. Despite this progress in reducing ischemic risk, the bleeding risk after PCI remains unchanged.

In antiplatelet therapy, escalation and de-escalation strategies aim to balance ischemic protection with bleeding risk. De-escalation involves reducing bleeding risk by shortening the duration of therapy, using less potent antiplatelet regimens or reducing drug dosage. In contrast, escalation strategies are most often used to enhance ischemic protection in high-risk individuals by intensifying antiplatelet treatment. Genotype-guided strategies build on this personalized approach by using a patient's genetic profile to inform optimal antiplatelet selection and dosing from the outset. A genotype-guided de-escalation strategy aims to reduce bleeding events without affecting efficacy by transitioning patients from the more potent ticagrelor or prasugrel to clopidogrel in NMs.[41] Conversely, an escalation strategy involves switching from clopidogrel to ticagrelor or prasugrel in IMs or PMs. The Popular Genetics trial evaluated a genotype-guided de-escalation approach in 2,488 patients undergoing primary PCI for STEMI.[42] In this study, all patients received aspirin; and in the genotype-guided group, IMs and PMs were treated with ticagrelor or prasugrel (39%), while extensive metabolizers (EMs) were prescribed clopidogrel (61%). Patients in the control group were treated with ticagrelor per current guidelines. Genotype-guided P2Y12-receptor inhibitor treatment was initiated within 24 hours of randomization, resulting in a lower incidence of bleeding compared to standard care with prasugrel or ticagrelor (9.8% vs. 12.5%, HR 0.78, 95% CI 0.61 to 0.98). Importantly, there was no evidence of increased thrombotic events in the genotype-guided group.

While these findings are promising, the implementation of such a strategy in clinical practice faces challenges.[43,44] Additionally, it is uncertain whether the results from this randomized controlled trial can be extrapolated to real-world settings.

OUTLINE OF THIS THESIS

This thesis focuses on personalized antithrombotic therapy and the implications of genetic polymorphisms on patient outcomes in cardiovascular care. In Part I the current landscape of personalized antiplatelet therapy is covered, with **Chapter 2** providing a comprehensive overview of personalized antithrombotic therapy. This chapter covers both the value of measuring and monitoring platelet response and genotype-guided therapy, and their role in optimizing antiplatelet treatment. **Chapter 3** reviews various genotype-guided antiplatelet strategies, examining recent findings and their potential impact on clinical practice. **Chapter 4** covers the specific benefits of *CYP2C19* genotype-guided antiplatelet treatment in elderly patients with ACS, addressing the specific challenges and considerations in this population.

Part II of the thesis evaluates the impact of genetic polymorphisms in clinical research. **Chapter 5** explores the association between *CYP2C9* polymorphisms and the risk of cardiovascular events in patients treated with clopidogrel, utilizing combined data from the POPular Genetics and POPular AGE trials. **Chapter 6** focuses on the effects of *CYP3A4*22* and *CYP3A5* on clinical outcomes in patients treated with ticagrelor for ST-segment elevation myocardial infarction, presenting insights from a sub-study of the POPular Genetics trial. **Chapter 7** presents the results of an individual patient meta-analysis comparing various de-escalation strategies, including a genotype-guided strategy, with standard DAPT. **Chapter 8** builds on this by focusing specifically on an individual patient data meta-analysis of the two largest randomized trials investigating genotype-guided strategies. **Chapter 9** discusses the role of genetic testing in P2Y12-receptor inhibition in a distinct population of patients requiring oral anticoagulation after PCI, based on findings from the SWAP-AC-2 study.

In Part III, the thesis addresses the clinical implementation of genotype-guided antiplatelet therapy. **Chapter 10** reviews the insights gained from the FORCE-ACS registry regarding the clinical implementation of *CYP2C19* genotyping in patients with ACS, highlighting the challenges, successes, and key implementation outcomes observed in practice. **Chapter 11** evaluates the first clinical outcomes of the real-world implementation of a genotype-guided P2Y12-receptor inhibitor de-escalation strategy in ACS patients. **Chapter 12** assesses the cost-effectiveness of implementing a genotype-guided de-escalation strategy in ACS patients, providing valuable economic insights into this approach. Finally, **Chapter 13** presents the impact of a genotype-guided P2Y12-receptor inhibitor de-escalation strategy on clinical outcomes in a large cohort, summarizing the findings and implications for future practice.

REFERENCES

1. Koop Y, Wimmers RH, Bots ML. Hart- en vaatziekten in Nederland 2021. Cijfers over incidentie, prevalentie ziekte en sterfte. 2021;
2. NHR. Jaarcijfers coronairlijden.
3. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of Plaque Formation and Rupture. Circ Res. 2014 Jun;114(12):1852–66.
4. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. J Intern Med. 2014 Dec;276(6):618–32.
5. Olie RH, van der Meijden PEJ, Ten Cate H. The coagulation system in atherothrombosis: Implications for new therapeutic strategies. Res Pract Thromb Haemost [Internet]. 2018 Apr;2(2):188–98. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30046721
6. Alkarithi G, Duval C, Shi Y, Macrae FL, Ariëns RAS. Thrombus Structural Composition in Cardiovascular Disease. Arterioscler Thromb Vasc Biol [Internet]. 2021 Sep;41(9):2370–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/34261330
7. Passacquale G, Sharma P, Perera D, Ferro A. Antiplatelet therapy in cardiovascular disease: Current status and future directions. Br J Clin Pharmacol. 2022 Jun;88(6):2686–99.
8. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Aug;44(38):3720–826.
9. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet (London, England). 1988 Aug;2(8607):349–60.
10. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996 Nov;348(9038):1329–39.
11. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, et al. A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents. N Engl J Med. 1996 Apr;334(17):1084–9.
12. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet [Internet]. 2001 Aug;358(9281):527–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673601057014
13. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Eur Heart J. 2007 May;28(13):1598–660.
14. 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):1045–57.
15. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2007;357(20):2001–15.

16. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Vol. 32, European Heart Journal. 2011. p. 2999–3054.
17. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009 Jan;360(4):363–75.
18. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med. 2009;360(4):354–62.
19. Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, et al. Cytochrome P450 Enzymes and Drug Metabolism in Humans. Int J Mol Sci. 2021 Nov;22(23).
20. Pinto N, Dolan ME. Clinically relevant genetic variations in drug metabolizing enzymes. Curr Drug Metab [Internet]. 2011 Jun;12(5):487–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21453273
21. Marín F, González-Conejero R, Capranzano P, Bass TA, Roldán V, Angiolillo DJ. Pharmacogenetics in Cardiovascular Antithrombotic Therapy. J Am Coll Cardiol [Internet]. 2009 Sep;54(12):1041–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109709021469
22. Agundez J, Martinez C, Perez-Sala D, Carballo M, Torres M, Garcia-Martin E. Pharmacogenomics in Aspirin Intolerance. Curr Drug Metab. 2010;10(9).
23. Postula M, Janicki PK, Rosiak M, Kaplon-Cieslicka A, Kondracka A, Trzepla E, et al. Effect of common single-nucleotide polymorphisms in acetylsalicylic acid metabolic pathway genes on platelet reactivity in patients with diabetes. Med Sci Monit. 2013;19(1):394–408.
24. Gurbel PA, Rout A, Tantry US. Pharmacogenetic considerations in antiplatelet therapy. Expert Rev Precis Med Drug Dev [Internet]. 2020 Jul 3;5(4):235–8. Available from: https://www.tandfonline.com/doi/full/10.1080/23808993.2020.1768844
25. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y12 receptor antagonist, in healthy subjects. Eur J Clin Pharmacol. 2010;66(5):487–96.
26. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost. 2007;5(12):2429–36.
27. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation [Internet]. 2009 May 19;119(19):2553–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19414633
28. Giorgi MA, Cohen Arazi H, Gonzalez CD, Di Girolamo G. Beyond efficacy: Pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. Vol. 12, Expert Opinion on Pharmacotherapy. 2011. p. 1285–95.
29. Ancrenaz V, Daali Y, Fontana P, Besson M, Samer C, Dayer P, et al. Impact of genetic polymorphisms and drug-drug interactions on clopidogrel and prasugrel response variability. Curr Drug Metab [Internet]. 2010 Oct;11(8):667–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20942779
30. Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos. 2010;38(1):92–9.

31. Harmsze AM, Van Werkum JW, Ten Berg JM, Zwart B, Bouman HJ, Breet NJ, et al. CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: A case-control study. Eur Heart J. 2010;31(24):3046–53.
32. Harmsze A, Van Werkum JW, Bouman HJ, Ruven HJ, Breet NJ, Ten Berg JM, et al. Besides CYP2C19*2, the variant allele CYP2C9*3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. Pharmacogenet Genomics. 2010;20(1):18–25.
33. Breet NJ, Van Werkum JW, Bouman HJ, Kelder JC, Ruven HJT, Bal ET, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA - J Am Med Assoc. 2010;303(8):754–62.
34. 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;376(9749):1312–9.
35. Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van De Werf F, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. J Am Coll Cardiol. 2016;67(18):2135–44.
36. Ismail N, Jordan KP, Rao S, Kinnaird T, Potts J, Kadam UT, et al. Incidence and prognostic impact of post discharge bleeding post acute coronary syndrome within an outpatient setting: a systematic review. BMJ Open [Internet]. 2019 Feb 20;9(2):e023337. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2018-023337
37. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2015;66(9):1036–45.
38. Piccolo R, Oliva A, Avvedimento M, Franzone A, Windecker S, Valgimigli M, et al. Mortality after bleeding versus myocardial infarction in coronary artery disease: A systematic review and meta-analysis. EuroIntervention. 2021;17(7):550–60.
39. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J [Internet]. 2016 Nov 13;38(11):804–10. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehw525
40. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, et al. Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents. JACC Cardiovasc Interv [Internet]. 2013 Dec;6(12):1267–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1936879813014519
41. Capodanno D, Angiolillo DJ. Personalised antiplatelet therapies for coronary artery disease: what the future holds. Eur Heart J. 2023 Jun;
42. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. N Engl J Med. 2019;381(17):1621–31.
43. Thomas CD, Williams AK, Lee CR, Cavallari LH. Pharmacogenetics of P2Y12 receptor inhibitors. Pharmacotherapy. 2023 Feb;43(2):158–75.
44. Weitzel KW, Elsey AR, Langaee TY, Burkley B, Nessl DR, Obeng AO, et al. Clinical pharmacogenetics implementation: Approaches, successes, and challenges. Am J Med Genet Part C Semin Med Genet. 2014 Mar;166(1):56–67.

PART I

Current Landscape of Personalized Antiplatelet Therapy

CHAPTER 2

Personalized antithrombotic therapy: Measuring Individual Variation and Monitoring

W.W.A. van den Broek, J.M. ten Berg, D. Sibbing, K.D. Rizas

Chapter from The ESC Textbook of Thrombosis. The European Society of Cardiology Series

SUMMARY

Antithrombotic drugs are frequently prescribed in patients with coronary artery disease, embolic stroke, or atrial fibrillation to prevent thrombosis. However, patients vary widely in their response to these drugs. This interindividual variability can be a result of genetic variation in enzymes that play a role in drug metabolism, though it can also be a consequence of other patient characteristics. A personalized antithrombotic treatment accounts for this interindividual variability with the aim of optimizing the balance between the risk of bleeding and thrombosis. Personalization of antithrombotic therapy might be done by testing for genetic polymorphisms or measuring the patient's response on treatment, both of which have their advantages and disadvantages. This chapter describes the different ways that antithrombotic therapy can be personalized, provides the latest evidence for these strategies, and focuses on the treatment strategies with the most clinical impact.

INTRODUCTION: PERSONALIZED ANTITHROMBOTIC THERAPY

Patients vary widely in their response to drugs. To a great extent this can be explained by genetic variation, though also different patient characteristics, such as age, body-weight, kidney disease and diabetes mellitus, play a part in this.[1] As this variable response can influence the efficacy or safety of antithrombotic treatment, a personalized antithrombotic therapy could in theory optimize patient outcomes. Personalizing antithrombotic therapy can be done by testing for genetic polymorphisms or measuring the patients' response on treatment. With vitamin-K antagonists, this is already standard of care, as the daily dose is based on the International Normalized Ratio (INR). Regarding antiplatelet therapy, personalizing treatment can be based on specific genetic polymorphisms or by platelet function testing (PFT) (see **Figure 1**). Although, there is a growing body of evidence suggesting that a personalized antiplatelet therapy can optimize patients outcomes, it is not (yet) routinely used in clinical care. In this chapter we provide the latest evidence, guideline recommendations and promising developments regarding the personalization of anticoagulants and antiplatelet therapy in patients with cardiovascular disease.

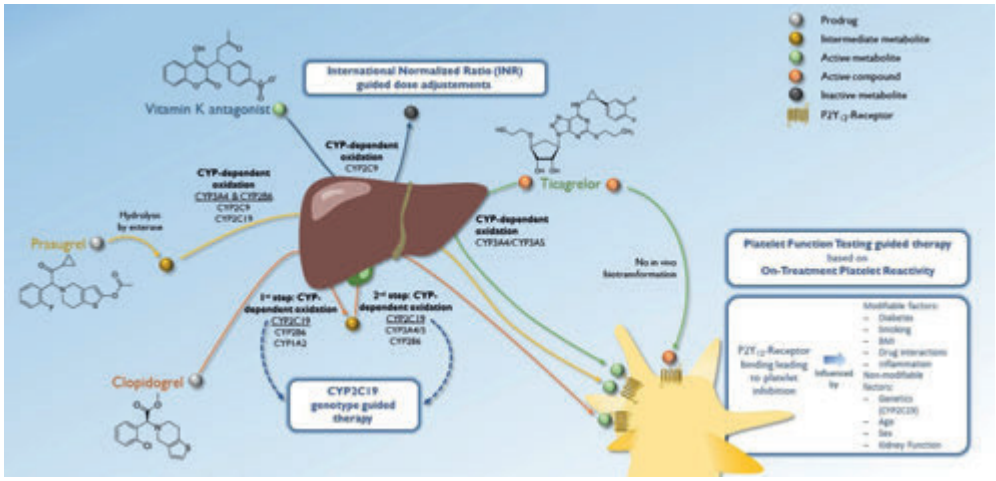

Figure 1. Biotransformation and metabolization of the different antithrombotic agents.
Antithrombotic therapy can be personalized by (1) using CYP2C19 genotype-guided therapy, which is the only genetic polymorphism for which a genotype-guided therapy is assessed in randomized clinical trials regarding clinical outcomes or (2) assessing the actual responsiveness to antithrombotic therapy by measuring the International Normalized Ratio (INR) or on-treatment platelet reactivity, which is influenced by various modifiable and non-modifiable factors.

Pharmacogenetics

Pharmacogenetics is a field studying how variation in genes can affect a person's response to drugs. Genetic polymorphisms are nucleotide changes in the reference sequence of a gene that occur in more than 1 percent of the population.[2] These polymorphisms can influence a drug's action by altering its

pharmacokinetics or pharmacodynamics, often caused by genetic variation in the drug-metabolizing cytochrome P450 (CYP450) enzymes. CYP450-enzymes play a major role in the phase 1 reactions (oxidation, reduction and hydrolysis) of drug metabolism, by either converting a drug to its active metabolite or de-activating an active metabolite. In pharmacogenetics, different polymorphisms are indicated with different labels, consisting of an asterisk (*) followed by an Arabic numeral, in which *1 corresponds to a genotype with two standard copies of the normally functional allele, corresponding to the phenotype extensive metabolizers (EMs). Patients who carry one (heterozygous) or two (homozygous) loss-of-function (LOF) alleles leading to a reduced function of the enzyme are known as intermediate (IMs) or poor metabolizers (PMs), respectively (see **Table 1**).[3]

Table 1. CYP2C19 phenotypes, clopidogrel response and therapeutic recommendations

Metabolizer phenotype	Examples of CYP2C19 diplotypes	Response to clopidogrel	Therapeutic recommendation[54]	Classification of recommendation (CPIC)[54]
Ultra-rapid metabolizer (UM)	*17/*17	Normal or increased antiplatelet response to clopidogrel	If considering clopidogrel, use at standard dose	Strong
Rapid metabolizer (RM)	*1/*17	Normal or increased antiplatelet response to clopidogrel	If considering clopidogrel, use at standard dose	Strong
Extensive metabolizer (EM)	*1/*1	Normal antiplatelet response to clopidogrel	If considering clopidogrel, use at standard dose	Strong
Intermediate metabolizer (IM)	*1/*2, *1/*3, *2/*17 or *3/*17	Reduced antiplatelet response to clopidogrel	Avoid standard dose clopidogrel. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong
Poor metabolizer (PM)	*2/*2, *2/*3 or *3/*3	Significantly reduced antiplatelet response to clopidogrel	Avoid clopidogrel. Use prasugrel or ticagrelor at standard dose if no contraindication	Strong

Anticoagulants

The different oral anticoagulants can be divided into two groups, the vitamin K antagonists (VKAs) and the direct oral anticoagulants (DOACs), both primarily used to prevent thrombus formation in low shear stress environments (e.g. fibrillating atria, veins). VKAs (such as acenocoumarol, phenprocoumon and warfarin) have both a high inter-individual and a high intra-individual variability, due to multiple significant food and drug interactions, but their effectivity is also affected by different genetic polymorphisms.[4] Consequently, VKAs have a very narrow therapeutic window, which complicates dosing and necessitates frequent INR measurements. Especially the first month of VKA treatment is problematic as the therapeutic dose is empirically assessed, with further adjustments made on the basis

of trial-and-error, leading to possible over-or under-anticoagulation with associated potential bleeding or thrombotic events. There are many studies that have assessed the impact of genetic variations on VKA treatment.[5] The genes with the strongest literature support are *CYP2C9* and vitamin K epoxide reductase complex 1 (*VKORC1*), both associated with lower VKA dose requirements and even a higher risk of bleeding.[6] CYP2C9 converts the active drug into inactive metabolites (see **Figure 1**). Polymorphisms in *CYP2C9* can lead to high variations in dose response.[7,8] Polymorphisms in the gene encoding *VKORC1*, which converts vitamin K into its active form and is inhibited by VKAs, also affects the inter-individual variability in warfarin dosing.[9] In 2005, the first warfarin dosing algorithm was published, which included age, height and *CYP2C9* and *VKORC1* genotype.[10] This led the US Food and Drug Administration (FDA) to modify the warfarin label to include the impact of *CYP2C9* or *VKORC1* polymorphisms on dosing in 2007, followed by an additional modification including a pharmacogenetic-guided dosing scheme in 2010. Since then, multiple randomized clinical trials (RCTs) have evaluated the clinical benefit of a personalised VKA strategy using pharmacogenetic algorithm-guided dosing compared to standard dosing strategies.[11–15] A number of meta-analyses have been published showing that genotype-guided dosing improves the time within the therapeutic INR range.[16–18] Moreover, the use of pharmacogenetics in VKA dosing may also reduce bleeding complications, however, not all study results are unequivocal on this.[19–21] Altogether, a personalized pharmacogenetic algorithm can facilitate and improve daily dosing of VKAs, especially when initiating treatment. Hence, the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends to use these pharmacogenetic algorithms to calculate warfarin dosing.[5] The newer DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) have a more convenient therapeutic window and do not necessitate routine coagulation monitoring, as opposed to VKAs.[22] Despite this, DOACs also have a notable inter-individual variability, which may be caused by genetic polymorphisms. Pharmacogenetic testing may help physicians in choosing the most appropriate DOAC treatment. However, currently the evidence is too scarce to recommend routinely genetic testing in patients treated with DOACs.[23]

Antiplatelet therapy

In patients with coronary artery disease (CAD) dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (ticagrelor, prasugrel and clopidogrel) represents the cornerstone of medical therapy to prevent the recurrence of thrombotic events.[24–27] Both ticagrelor and prasugrel have a more potent inhibitory effect on platelets, reducing thrombotic events when compared to clopidogrel in large RCTs.[28,29] Accordingly, in patients with acute coronary syndrome (ACS), ticagrelor or prasugrel are recommended over clopidogrel in the guidelines.[24,25] However, this benefit regarding thrombotic events is counterbalanced by an increased bleeding risk.[28,29] As the prognostic impact of a major bleeding event is comparable to a recurrent thrombotic event, reducing the bleeding risk without affecting efficacy is an extremely important and valuable goal when prescribing DAPT.[30–32]

Aspirin (acetylsalicylic acid) is metabolized by different enzymes (e.g., Uridine diphosphate (UDP)-glucuronosyltransferase 1A6, CYP2C9 and N-acetyl transferase 2), but so far no association between genetic polymorphisms and platelet reactivity or clinical outcomes has been demonstrated.[33,34] Ticagrelor is a direct-acting drug, whereas clopidogrel and prasugrel (both thienopyridines) are prodrugs that require cytochrome P450-based in vivo conversion to an active metabolite to irreversibly inhibit the $P2Y_{12}$-receptor.[35] The enzyme CYP3A4/5 plays a role in the metabolism of ticagrelor, but no clinically relevant interactions between ticagrelor and genetic polymorphisms are currently known.[36,37] Prasugrel is metabolized to its active metabolite primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19.[38] Common polymorphisms in *CYP3A4*, *CYP2B6*, *CYP2C9* and *CYP2C19* have not been related to relevant pharmacokinetic or pharmacodynamics changes, and carriers of these polymorphisms, treated with prasugrel, did not have an elevated risk of cardiovascular events.[38–40] With clopidogrel it is a different story, as there is a large inter-individual variability in pharmacokinetic and pharmacodynamic effects between patients treated with clopidogrel.[41] As a consequence, 30% of patients do not adequately respond to treatment with clopidogrel.[42]

Multiple CYP-enzymes play a part (CYP2C19, CYP3A4/5, CYP1A2, CYP2B6, CYP2C9) in the two-step conversion of clopidogrel to its active metabolite, however CYP2C19 is the main contributor in both steps (**Figure 1**).[43] Carriers of *CYP2C19* LOF-alleles have a dysfunctional CYP2C19-enzyme, resulting in an impaired metabolization of clopidogrel and, as a consequence, lower levels of the active metabolite.[40] The prevalence of the *CYP2C19* polymorphisms (*2 and *3) is estimated to be ~25%, ~33% and ~55% in the Caucasian, African American and Asian populations, respectively.[35,44,45] Multiple studies have confirmed that carriers of *CYP2C19* LOF-alleles have a decreased antiplatelet response and an increased prevalence of high platelet reactivity (HPR).[46–51] Consequently, these patients are at higher risk for thrombotic events, including stent thrombosis.[46,52] This prompted the US Food and Drug Administration (FDA) to add a Boxed Warning on the clopidogrel label in 2010 alerting patients and health care professionals that clopidogrel treatment is less effective in PM.[53]

Clinical evidence for a genotype-guided antithrombotic therapy

This US Food and Drug Administration Boxed Warning was followed by multiple studies assessing the efficacy and safety of a CYP2C19 genotype-guided strategy in patients with CAD.[42,55–61] The various strategies can be distinguished into "de-escalation" or "escalation" of the P2Y12 inhibitor therapy. A de-escalation strategy involves switching from the more potent drugs ticagrelor or prasugrel to the less potent clopidogrel in EMs, while escalation involves switching from clopidogrel to ticagrelor or prasugrel in IMs or PMs. De-escalation can be applied in patients with ACS, where current standard treatment is ticagrelor or prasugrel. Escalation of P2Y12 inhibitor therapy can be done in patients with chronic coronary syndrome (CCS) undergoing percutaneous coronary intervention (PCI), stroke or peripheral artery disease, where clopidogrel is standard care.

In patients with CAD, multiple randomized trials and non-randomized studies have provided evidence in support for genotyping. The largest randomized trials until now are the POPular Genetics and the

TAILOR-PCI studies.[62,63] In the Popular Genetics trial a genotype-guided de-escalation strategy was assessed in 2,488 patients undergoing primary PCI for ST-segment elevation myocardial infarction (STEMI). In both groups all patients were treated with aspirin, however, in the genotype-guided group, IMs and PMs were treated with ticagrelor or prasugrel (39%), whereas EMs received clopidogrel (61%). Patients in the control group were treated with ticagrelor according to current guidelines. Genotype-guided P2Y12 inhibitor treatment was initiated within 24 hours after randomization, and resulted in a lower bleeding incidence compared with standard care with prasugrel or ticagrelor (9.8 vs 12.5%, HR 0.78, 95% CI 0.61 to 0.98, P = 0.04). There was no evidence for an increase in thrombotic events in the genotype-guided group.

The TAILOR-PCI study randomized 5,302 patients undergoing PCI for ACS or stable CAD between a genotype-guided escalation strategy or conventional therapy.[63] In the genotype-guided group, those identified as *CYP2C19* LOF carriers (IMs or PMs) were prescribed ticagrelor (31%), and noncarriers were prescribed clopidogrel (68%). This strategy was compared with a treatment of clopidogrel in the conventional therapy group. The primary analysis was undertaken in only those patients who were *CYP2C19* LOF-carriers. There was no statistical difference in primary outcomes, regarding cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months (HR, 0.66, 95% CI 0.43-1.02; P = 0.06), though the reduced event rates suggest a clinical benefit with the genotype-guided therapy regarding thrombotic outcomes. There was no significant difference in bleeding (TIMI major or minor bleeding) in the primary analysis cohort. Although the trial was underpowered to detect an effect size less than the pre-specified expected 50% relative risk reduction, it showed promising results that offers support for the benefit of a genetically-guided therapy. This was also supported by a post-hoc analysis for the first 3 months post-PCI, which demonstrated a HR of 0.21 (95% CI 0.08-0.54), indicating that the genotype-guided therapy significantly reduced thrombotic risk in the first months, generally the most vulnerable period, after PCI. Furthermore, when allowing for multiple events instead of a time-to-first event analysis, the genotype-guided therapy was superior to the conventional therapy (HR 0.60, 95% CI 0.41-0.89).

These results are also backed-up by a meta-analysis including 15.949 patients with CAD, showing that carriers of a *CYP2C19* LOF-allele (**2* or **3*) had improved thrombotic outcomes when treated with ticagrelor or prasugrel as compared with those treated with clopidogrel.[64] When ticagrelor or prasugrel were compared with clopidogrel in only wild-type patients (EM, **1/*1*), clopidogrel had comparable efficacy in the prevention of thrombotic events. These results are also consistent with previous large meta-analyses, which demonstrated that clopidogrel-treated patients undergoing PCI who are *CYP2C19* IMs or PMs have a higher risk for major adverse cardiovascular events (MACEs) and stent thrombosis compared with *CYP2C19* EMs (**1/*1*).[65–69] Based on all this evidence, the CPIC recommends to avoid clopidogrel in *CYP2C19* IMs and PMs and use an alternative antiplatelet agent, such as prasugrel or ticagrelor, if there are no contraindications.[54] Despite this, a genotype-guided antiplatelet therapy is not yet recommended as standard care in patients with CAD: a genotype-guided de-escalation of $P2Y_{12}$-inhibition currently has a class IIb recommendation, and can be considered for ACS patients deemed unsuitable for potent platelet inhibition.[25]

Nevertheless, based on the growing base of evidence for a genotype-guided DAPT, some centers have implemented a genotype-guided strategy into their clinical practice.[70] Their results are in line with previous meta-analyses, showing that *CYP2C19* LOF-carriers treated with alternative therapy (ticagrelor or prasugrel) have a lower thrombotic risk when compared with clopidogrel, though the thrombotic risk is similar in those without a LOF-allele treated with clopidogrel compared to alternative therapy.

Although most evidence for a genotype-guided antiplatelet treatment comes from trials conducted in patients with CAD, vascular disease is a universal pathophysiological phenomenon that does not adhere to the boundaries of a particular organ. Coherently, a meta-analysis has shown that also in patients with ischemic stroke or transient ischemic attack (TIA), carriers of *CYP2C19* LOF-allele are at greater risk of stroke and of a composite of vascular events than non-carriers.[71] These results are supported by clinical data from the CHANCE-2 trial, which was a RCT in 6,412 patients with acute ischemic stroke or TIA.[72] The trial exclusively enrolled carriers of *CYP2C19* LOF-alleles, and compared the effects of ticagrelor plus aspirin to standard-dose clopidogrel (75 mg/day) plus aspirin over 90 days. Compared with clopidogrel, ticagrelor-treated IMs and PMs experienced significantly lower rates of stroke and major vascular events, without an increase in moderate or severe bleeding. However, ticagrelor was associated with higher rates of mild bleeding events.

Genetic testing can thus be a valuable tool to aid clinical decision, allowing the optimal choice of $P2Y_{12}$-inhibiting therapy. It also has the following advantages; there is no inter-assay variability: no variability of results over time; results are not influenced by extra-patient factors (e.g., timing of the test); and there is no need for the patient to be on treatment. However, genetic testing cannot account for other factors (both modifiable and non-modifiable) affecting the response on antithrombotic drugs (**Figure 1**), and might thus be less accurate in identifying patients with HPR. This can be overcome by the use of platelet function testing, which provides a direct measure of an individual's response to P2Y12 inhibitors and automatically accounts for the influence on platelet reactivity of factors like co-morbidities, age, gender and genetics.

PLATELET FUNCTION TESTING

Platelet function testing refers to different ex-vivo methods aiming to test the ability of platelets to aggregate to each other in response to external aggregating agents. The assessment of PFT has found application in various clinical conditions, including transfusion medicine, identification of patients with bleeding disorders and monitoring the response to antiplatelet treatment. In particular, monitoring the response of platelets to treatment with $P2Y_{12}$ inhibitors has been evaluated by means of the reactivity of platelet aggregation in response to stimulation with adenosine diphosphate (ADP). The different assays used for the ex-vivo assessment of platelet reactivity to ADP are classified as point-of-care (VerifyNow, Multiplate, thromboelastography) and laboratory-based methods, such as measurement of vasodilator-

stimulated phosphoprotein (VASP) phosphorylation using flow cytometry[73] and light transmission aggregometry (LTA). LTA is considered the gold standard method to investigate patients with suspected abnormalities of primary haemostasis, due to inherited or acquired defects of platelet function. This technique determines platelet aggregation percentage in platelet-rich plasma by measuring the increase in light transmission in response to the addition of a platelet agonist to the platelet suspension. However, several aspects of the LTA methodology have not been adequately standardized[74] and this method is not routinely used for monitoring subjects on antiplatelet therapy.[75] Regardless of the assay used, the response of platelet aggregation to ADP-stimulation has been classified as high platelet reactivity (HPR), low-platelet reactivity (LPR) and optimal platelet reactivity (OPR)[76], which is defined as the therapeutic window between LPR and HPR. HPR is associated with increased risk for thrombosis, while LPR is linked to higher risk for bleeding complications.[77] Consequently, patients within the therapeutic window of platelet reactivity have the lowest risk for adverse events.[73] The cut-off values for this categorization are highly dependent on the assay used. Cut-off values for HPR and LPR for the different assays are summarized in **Table 2**.[73]

Table 2. Definition of low- (LPR) and high- platelet reactivity (HPR) for different ex-vivo assessment methods (point-of care: VerifyNow, Multiplate Analyzer and Thromboelastography) and laboratory-based methods using flow-cytometry (measurement of VASP phosphorylation) and light transmission aggregometry (LTA).

Assay	LPR	HPR
VerifyNow P2Y12	85 PRU	208 PRU
Multiplate Analyzer	18 U	46 U
Thromboelastography (TEG)	31 mm	47 mm
Measurement of VASP phosphorylation	16% PRI	50% PRI
Light transmission aggregometry (LTA)	NA	≥ 70%

HPR: high platelet reactivity; LPR: low-platelet reactivity; PRI: platelet reactivity index; PRU: platelet reactivity units; VASP: Vasodilator-stimulated phosphoprotein.

Platelet function testing as predictor of events

Current guidelines for antithrombotic therapy in patients undergoing PCI recommend the implementation of DAPT consisting of aspirin and a P2Y12 inhibitor for 1 to 12 months.[25,78,79] However, treatment with all currently available P2Y12 inhibitors has been associated with an increased risk for bleeding complications.[28,29,80–82] Moreover, both ischaemic and bleeding events are key counterparts determining the overall patient survival.[83] Therefore, an effort to minimize both complications in PCI-treated patients is an important goal in modern cardiology.[24,84] Monitoring platelet reactivity during treatment with P2Y12 inhibitors has been shown to be an important predictor of both bleeding and ischaemic complications, as HPR has been linked to a greater risk for ischaemic complications, while LPR has been associated with a higher incidence of bleeding events.[77] In a meta-analysis combining the results of 17 observational and randomized studies with inclusion of more than 20,000 patients, Aradi et al. demonstrated that, compared with OPR, HPR was associated with a 2.7-fold higher risk for definite or

probable stent thromboses (weighted relative risk [RR] 2.73; 95% CI 2.03 – 3.69; P < 0.001).[76] There was no significant advantage of LPR compared to OPR with respect to stent-thromboses (RR 1.06; 95% CI 0.68 – 1.65; P = 0.78). However, LPR was associated with a 1.7-fold increased risk for clinically relevant major bleeding complications, defined as TIMI major or BARC type ≥2 bleeding events (RR 1.74; 95% CI 1.47 – 2.05; P <0.001).[76] HPR compared to OPR further decreased the bleeding events by 16% (RR 0.84; 95% CI 0.71 – 0.99; P = 0.04). However, it is important to note that, compared with OPR, HPR was associated with higher mortality (RR 1.54; 95 % CI 1.22 – 1.94; P < 0.001), while there was no significant difference between LPR and OPR (RR 1.03; 95% CI 0.76 – 1.40) with respect to all-cause mortality. Based on these results it can be concluded that a platelet reactivity within the therapeutic window warrants the lowest rate of ischaemic events and bleeding complications.

PFT-guided escalation in clinical trials

Current guidelines recommend treatment with DAPT based on a potent P2Y12 inhibitor (prasugrel or ticagrelor) in patients with ACS undergoing PCI[25,78] and a DAPT therapy with clopidogrel in patients undergoing elective PCI because of stable CAD.[26] Based on the results of previous studies and meta-analyses, the reasonable hypothesis was formulated that PFT-guided DAPT escalation from clopidogrel to a potent P2Y12 inhibitor (prasugrel or ticagrelor) or de-escalation from a potent P2Y12 inhibitor to clopidogrel could improve outcomes by reducing both ischaemic and bleeding complications. The concept of PFT-guided escalation of DAPT refers to upgrading P2Y12 inhibitor from clopidogrel to prasugrel or ticagrelor in patients with stable CAD undergoing elective PCI exhibiting HPR on clopidogrel. Although this assumption sounds reasonable, none of the major trials testing this hypothesis succeeded in meeting their primary endpoints. The GRAVITAS trial (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety)[85] was the first major randomized trial in the field of PFT-guided treatment. In this trial high-dose clopidogrel, instead of a potent P2Y12 inhibitor, was used as an escalated regimen. The trial failed to show a benefit of this specific strategy over standard-dosed clopidogrel. The TRIGGER-PCI trial (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel),[86] which tested prasugrel for PFT-guided treatment escalation in patients undergoing elective PCI, was stopped prematurely because of futility. Finally, the ARCTIC trial (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting), which used high-dose clopidogrel or short acting intravenous glycoprotein IIb/IIIa inhibitors or prasugrel (in less than 10% of patients) as escalated antiplatelet regimens also failed to show a benefit of escalated DAPT vs clopidogrel.[87] The current ESC-guidelines recommend a non-guided escalation strategy (Class of recommendation IIb, Level of evidence: C; **Figure 2**) from clopidogrel to prasugrel or ticagrelor in specific high-risk situations of elective PCI, like suboptimal stent deployment or a complex-PCI procedure (C-PCI). A PFT-guided approach, although not tested in large, randomized trials, might be beneficial in this setting. In a recently-published registry-based analysis of long-term outcomes in patients undergoing elective chronic total occlusion PCI, HPR (defined as LTA ≥ 70%) on clopidogrel not being escalated to a potent P2Y12 inhibitor

was associated with a higher 3-year cardiac mortality rate compared to patients with OPR on clopidogrel (16.8 ± 3.8% vs 4.7 ± 0.8%; P < 0.001). Whether patients undergoing elective C-PCI can benefit from a PFT-guided escalation from clopidogrel to a potent P2Y12 inhibitor should be further evaluated in future randomized-controlled trials.

PFT-guided de-escalation in clinical trials

De-escalation of antiplatelet therapy from potent P2Y12 inhibitors to clopidogrel in patients with ACS undergoing PCI is common in everyday clinical practice and is mainly attributed to bleeding and non-bleeding complications, as well as socio-economic factors.[88] It is estimated that the prevalence of unplanned in-hospital de-escalation ranges from 5 to 14%, with an additional 5 to 8% of unplanned de-escalation taking place after hospital discharge.[84] Moreover, the clinical utility of planned de-escalation of potent P2Y12 inhibitors to clopidogrel in patients with ACS undergoing PCI has been tested in three randomized clinical trials. In the Popular Genetics trial a genotype-guided de-escalation strategy was assessed (see above).[62] The randomized TOPIC trial (Timing of Optimal Platelet Inhibition After Acute Coronary Syndrome) showed that, in patients who have been event-free for the first month after an ACS on a combination of aspirin plus a potent P2Y12 inhibitor, de-escalation to aspirin plus clopidogrel was associated with reduced bleeding complications.[89] This study did not show any differences in thrombotic events between treatment groups. However, given the limited size of the trial (N = 646) this result should be interpreted cautiously. The TROPICAL-ACS trial (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for ACS) was a larger trial, which randomized 2610 patients with ACS undergoing PCI to either standard treatment with prasugrel for 12 months or a de-escalation regimen (1 week of prasugrel followed by 1 week of clopidogrel and PFT–guided maintenance therapy with clopidogrel or re-escalation to prasugrel from day 14 after hospital discharge to month 12).[90] Taking into consideration the results of the above mentioned trials, recent practice guidelines have been updated with a Class IIb (Level of Evidence A) recommendation for a guided (based on PFT or *CYP2C19* genotyping) DAPT de-escalation strategy, which may be considered as an alternative DAPT strategy, especially for patients with ACS, deemed unsuitable for 12-month potent platelet inhibition[8] (**Figure 2**).

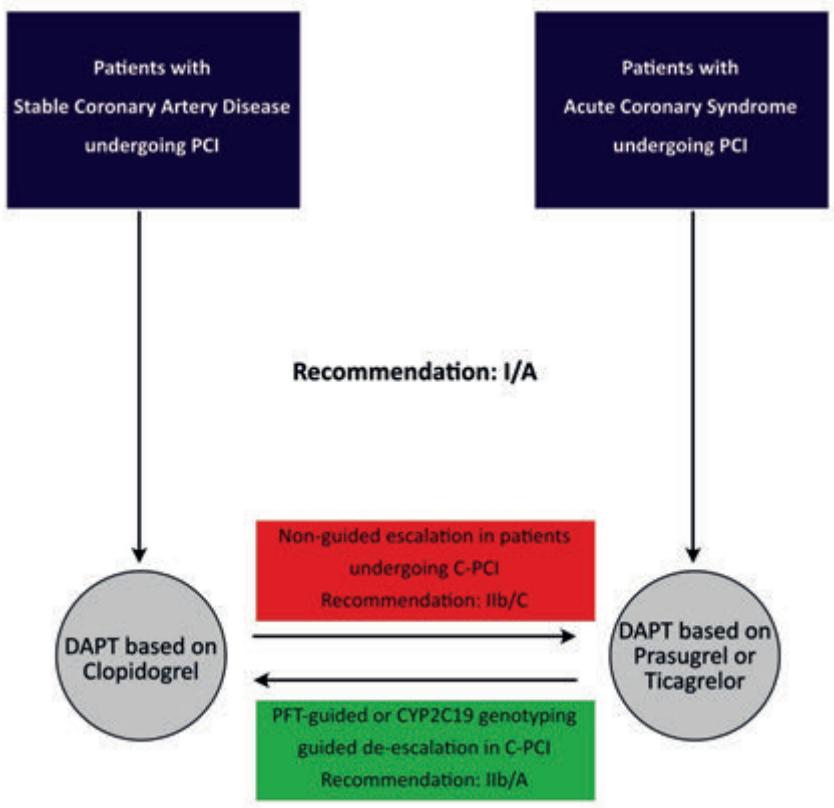

Figure 2. Guideline based recommendations for therapy with P2Y12 inhibitors in patients with stable coronary artery disease undergoing elective PCI[26] and patients undergoing PCI because of an acute coronary syndrome.[25,78]

The bottom panel illustrates the recommendations for non-guided escalation in patients undergoing complex PCI (C-PCI) procedures and guided de-escalation based on the results of platelet function testing (PFT) or *CYP2C19*-genotyping.

Guided selection of antiplatelet therapy: an appraisal

As discussed above, multiple trials have tried to optimize clinical outcomes by tailoring the P2Y12 inhibitor through a genotype- or PFT-guided strategy. However, most of these studies were not powered for hard efficacy outcomes and did not provide unequivocal results. To overcome the limitation of a lack of power, a meta-analysis by Galli et al. was performed to assess the safety and efficacy of guided versus standard selection of antiplatelet therapy in patients, both with CCS and ACS, undergoing PCI.[91] In this analysis, including 11 RCTs and more than 20,000 patients, guided selection of antiplatelet therapy was associated with a reduction of major adverse cardiovascular events (MACE) compared with standard therapy. In addition, guided antiplatelet therapy also resulted in a reduction of individual efficacy and safety outcomes, like cardiovascular death, myocardial infarction, stent thrombosis, stroke and minor

bleeding. The results were consistent, independent of the test used for guided selection of therapy (PFT vs genetic testing). Outcomes differed according to the strategy used. An escalation strategy was associated with a reduction in ischaemic events without an increase in bleeding, and a de-escalation strategy with a reduction in bleeding, without an increase in ischaemic events. Nevertheless, in the specific setting of ACS physicians may still favour potent $P2Y_{12}$-inhibition, on the one hand due to evidence in support of their use by the large-scale pivotal RCTs[28,29], and on the other hand since guided selection requires implementation of additional (costly) testing at their local site. However, in a more recent network meta-analysis by Galli et al. the safety and efficacy of guided versus standard selection of antiplatelet therapy was assessed in patients with ACS only, which included 15 RCTs and more than 60,000 patients with ACS.[92] In this analysis clopidogrel was used as the reference treatment. Compared with ticagrelor and prasugrel, a guided antiplatelet approach was the only strategy associated with a reduction in MACE without any significant trade-off in any bleeding, demonstrating that a guided selection of $P2Y_{12}$-inhibition is the strategy with the most favourable balance between safety and efficacy. A guided strategy may also be preferred to standard therapy from an economic perspective. Multiple cost-effectiveness analyses have demonstrated that, by improving outcomes and reducing costs due to the more frequent use of clopidogrel (especially in the setting of ACS), guided selection of antiplatelet therapy can be a cost-effective strategy.[93–95]

PERSPECTIVE

Currently, a personalized antithrombotic therapy is not (yet) recommended as standard care in the guidelines; however, it can be definitely of great value in selective scenarios. For escalation of $P2Y_{12}$-inhibition, these could be scenarios in which thrombotic risk outweighs bleeding risk. Examples include left main coronary artery stenting, complex lesions, bifurcation PCI, prior stent thrombosis, For de-escalation strategies, this would include scenarios where patients are at increased risk of bleeding or have experienced bleeding complications. Thus, when personalizing antithrombotic therapy, the patient should be central, taking into consideration various clinical, angiographic, procedural, and socio-economic variables before opting for a specific strategy. If a guided antiplatelet strategy is implemented, the choice between PFT and genetic testing may depend on the availability of tests and local experience. In general, it is recommended to use point-of-care assays instead of laboratory-based assays. Ultimately, as evidence on PFT- and genotype-guided therapy is increasing over the years, with ongoing trials probably further refining the existing evidence, a personalized antithrombotic therapy could become the standard of care in patients undergoing PCI in the future.

What's New

- In this chapter we provide the latest evidence regarding precision medicine in antithrombotic therapy, based on pharmacogenetics or/and platelet function testing.
- A genotype-guided antithrombotic therapy focuses on identifying common genetic polymorphisms that might influence the antithrombotic effect exerted by oral anticoagulants and antiplatelet medication. As far, *CYP2C19* polymorphisms are the only genetic variations, for which, a genotype-guided therapy has been tested in clinical trials with respect to clinical outcomes in patients with acute coronary syndrome.
- A recent network meta-analysis demonstrated that compared to ticagrelor and prasugrel, a guided antiplatelet approach (based on platelet function testing or *CYP2C19* genotyping) was associated with a reduction in major adverse cardiovascular events without a *significant* increase in bleeding complications.

Guideline Recommendations

- The Clinical Pharmacogenetics Implementation Consortium recommends avoiding clopidogrel in *CYP2C19* intermediate or poor metabolizers in order to prevent major adverse cardiovascular events and stent thrombosis and use an escalated P2Y12 inhibitor, such as prasugrel or ticagrelor.
- A platelet reactivity within the therapeutic window warrants the lowest rate of ischaemic events and bleeding complications.
- The current ESC-guidelines recommend a non-guided escalation strategy (Class of recommendation IIb, Level of evidence: C) from clopidogrel to prasugrel or ticagrelor in specific high-risk situations of elective percutaneous coronary intervention.
- A guided de-escalation of $P2Y_{12}$-inhibition from prasugrel or ticagrelor to clopidogrel, based on platelet function testing or *CYP2C19* genotyping, can be considered in patients with acute coronary syndrome deemed unsuitable for treatment with potent platelet inhibitors (Class IIb recommendation, level of Evidence A).

Drug Doses

- Aspirin: loading dose (LD) of 150-300 mg orally or 75-250 mg intravenous if oral ingestion is not possible, followed by oral MD of 75-100 mg once daily (o.d.)
- Clopidogrel: LD of 300-600 mg orally, followed by a (MD) of 75 mg o.d., no specific dose adjustment in chronic kidney disease (CKD) patients.
- Prasugrel: LD of 60 mg orally, followed by a MD of 10 mg o.d. In patients with body weight <60 kg, a MD of 5 mg o.d. is recommended. In patients aged >_75 years, prasugrel should be used with caution, but a dose of 5 mg o.d. should be used if treatment is. deemed necessary. No specific dose adjustment in CKD patients. Prior stroke is a contraindication for prasugrel.
- Ticagrelor: LD of 180 mg orally, followed by a MD of 90 mg b.i.d., no specific dose adjustment in CKD patients.

What's next

- Currently, a personalized antithrombotic therapy is not recommended as standard care in the guidelines; however, it can be of great value as escalation strategy in patients with high thrombotic risk or as de-escalation strategy in patients in which bleeding risk overweighs thrombotic risk. As evidence on PFT- and genotype-guided therapy is increasing over time, a personalized antithrombotic therapy could become the standard of care in patients undergoing PCI in the future.

REFERENCES

1. Angiolillo DJ, Capodanno D, Danchin N, et al. Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC Cardiovasc Interv 2020;13(5):606–17.
2. Belle DJ, Singh H. Genetic factors in drug metabolism. Am. Fam. Physician. 2008;77(11):1553–60.
3. Pinto N, Dolan ME. Clinically relevant genetic variations in drug metabolizing enzymes. Curr Drug Metab [Internet] 2011;12(5):487–97. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21453273
4. Marín F, González-Conejero R, Capranzano P, Bass TA, Roldán V, Angiolillo DJ. Pharmacogenetics in Cardiovascular Antithrombotic Therapy. J Am Coll Cardiol [Internet] 2009;54(12):1041–57. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109709021469
5. Johnson J, Caudle K, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update. Clin Pharmacol Ther [Internet] 2017;102(3):397–404. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cpt.668
6. Verhoef TI, Redekop WK, Daly AK, van Schie RMF, de Boer A, Maitland-van der Zee A-H. Pharmacogenetic-guided dosing of coumarin anticoagulants: algorithms for warfarin, acenocoumarol and phenprocoumon. Br J Clin Pharmacol [Internet] 2014;77(4):626–41. Available from: https://onlinelibrary.wiley.com/doi/10.1111/bcp.12220
7. Rettie AE, Korzekwa KR, Kunze KL, et al. Hydroxylation of warfarin by human cDNA-expressed cytochrome P-450: a role for P-4502C9 in the etiology of (S)-warfarin-drug interactions. Chem Res Toxicol [Internet] 1992;5(1):54–9. Available from: https://pubs.acs.org/doi/abs/10.1021/tx00025a009
8. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet [Internet] 1999;353(9154):717–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673698044742
9. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose. N Engl J Med [Internet] 2005;352(22):2285–93. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa044503
10. Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood [Internet] 2005;106(7):2329–33. Available from: https://ashpublications.org/blood/article/106/7/2329/21662/The-impact-of-CYP2C9-and-VKORC1-genetic
11. Verhoef TI, Ragia G, de Boer A, et al. A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon. N Engl J Med [Internet] 2013;369(24):2304–12. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1311388
12. Pirmohamed M, Burnside G, Eriksson N, et al. A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med [Internet] 2013;369(24):2294–303. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1311386
13. Kimmel SE, French B, Kasner SE, et al. A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing. N Engl J Med [Internet] 2013;369(24):2283–93. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1310669
14. Cerezo-Manchado JJ, Roldán V, Corral J, et al. Genotype-guided therapy improves initial acenocoumarol dosing. Thromb Haemost [Internet] 2016;115(01):117–25. Available from: http://www.thieme-connect.de/DOI/DOI?10.1160/TH14-09-0814

15. Tong H, Borobia A, Quintana-Díaz M, et al. Acenocoumarol Pharmacogenetic Dosing Algorithm versus Usual Care in Patients with Venous Thromboembolism: A Randomised Clinical Trial. J Clin Med [Internet] 2021;10(13):2949. Available from: https://www.mdpi.com/2077-0383/10/13/2949
16. Tang T, Liu J, Zuo K, et al. Genotype-Guided Dosing of Coumarin Anticoagulants. J Cardiovasc Pharmacol Ther [Internet] 2015;20(4):387–94. Available from: http://journals.sagepub.com/doi/10.1177/1074248414565666
17. Belley-Cote E, Hanif H, D'Aragon F, et al. Genotype-guided versus standard vitamin K antagonist dosing algorithms in patients initiating anticoagulation. Thromb Haemost [Internet] 2015;114(10):768–77. Available from: http://www.thieme-connect.de/DOI/DOI?10.1160/TH15-01-0071
18. Danese E, Raimondi S, Montagnana M, et al. Effect of CYP 4F2 , VKORC 1 , and CYP 2C9 in Influencing Coumarin Dose: A Single-Patient Data Meta-Analysis in More Than 15,000 Individuals. Clin Pharmacol Ther [Internet] 2019;105(6):1477–91. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cpt.1323
19. Tse G, Gong M, Li G, et al. Genotype-guided warfarin dosing vs . conventional dosing strategies: a systematic review and meta-analysis of randomized controlled trials. Br J Clin Pharmacol [Internet] 2018;84(9):1868–82. Available from: https://onlinelibrary.wiley.com/doi/10.1111/bcp.13621
20. Franchini M, Mengoli C, Cruciani M, Bonfanti C, Mannucci PM. Effects on bleeding complications of pharmacogenetic testing for initial dosing of vitamin K antagonists: a systematic review and meta-analysis. J Thromb Haemost [Internet] 2014;12(9):1480–7. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jth.12647
21. Stergiopoulos K, Brown DL. Genotype-Guided vs Clinical Dosing of Warfarin and Its Analogues. JAMA Intern Med [Internet] 2014;174(8):1330. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2014.2368
22. Maier CL, Duncan A, Hill CE. Pharmacogenetics in Oral Antithrombotic Therapy. Clin Lab Med [Internet] 2016;36(3):461–72. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272271216300324
23. Raymond J, Imbert L, Cousin T, et al. Pharmacogenetics of Direct Oral Anticoagulants: A Systematic Review. J Pers Med [Internet] 2021;11(1):37. Available from: https://www.mdpi.com/2075-4426/11/1/37
24. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-thoracic Surg 2017;53(1):34–78.
25. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J [Internet] 2020;42(14):1289–367. Available from: https://academic.oup.com/eurheartj/article/42/14/1289/5898842
26. Knuuti J, Wijns W, Flachskampf FA, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur. Heart J. 2020;41(3).
27. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/acc guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64(24):139–228.
28. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2007;357(20):2001–15.
29. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med 2009;361(11):1045–57.

30. Vranckx P, Leonardi S, Tebaldi M, et al. Prospective validation of the bleeding academic research consortium classification in the all-comer PRODIGY trial. Eur Heart J 2014;35(37):2524–9.
31. Vranckx P, White HD, Huang Z, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. J Am Coll Cardiol 2016;67(18):2135–44.
32. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol 2015;66(9):1036–45.
33. Agundez J, Martinez C, Perez-Sala D, Carballo M, Torres M, Garcia-Martin E. Pharmacogenomics in Aspirin Intolerance. Curr Drug Metab 2010;10(9).
34. Postula M, Janicki PK, Rosiak M, et al. Effect of common single-nucleotide polymorphisms in acetylsalicylic acid metabolic pathway genes on platelet reactivity in patients with diabetes. Med Sci Monit 2013;19(1):394–408.
35. Gurbel PA, Rout A, Tantry US. Pharmacogenetic considerations in antiplatelet therapy. Expert Rev Precis Med Drug Dev [Internet] 2020;5(4):235–8. Available from: https://www.tandfonline.com/doi/full/10.1080/23808993.2020.1768844
36. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. Drug Metab Dispos 2010;38(9):1514–21.
37. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral P2Y12 receptor antagonist, in healthy subjects. Eur J Clin Pharmacol 2010;66(5):487–96.
38. Efient: EPAR - Product Information [Internet]. [cited 2022 May 2];Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/efient
39. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation [Internet] 2009;119(19):2553–60. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19414633
40. Giorgi MA, Cohen Arazi H, Gonzalez CD, Di Girolamo G. Beyond efficacy: Pharmacokinetic differences between clopidogrel, prasugrel and ticagrelor. Expert Opin. Pharmacother. 2011;12(8):1285–95.
41. Ancrenaz V, Daali Y, Fontana P, et al. Impact of genetic polymorphisms and drug-drug interactions on clopidogrel and prasugrel response variability. Curr Drug Metab [Internet] 2010;11(8):667–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20942779
42. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet (London, England) [Internet] 2012;379(9827):1705–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22464343
43. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug Metab Dispos 2010;38(1):92–9.
44. Stouffer GA, Klein MD, Williams AK, Lee CR. Clinical Utility of CYP2C19 Genotyping to Guide Antiplatelet Therapy in Patients With an Acute Coronary Syndrome or Undergoing Percutaneous Coronary Intervention Brief Review. Arter Thromb Vasc Biol [Internet] 2019;39:647–52. Available from: https://www.ahajournals.org/journal/atvb

45. Fricke-Galindo I, Céspedes-Garro C, Rodrigues-Soares F, et al. Interethnic variation of CYP2C19 alleles, 'predicted' phenotypes and 'measured' metabolic phenotypes across world populations. Pharmacogenomics J [Internet] 2016;16(2):113–23. Available from: https://www.nature.com/articles/tpj201570
46. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med 2009;360(4):354–62.
47. Breet NJ, Van Werkum JW, Bouman HJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA - J Am Med Assoc 2010;303(8):754–62.
48. Harmsze A, Van Werkum JW, Bouman HJ, et al. Besides CYP2C19*2, the variant allele CYP2C9*3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. Pharmacogenet Genomics 2010;20(1):18–25.
49. Hulot J-S, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood [Internet] 2006;108(7):2244–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16772608
50. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol [Internet] 2010;55(22):2427–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20510210
51. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA - J Am Med Assoc 2009;302(8):849–58.
52. Harmsze AM, Van Werkum JW, Ten Berg JM, et al. CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: A case-control study. Eur Heart J 2010;31(24):3046–53.
53. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug | FDA [Internet]. [cited 2022 Apr 29];Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor#ds
54. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther [Internet] 2022;Available from: http://www.ncbi.nlm.nih.gov/pubmed/35034351
55. Deiman BALM, Tonino PAL, Kouhestani K, et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Netherlands Hear J 2016;24(10):589–99.
56. Sánchez-Ramos J, Dávila-Fajardo CL, Toledo Frías P, et al. Results of genotype-guided antiplatelet therapy in patients who undergone percutaneous coronary intervention with stent. Int J Cardiol [Internet] 2016;225:289–95. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27744205
57. Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv 2018;11(2):181–91.

58. Xie X, Ma Y-T, Yang Y-N, et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. Int J Cardiol [Internet] 2013;168(4):3736–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23850318
59. Shen D-L, Wang B, Bai J, et al. Clinical Value of CYP2C19 Genetic Testing for Guiding the Antiplatelet Therapy in a Chinese Population. J Cardiovasc Pharmacol [Internet] 2016;67(3):232–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26727381
60. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Patients With Acute Coronary Syndromes: The PHARMCLO Trial. J Am Coll Cardiol [Internet] 2018;71(17):1869–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29540324
61. Tuteja S, Glick H, Matthai W, et al. Prospective CYP2C19 Genotyping to Guide Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Pragmatic Randomized Clinical Trial. Circ Genomic Precis Med [Internet] 2020;13(1):e002640. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31928229
62. 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(17):1621–31.
63. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes after Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA - J Am Med Assoc 2020;324(8):761–71.
64. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy: A Meta-Analysis. JACC Cardiovasc Interv 2021;14(7):739–50.
65. Biswas M, Kali MSK, Biswas TK, Ibrahim B. Risk of major adverse cardiovascular events of CYP2C19 loss-of-function genotype guided prasugrel/ticagrelor vs clopidogrel therapy for acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. Platelets. 2020;1–10.
66. Lyu SQ, Yang YM, Zhu J, et al. The efficacy and safety of CYP2C19 genotype-guided antiplatelet therapy compared with conventional antiplatelet therapy in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled tri. Platelets. 2020;31(8):971–80.
67. Yoon HY, Lee N, Seong JM, Gwak HS. Efficacy and safety of clopidogrel versus prasugrel and ticagrelor for coronary artery disease treatment in patients with CYP2C19 LoF alleles: a systemic review and meta-analysis. Br. J. Clin. Pharmacol. 2020;86(8):1489–98.
68. Kheiri B, Abdalla A, Osman M, et al. Personalized antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention: A network meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv 2019;94(2):181–6.
69. Kheiri B, Osman M, Abdalla A, et al. CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: A meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv [Internet] 2019;93(7):1246–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30403317
70. Beitelshees AL, Thomas CD, Empey PE, et al. CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention in Diverse Clinical Settings. J Am Heart Assoc [Internet] 2022 [cited 2022 Mar 14];11(4):e024159. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.121.024159

71. Pan Y, Chen W, Xu Y, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack. Circulation. 2017;135(1):21–33.
72. Wang Y, Meng X, Wang A, et al. Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. N Engl J Med [Internet] 2021;385(27):2520–30. Available from: http://www.nejm.org/doi/10.1056/NEJMoa2111749
73. Sibbing D, Aradi D, Alexopoulos D, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. JACC Cardiovasc Interv [Internet] 2019;12(16):1521–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31202949
74. Breddin HK. Can platelet aggregometry be standardized? Platelets [Internet] 2005;16(3–4):151–8. Available from: http://www.tandfonline.com/doi/full/10.1080/09537100400020161
75. Cattaneo M, Cerletti C, Harrison P, et al. Recommendations for the standardization of light transmission aggregometry: a consensus of the working party from the platelet physiology subcommittee of SSC/ISTH. J Thromb Haemost [Internet] 2013;11(6):1183–9. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jth.12231
76. Aradi D, Kirtane A, Bonello L, et al. Bleeding and stent thrombosis on P2Y 12 -inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J [Internet] 2015;36(27):1762–71. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehv104
77. Aradi D, Gross L, Trenk D, et al. Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. Eur Heart J [Internet] 2019;40(24):1942–51. Available from: https://academic.oup.com/eurheartj/article/40/24/1942/5477842
78. 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. Eur Heart J [Internet] 2018;39(2):119–77. Available from: https://academic.oup.com/eurheartj/article/39/2/119/4095042
79. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J [Internet] 2019;40(2):87–165. Available from: https://academic.oup.com/eurheartj/article/40/2/87/5079120
80. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet [Internet] 2001;358(9281):527–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673601057014
81. Antman EM, Wiviott SD, Murphy SA, et al. Early and Late Benefits of Prasugrel in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention. J Am Coll Cardiol [Internet] 2008;51(21):2028–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109708012709
82. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J [Internet] 2011;32(15):1854–64. Available from: https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehr204

83. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off ofmyocardial infarction vs. bleeding types onmortality after acute coronary syndrome: Lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;38(11):804–10.
84. Angiolillo DJ, Rollini F, Storey RF, et al. International Expert Consensus on Switching Platelet P2Y 12 Receptor–Inhibiting Therapies. Circulation [Internet] 2017;136(20):1955–75. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.031164
85. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA [Internet] 2011;305(11):1097–105. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2011.290
86. Trenk D, Stone GW, Gawaz M, et al. A Randomized Trial of Prasugrel Versus Clopidogrel in Patients With High Platelet Reactivity on Clopidogrel After Elective Percutaneous Coronary Intervention With Implantation of Drug-Eluting Stents. J Am Coll Cardiol [Internet] 2012;59(24):2159–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109712009783
87. Collet J-P, Cuisset T, Rangé G, et al. Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting. N Engl J Med [Internet] 2012;367(22):2100–9. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1209979
88. 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. Am Heart J [Internet] 2017;183:62–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002870316302277
89. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J [Internet] 2017;38(41):3070–8. Available from: http://academic.oup.com/eurheartj/article/38/41/3070/3827697
90. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390(10104):1747–57.
91. Galli M, Benenati S, Capodanno D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet [Internet] 2021;397(10283):1470–83. Available from: https://linkinghub.elsevier.com/retrieve/pii/S014067362100533X
92. Galli M, Benenati S, Franchi F, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J [Internet] 2022;43(10):959–67. Available from: https://academic.oup.com/eurheartj/article/43/10/959/6464193
93. 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(5):724–35.
94. 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 [Internet] 2020;25(3):201–11. Available from: http://journals.sagepub.com/doi/10.1177/1074248420902298

95. Lomakin N, Rudakova A, Buryachkovskaya L, Serebruany V. Cost-effectiveness of Platelet Function-Guided Strategy with Clopidogrel or Ticagrelor. Eur Cardiol Rev [Internet] 2019;14(3):175–8. Available from: https://www.ecrjournal.com/articles/Platelet-Function-Guided-Strategy-Clopidogrel-Ticagrelor

CHAPTER 3

Genotype guided antiplatelet therapy
JACC Review Topic of the Week

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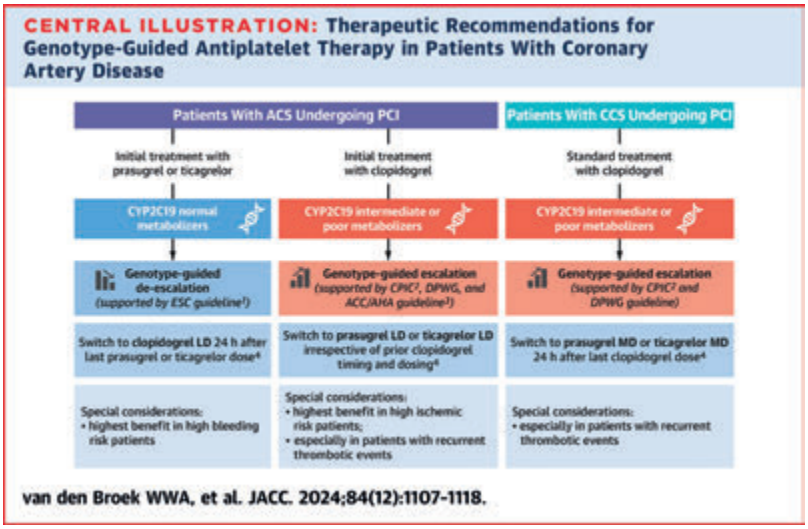
ABSTRACT

The clinical efficacy and safety of antiplatelet agents vary among patients. Consequently, some patients are at increased risk of recurrent ischemic events during treatment. This interindividual variability can be a result of genetic variants in enzymes that play a role in drug metabolism. The field of pharmacogenomics explores the influence of these genetic variants on an individual's drug response. Tailoring antiplatelet treatment based on genetic variants can potentially result in optimized dosing or a change in drug selection. Most evidence supports guiding therapy based on the *CYP2C19* allelic variants in patients with an indication for dual antiplatelet therapy. In ticagrelor-treated or prasugrel-treated patients, a genotype-guided de-escalation strategy can reduce bleeding risk, whereas in patients treated with clopidogrel, an escalation strategy may prevent ischemic events. Although the clinical results are promising, few hospitals have implemented these strategies. New results, technological advancements, and growing experience may potentially overcome current barriers for implementation in the future.



Central Illustration. Therapeutic Recommendations for Genotype Guided Antiplatelet Therapy in Patients with Coronary Artery Disease.

This flow diagram outlines the therapeutic recommendations for acute coronary syndrome (ACS) patients and chronic coronary syndrome (CCS) patiensts undergoing percutaneous coronary intervention (PCI) based on current guidelines. For ACS patients, the initial treatment determines if a genotype-guided de-escalation or escalation strategy is advised. Special considerations below illustrate the settings where each strategy offers the highest value.

[1] Based on a Class IIb Level of Evidence A recommendation in the 2020 ESC Guidelines for the management of ACS in patients presenting without persistent ST-segment elevation

[2] Recommendation is classified as strong

[3] Based on a Class IIb recommendation (weak)

[4] Based on the 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease and 2017 International Expert Consensus on Switching Platelet P2Y12 Receptor Inhibiting Therapies

ESC, European Society of Cardiology; NM, normal metabolizers; IM, intermediate metabolizers; PM, poor metabolizers; CPIC, Clinical Pharmacogenetics Implementation Consortium; DPWG, Dutch Pharmacogenetics Working Group; ACC/AHA, American College of Cardiology/American Heart Association

INTRODUCTION

Individuals exhibit significant variations in their response to drugs. The first observation of this phenomenon dates back to Pythagoras (510 B.C.), who noted that ingestion of fava beans caused a potentially fatal reaction in certain individuals, while others remained unaffected.[1] Later, it was revealed that this discrepancy resulted from a deficiency in glucose-6-phosphate dehydrogenase, leading to haemolytic anaemia. Many years later in 1959, Dr. Vogel was the first to coin the term "pharmacogenetics", to describe the relationship between genetic factors and response to medications. This variable response also affects the efficacy and safety of antiplatelet treatment.[2] Despite adequate treatment, a considerable number of treated patients will continue to incur a new ischemic event.[3] Although recurrent ischemic events have a multifactorial cause, certain antiplatelet drugs are heavily influenced by genetic sequence variants, significantly impacting their clinical efficacy.[4] On the other side, antiplatelet therapy elevates the risk for bleeding, an adverse effect with unfavourable prognostic implications, including increased mortality.[5,6] Tailoring antiplatelet therapy to a patient's genotype may mitigate the associated thrombotic and bleeding risk.[7]

In recent years, the field of pharmacogenetics has advanced from discovery to clinical implementation. It not only deepens our understanding of interindividual heterogeneity in drug effectiveness and safety, but, through its application in clinical trials, has shown its potential for personalised treatment, resulting in optimal therapy and reduced risk of adverse drug events.[8] In this review, we explore the clinical utility of pharmacogenetics in decision-making for antiplatelet therapy, encompassing the most recent evidence and future prospects.

Antiplatelet therapy

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard of care after percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS).[9] Current guidelines recommend the use of a P2Y12 inhibitor with more potent platelet inhibitory effects (i.e., prasugrel or ticagrelor) over clopidogrel in patients with ACS, while clopidogrel is preferred in chronic coronary syndrome (CCS).[10–12] Ticagrelor and prasugrel exhibit more potent and consistent antiplatelet effects compared to clopidogrel. While both ticagrelor and prasugrel are metabolized by various cytochrome P450 (CYP-)enzymes, as of now, no genetic variants have been identified that significantly impact their antiplatelet effects, clinical efficacy or safety (**Figure 1**).[13–15] Clopidogrel is a prodrug that requires a two-step oxidation process by multiple CYP-enzymes to become active, of which *CYP2C19* has the greatest contribution (**Figure 1, Table 1**). Patients who are rapid metabolizers (*1/*17) or ultra-rapid metabolizers (*17/*17) have increased active metabolite formation, although there is no association with bleeding risk when these phenotypes are compared to normal metabolizers.[16] Patients with one (intermediate metabolizers) or two (poor metabolizers) *2 or *3 alleles have reduced active metabolite formation.[17] Given that the frequency of *CYP2C19* loss-of-function (LOF) alleles ranges from 30% in Europeans to 60% in East Asian patients, impaired metabolism is prevalent.[18,19] Pharmacokinetic studies have demonstrated a 40% reduction in active metabolites in LOF carriers compared to non-carriers, resulting to a subsequent

decrease in the pharmacodynamic response, which in turn raises the incidence of high on-treatment platelet reactivity (HPR) by 2-3 times.[20–22]

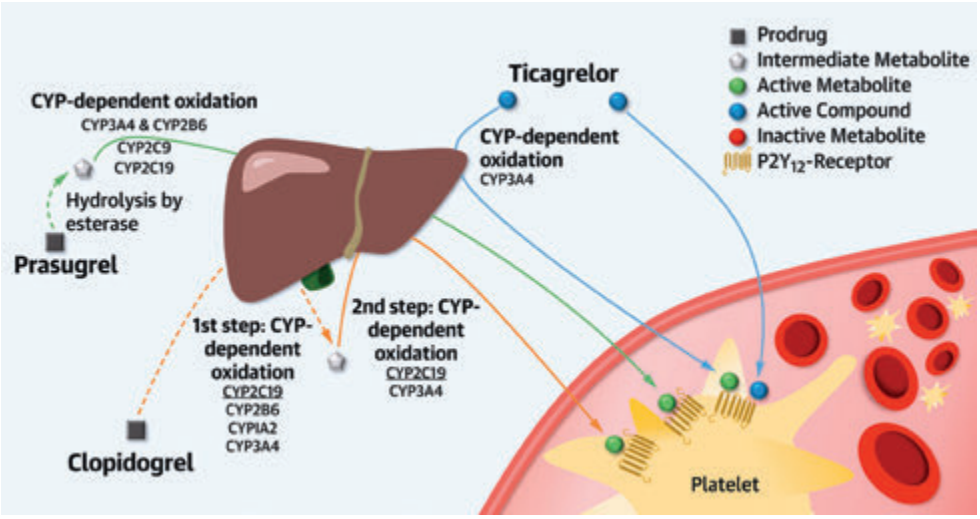


Figure 1. Biotransformation and metabolization of the different P2Y12 inhibitors agents.

After absorption, ticagrelor is a direct-acting drug, and is partially metabolized by CYP3A4. Prasugrel is a prodrug that requires a one-step cytochrome (CYP) P450-based (mainly by CYP3A4 and CYP2B6) conversion to its active metabolite. Clopidogrel is a prodrug that necessitates a two-step oxidation process by multiple CYP-enzymes to become active, of which *CYP2C19* has the greatest contribution.

Consequently, multiple studies have demonstrated an increased risk of ischemic events among LOF carriers treated with clopidogrel, particularly in post-PCI populations.[20,23] Although universal use of prasugrel or ticagrelor seems like a simple solution, the increased bleeding risk, higher costs, twice daily dosing, lower adherence with ticagrelor, and unique non-bleeding side effects (especially dyspnoea with ticagrelor) make this approach less appealing.[24,25] These factors collectively form the foundation for applying genotype guided strategies in randomized clinical trials.

Table 1. *CYP2C19* phenotypes, genotypes and response to clopidogrel.

Metabolizer phenotype	Genotype	Response to clopidogrel and clinical impact
Ultra-rapid (UM)	*17/*17	Normal or increased antiplatelet response to clopidogrel
Rapid (RM)	*1/*17	Normal or increased antiplatelet response to clopidogrel
Normal (NM)	*1/*1	Normal antiplatelet response to clopidogrel
Intermediate (IM)	1 LOF allele (*1/*2, *1/*3, *2/*17, *3/*17)*	Reduced antiplatelet response to clopidogrel; increased risk for adverse cardiovascular events
Poor (PM)	2 LOF alleles (*2/*2, *2/*3, *3/*3)*	Significantly reduced antiplatelet response to clopidogrel; increased risk for adverse cardiovascular events

**CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7*, and *CYP2C19*8* are more rare examples of loss-of-function variants and are excluded from the table above and most guidelines due to their lower clinical relevance and sparse data. Several studies have suggested the involvement of variants in additional genes linked to clopidogrel response, such as ABCB1, B4GALT2, CES1, CYP2B6, CYP2C9, P2RY12, and PON1; nevertheless, consistent replication of these findings has yet to be achieved.[17] LOF = loss-of-function

Genotype guided strategies

The various strategies applied in clinical research can be distinguished into "de-escalation" or "escalation" of the P2Y12 inhibitor therapy (**Figure 2**). A de-escalation strategy by switch entails transitioning from the more potent ticagrelor or prasugrel to clopidogrel in normal metabolizers (NMs), whereas an escalation strategy involves switching from clopidogrel to ticagrelor or prasugrel in intermediate metabolizers (IMs) or poor metabolizers (PMs).[26] De-escalation by switch can be applied to patients with ACS, where the current preferred P2Y12-inihbitor is prasugrel (or ticagrelor, if contraindication to prasugrel exists).[10] Escalation by switch of P2Y12 inhibitor therapy can be considered in situations where clopidogrel is standard of care, such as patients with CCS undergoing PCI, stroke, or peripheral artery disease. The rationale for the escalation strategy is evident: carriers of a *CYP2C19* LOF allele have an increased ischaemic risk when treated with clopidogrel and switching to an alternative agent may reduce the risk for these ischemic events. Conversely, the rationale behind the de-escalation strategy centres on reducing bleeding events without a trade-off in efficacy. Reducing bleeding is gaining relevance, as bleeding after PCI is a clinically important metric related to significant morbidity and mortality.[6,27] As contemporary drug-eluting stents have dramatically reduced stent thrombosis (ST) rates to below 1% in the first year, strategies to improve post-PCI bleeding rates, rather than further reduce ST rates, are more likely to beneficial for overall morbidity and mortality.[28]

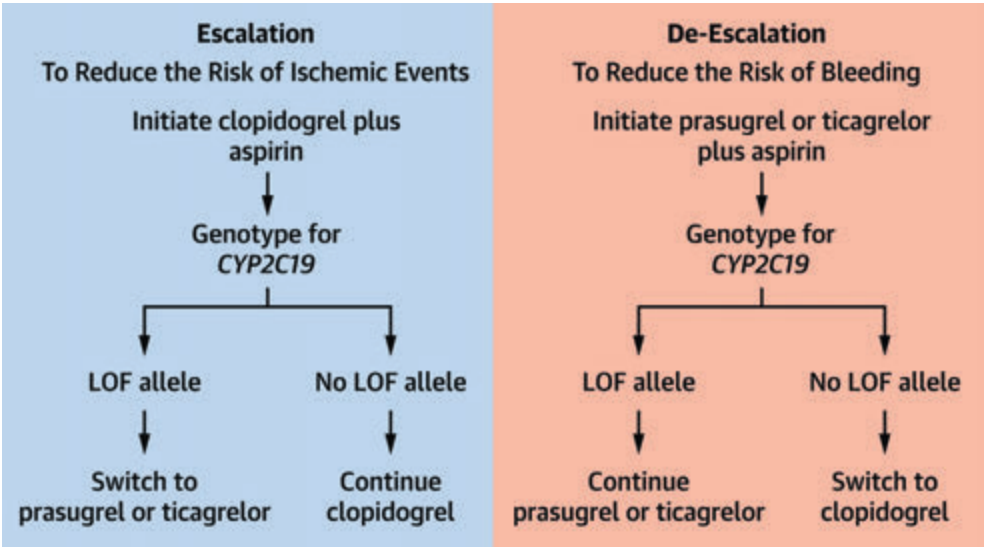


Figure 2. Flow diagram illustrating the genotype guided escalation and de-escalation P2Y12 inhibitor strategies.

The escalation strategy aims to reduce ischemic events by identifying clopidogrel-treated patients with a loss-of-function (LOF) allele and switching them to a more potent P2Y12 inhibitor. The de-escalation strategy seeks to minimize bleeding by identifying *CYP2C19* normal metabolizers among prasugrel or ticagrelor-treated patients and switching them to clopidogrel, which is associated with a lower bleeding risk.

Trials Studying Genotyping after PCI

Multiple studies have assessed the efficacy and safety of a *CYP2C19* genotype-guided strategy in patients with atherosclerotic coronary artery disease (CAD) (**Figure 3 & 4, Supplementary Table S1**).[29–38] The TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased Clopidogrel Response After Percutaneous Coronary Intervention) trial, an international multicentre RCT involving 5,302 patients with both CCS (16%) and ACS (84%) undergoing PCI, stands as the largest trial conducted in this context. The primary goal was determining if point-of-care genotype-guided selection of P2Y12 inhibitor would reduce ischemic outcomes by 50% at one year in patients prescribed DAPT using an escalation strategy. A non-statistically significant 34% reduction in ischemic events at one year after PCI was seen in *CYP2C19* LOF allele carriers randomized to the genotype-guided arm [adjusted hazard ratio (HR) 0.66, p=0.056]. However, a nearly 80% reduction (HR 0.21; p=0.001) in ischemic events was seen in the first three months following PCI, highlighting the value of adequate antiplatelet therapy during this period.[37] A prespecified analysis highlighted a statistically significant 40% reduction in the total number of ischemic events per patient in those receiving genotype-guided P2Y12 inhibitor therapy (HR 0.60; p=0.011).[39] The higher use of ticagrelor in the genotype-guided arm did not result in an increase of the primary bleeding endpoint (TIMI major or minor bleeding, HR 1.22; 95% CI 0.60-2.51).

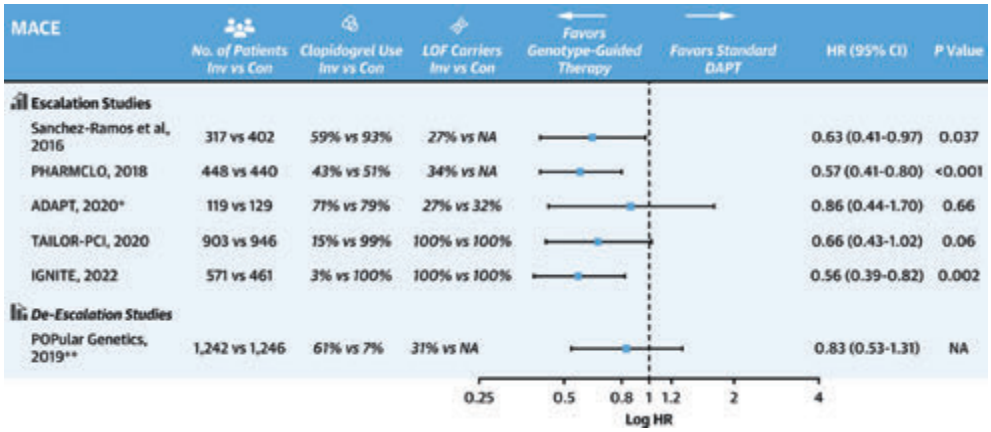


Figure 3. Forest plot of genotype guided de-escalation and escalation strategies vs. standard DAPT for MACE in patients with CAD.

This forest plot illustrates the impact of both genotype-guided de-escalation and genotype-guided escalation strategies on major adverse cardiovascular events (MACE) based on studies comparing a genotype-guided group with a group of patients treated with standard dual antiplatelet therapy (DAPT). To illustrate the uptake of the genotype-guided intervention, the columns in gray provide additional information on the use of clopidogrel and the distribution of *CYP2C19* loss-of-function (LOF) allele carriers in both groups if available. *The HR is based on the subgroup analysis in acute coronary syndrome patients only. **The P value was not provided in the publication. ADAPT = Assessment of Prospective *CYP2C19* Genotype Guided Dosing of Anti-Platelet Therapy in Percutaneous Coronary Intervention; Con = control arm; IGNITE = Implementing Genomics in Practice Network; Inv = intervention arm; PHARMCLO = Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes; TAILOR-PCI = Tailored Antiplatelet Initiation to Lessen Outcomes due to decreased Clopidogrel Response After Percutaneous Coronary Intervention.

In **Figure 3** we summarize the different studies that evaluated a genotype-guided treatment arm compared to a non-guided control arm.[30,35–37,40] A noticeable trend towards a decrease in ischemic events is evident in the genotype-guided arm, with varying effects depending on the utilization of alternative therapy in patients with LOF alleles. There is no evident increase in bleeding events, despite escalating antiplatelet therapy (**Figure 4**). However, it is important that none of these studies were powered to detect any differences in bleeding events.

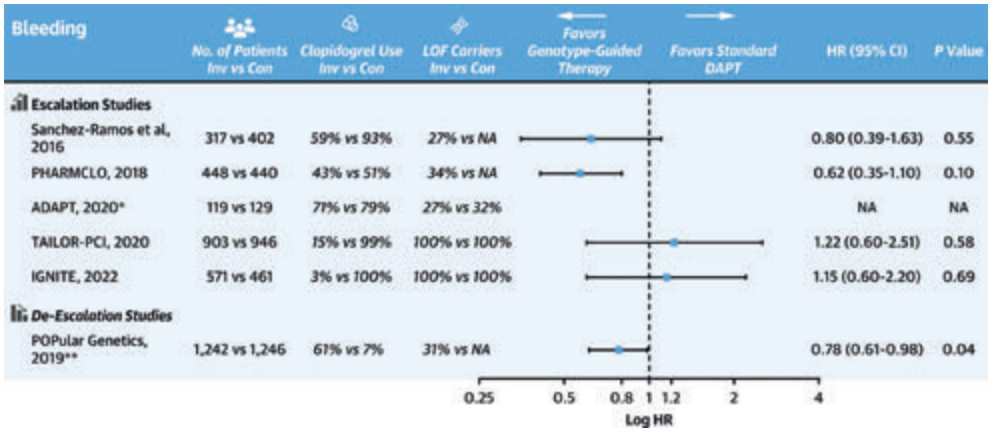


Figure 4. Forest plot of genotype guided de-escalation and escalation strategies vs. standard DAPT for bleeding outcomes in patients with CAD.

This forest plot illustrates the impact of both genotype-guided de-escalation and genotype-guided escalation strategies on nonmajor clinically relevant or major bleeding based on studies comparing a genotype-guided group with a group of patients treated with DAPT. To illustrate the uptake of the genotype-guided intervention, the columns in gray provide additional information on the use of clopidogrel and the distribution of *CYP2C19* LOF allele carriers in both groups if available. Abbreviations as in Figure 3.

POPular Genetics (Cost-effectiveness of *CYP2C19* genotype guided treatment with antiplatelet drugs in patients with ST-segment-elevation myocardial infarction undergoing immediate percutaneous coronary intervention with stent implantation: optimization of treatment), a non-inferiority RCT of PCI treated STEMI patients, is still the only large RCT assessing a de-escalation strategy. *CYP2C19* LOF carriers in the genotype-guided arm received ticagrelor or prasugrel and non-carriers received clopidogrel. Ticagrelor was given to the standard therapy group. Genotype guided therapy was non-inferior to standard therapy for the primary combined ischemic and bleeding outcome at one year. There were no significant differences when evaluating for ischemic outcomes separately, but there was a statistically significant reduction in major or minor bleeding outcomes in the genotype-guided group compared the standard therapy group at 12 months (HR 0.78, 95% CI 0.61–0.98), **Figure 3 and 4**).[38]

A meta-analysis comprised of seven RCTs and nearly 16,000 patients demonstrated a statistically significant 30% reduction in ischemic events in LOF patients treated with ticagrelor or prasugrel compared to clopidogrel.[41] There was no difference in outcomes in non-carriers when prescribed ticagrelor or prasugrel as compared to clopidogrel. The significant test for interaction strongly suggested that the reduction in ischemic events with ticagrelor or prasugrel is primarily attributable to the presence of the *CYP2C19* LOF genotype. Another meta-analysis highlighted that a precision medicine approach using genetic or platelet function testing, results not only in improved ischemic outcomes (major adverse cardiovascular events RR 0.78, p=0.015) but also a reduction in minor bleeding events (RR 0.78, p=0.003) in patients undergoing PCI.[42] These results were strengthened by a network meta-analysis, indicating

that among ACS patients, a guided selection of P2Y12 inhibitor therapy demonstrated the most favourable balance between safety and efficacy, surpassing routine potent P2Y12-inhibiting therapy.[43]

In patients undergoing PCI treated with oral anticoagulation (e.g., due to atrial fibrillation), clopidogrel is the P2Y12 inhibitor of choice. However, there is lack of evidence regarding the impact of *CYP2C19* allelic variants in these patients. Recently, the SWAP-AC2 (Tailoring P2Y12 Inhibiting Therapy in Patients Requiring Oral Anticoagulation After PCI) study showed that ticagrelor (at a 60 mg twice a day regimen) showed that ticagrelor (at a 60 mg bid regimen) reduced rates of HPR compared to clopidogrel, in patients treated with novel oral anticoagulants and impaired clopidogrel response as assessed by the ABCD-GENE (Age, Body Mass Index, Chronic Kidney Disease, Diabetes, and Genotyping) score.[44]

Cost Efficacy and other Considerations when Selecting P2Y12 inhibitor

In multiple studies, a genotype guided strategy has proven to be cost-effective compared to standard DAPT.[45–47] Clopidogrel therapy for a year costs around €22 in Europe (Dutch tariffs in 2023) and $59 in the United States (US tariffs in 2022), whereas prasugrel and ticagrelor are considerably more expensive at approximately €526 and €788 in the Netherlands and $117 and $4,865 in the US, respectively.[48,49] Notably, adherence with such expensive medications is worse, based on data from a large US national health insurer.[50] The point-of-care *CYP2C19* testing costs approximately €150 in Europe and $280 in the US. While universal testing adds to the upfront expense of a genotype guided strategy, the savings from prescribing less ticagrelor (in case of a de-escalation strategy) and reduced bleeding related costs is projected to offset the expense of the genotyping.

Aside from the expense, ticagrelor requires twice daily dosing compared to clopidogrel. Prasugrel requires special considerations prior to prescribing: (1) dose reduction to 5 mg/day in patients less than 60 kg and over age 75; (2) an absolute contraindication if prior TIA/stroke.[10] Unique side effects of ticagrelor, such as bradycardia and dyspnoea, are other considerations that can impact long term compliance.[51]

GUIDELINE RECOMMENDATIONS

Clinical guidelines vary regarding recommendations for *CYP2C19* testing and genotype-guided antiplatelet therapy (**Table 2)**.[17,52–55] The Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) provide evidence-based prescribing recommendations based on the assumption that genotype results are available. Both CPIC and the DPWG recommend the use of prasugrel or ticagrelor in *CYP2C19* IMs or PMs in the setting of ACS or in CCS after PCI.[17,52] Guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology

Table 2. Oversight of current guideline recommendations of genotype guided antithrombotic therapy

Guideline	Year published	Indication	Intermediate metabolizers	Poor metabolizers
U.S. FDA[53,a]	2020	Not specified	Consider use of another platelet P2Y12 inhibitor	Boxed Warning - Consider use of another platelet P2Y12 inhibitor
DPWG[52]	2019	PCI; Stroke or TIA; Other indications (PM only)	Choose an alternative P2Y12 inhibitor (or double the clopidogrel dose to 150 mg/day[b])	Avoid clopidogrel. Choose an alternative P2Y12 inhibitor
CPIC[17]	2022	ACS and/or PCI;	Avoid standard dose (75 mg) clopidogrel if possible. Use prasugrel or ticagrelor if no contraindications	Avoid clopidogrel if possible. Use prasugrel or ticagrelor if no contraindications
		PAD or stable CAD patients outside the setting of PCI	No recommendation	Avoid clopidogrel if possible. Use prasugrel or ticagrelor if no Contraindications-
		Neurovascular indications	Consider an alternative P2Y12 inhibitor (e.g., ticagrelor) if no contraindications	Avoid clopidogrel if possible. Consider an alternative P2Y12 inhibitor (e.g., ticagrelor) if no contraindications
ACC/AHA[54]	2011	PCI	Treatment with an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) may be considered	Treatment with an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) may be considered
			Normal, Rapid or Ultrarapid metabolizer	
ESC[55]	2020	NSTEMI / ACS	De-escalation of P2Y12 inhibitor treatment (e.g., switch from prasugrel or ticagrelor to clopidogrel), guided by *CYP2C19* genotyping, may be considered (Class IIb)	

[a] Similar information in the label is provided the by the European Medicines Agency, which is annotated on the Pharmacogenomics Knowledgebase website (https://www.pharmgkb.org/).

ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; CAD = coronary artery disease; CCS = chronic coronary syndrome; CPIC = Clinical Pharmacogenetics Implementation Consortium; DAPT = dual antiplatelet therapy; DPWG = Dutch Pharmacogenetics Working Group; ESC = European

Society of Cardiology; NSTEMI = non-ST-elevation myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PM = poor metabolizer; TIA = transient ischemic attack; U.S. FDA = United States Food & Drug Administration.

[b] In contrast to the 2019 DPWG recommendation, the CPIC 2022 guideline indicated that current evidence does not support a clopidogrel dose escalation strategy based on *CYP2C19* genotype. However, if clopidogrel cannot be avoided, tripling the clopidogrel maintenance dose (225 mg/day) could be considered as an alternative treatment option in IMs.

(ESC) acknowledge that prescribers can consider *CYP2C19* genotyping to guide P2Y12 inhibitor therapy in high-risk patients undergoing PCI.[54] The 2020 ESC guidelines for the management of non-ST-segment elevation ACS provides a Class IIb recommendation that (genotype-guided) de-escalation of P2Y12 inhibitor therapy (e.g., switch from prasugrel or ticagrelor to clopidogrel) may be considered as an alternative strategy for ACS patients deemed unsuitable for 12 months of prasugrel or ticagrelor.[55] Based on these recommendations and further supported by recent evidence, we have formulated three key recommendations regarding genotype guided antiplatelet therapy in **Table 3**.

Table 3. Key recommendations for *CYP2C19* genotype guided antiplatelet therapy

Key recommendations
Patients identified as *CYP2C19* intermediate or poor metabolizers should avoid using clopidogrel.
ACS patients with an indication for DAPT and treated with a more potent agent, prasugrel or ticagrelor, genotype guided de-escalation should be considered to reduce bleeding events, especially in patients identified as having a high bleeding risk.
CCS patients with an indication for DAPT and treated with clopidogrel, genotype guided escalation should be considered to reduce the risk of stent-thrombosis and recurrent ischemic events, especially in patients with a high ischemic risk.

ACS, acute coronary syndrome; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy.

Despite accumulating evidence, the more recent 2021 ACC/AHA/ coronary artery revascularization and 2023 ESC ACS guidelines, do not provide specific recommendations for *CYP2C19* genotype-guided antiplatelet therapy.[10,56] The 2023 ESC ACS guideline does offer recommendations on strategies to mitigate bleeding risk, including de-escalation to clopidogrel or shortening the DAPT duration to 1 or 3-6 months. Since genotype guided de-escalation and shorter DAPT strategies have not been directly compared in clinical trials, the most optimal approach remains unclear.

CLINICAL IMPLEMENTATION

Genotype-guided P2Y12 inhibitor selection

Although not widely adopted, *CYP2C19* genotyping to guide post-PCI antiplatelet therapy is one of the most common examples of genotype-guided drug therapy in clinical practice.[17,57] Strategies for implementing testing vary across sites in terms of the type of genotype assay used, genotype turnaround time, and which patients are selected for testing.[58]

Data from real-world practice adds to the body of evidence on the beneficial impact of *CYP2C19*-guided antiplatelet therapy. A study by the Implementing GeNomics In pracTicE (IGNITE) Network included 1,815 patients who underwent PCI and clinical *CYP2C19* testing across seven U.S. medical centers.[31] For patients with a LOF allele and without contraindications, alternative therapy (e.g., prasugrel or ticagrelor) was recommended. The study showed a lower incidence of MACE (defined as death, MI, or ischemic stroke) in the 12-month period following PCI among patients with a LOF allele treated with alternative therapy versus clopidogrel. A subsequent IGNITE Network study in an expanded cohort of patients (n=3,342) confirmed an increased risk for adverse cardiovascular events (defined as death, MI, ischemic stroke, stent thrombosis, or hospitalization for unstable angina) with clopidogrel in patients with a LOF allele (**Figure 3 and 4**).[40] In addition, the study showed no difference in risk for cardiovascular events with clopidogrel versus alternative therapy in patients without a LOF allele, in line with data from the POPular Genetics trial.[38,59]

Challenges with Implementation

There are several challenges with genotype-guided antiplatelet therapy. When bound to laboratory-based testing, results may not be available until after the patient is discharged following a PCI procedure. Most sites do not have on-site genetic testing facilities, so samples must be sent to external facilities for testing. Moreover, it is common that laboratory-based testing is not performed on a daily basis, further delaying the availability of test results. Therefore, observed turnaround times for laboratory-based testing, from hospital admission to receiving test results, range from two to five days or longer.[31,60,61] A post-discharge plan is crucial to adjust therapy if necessary, including follow-up calls and pharmacy notifications. However, this can be avoided by adopting point-of-care testing, for which the turnover time ranges between one to six hours.[36,61,62] If implemented adequately, studies have demonstrated that this can result in genetic results being available for 99% of patients prior to their discharge.[62] Another viable approach is to utilize both laboratory-based and point-of-care testing, reserving point-of-care testing for patients expected to be discharged early.[61] Additionally, point-of-care testing is the preferred option in escalation strategies where patients are initially treated with clopidogrel and face prolonged risk if turnaround times are longer.

A second challenge is that besides genetics, the interindividual variable response to clopidogrel is also attributed to other factors, such as age, diabetes, Body Mass Index and kidney function. The ABCD-GENE score integrates these variables with the *CYP2C19* genotype, providing a straightforward method to identify patients at increased risk for HPR and adverse ischemic events.[63] While a simple genotype

guided treatment algorithm is most practical, physicians should always consider patients' characteristics (bleeding vs. ischemic risk) and technical aspects of interventions as well. Ideally, genetic results should be incorporated into a case-specific assessment of antiplatelet therapy, including bleeding/ischemic risk, clinical setting and complexity of intervention.

Another challenge is that a mechanism is needed to ensure that physicians remain aware of the genotype results so that clopidogrel is not inadvertently prescribed to a LOF allele carrier in the post-PCI follow-up period. Most sites address this by providing decision support that automatically alerts the prescriber through the Electronic Health Record (EHR) about patients that carry a LOF allele in response to a clopidogrel order.[58] Conversely, automatic alerts could notify prescribers if patients treated with ticagrelor or prasugrel are normal metabolisers for clopidogrel.

Additional challenges include, unknown insurance coverage for ticagrelor/prasugrel, which may delay transitioning therapy from clopidogrel in patients with a LOF allele while the provider or staff works to contact insurance companies and uncertain reimbursement for genotyping; this may burden hospitals or patients with additional costs. Hence, it is essential to initiate communication with insurance companies and the hospital's financial department, to discuss coverage of the genetic testing expenses.

When to Adapt a *CYP2C19* Genotype Guided Strategy

In most (implementation) studies, a genotype guided strategy was adopted in an all-comers population. Because clopidogrel has a safer bleeding profile, a de-escalation strategy may be the most advantageous for patients with a high bleeding risk (HBR).[64] An escalation strategy may offer the greatest benefits for those with a high ischemic risk without HBR, such as patients undergoing complex PCI. Complex PCIs often increases the thrombotic risk due to long segment or multivessel stenting, two stent bifurcation techniques or stent to last patent vessel. The ESC-guidelines provide a list of technical aspects, comorbidities and patient characteristics that enhance a patient's thrombotic risk, that can help identify patients at high ischemic risk. It should be considered to expand this list with carriage of a *CYP2C19* LOF allele, in case of treatment with clopidogrel.[41,65] Throughout, careful assessment weighing both the ischemic and bleeding risk is crucial when determining the best antiplatelet strategy.[66]

FUTURE DIRECTIONS

With the abundance of pharmacokinetic, pharmacodynamic, and clinical data indicating reduced effectiveness of clopidogrel in patients with a *CYP2C19* LOF-allele, one might expect routine genotype testing to be standard practice. Yet, it is not. Within cardiology, and especially in patients with ACS, the results from the POPular Genetics do support a genotype-guided de-escalation strategy for reducing bleeding risk. However, since the POPular Genetics was not powered for non-inferiority regarding ischemic events, patient-level meta-analyses incorporating future trials may be needed to overcome this limitation. Given strong and consistent evidence of reduced clopidogrel effectiveness in patients with a LoF allele, including from large meta-analyses, and observational data of improved outcomes with genotype-guided therapy, providers will need to consider whether additional randomized controlled trial data are truly needed to support a genotype-guided escalation strategy. The ongoing trials (**Table 4**) do not fully address these issues, but will definitely provide relevant insights into the value of genotype-guided antiplatelet treatment.

The growing understanding of pharmacogenetics is fuelling technological advancements, such as point-of-care and panel testing, thus expanding its accessibility.[67] The first steps toward implementing pre-emptive testing have been made.[8] Decreasing panel-testing costs could facilitate a broader adoption in clinical practice, potentially allowing for prior knowledge of a patient's genetic profile before an ACS event occurs.[68] This would bypass the limitations of on-site test facilities and enable the immediate prescription of the most suitable medication for each patient based on genotype results, eliminating the need for subsequent adjustments, not only for antiplatelet drugs but also for, for example, statins or beta-blockers.[4] Since this is not yet the case, implementing a single genetic test, preferably using point-of-care testing, is the fastest and most practical way to apply genetic testing in the clinical practice.

Finally, studies assessing genotype-guided strategies have predominantly involved European and East Asian populations, exposing a lack of racial and ethnic diversity that warrants attention in future research.

Table 4. Ongoing studies on genotype guided antithrombotic therapy

Study Name	NCT-number	Design	Sample size	Study population and design	Intervention	Control	Estimated completion date
GUARANTEE	NCT03783351	RCT	4,009	*CYP2C19* genotype-guided vs. standard antiplatelet therapy among PCI patients (both ACS and CCS)	DAPT with ticagrelor 90mg bid in LOF carriers, clopidogrel 75mg od in noncarriers	DAPT with clopidogrel 75mg od or ticagrelor 90mg bid based on clinical presentation	January, 2023
POPular Strategy PD	NCT05773989	RCT	88	*CYP2C19* genotype-guided P2Y12 inhibitor monotherapy vs. standard DAPT in CCS patients undergoing PCI.	Ticagrelor 90mg bid or prasugrel 10mg od monotherapy in LOF carriers, clopidogrel 75mg od monotherapy in noncarriers for 6 months	DAPT with clopidogrel 75mg od for 6 months	May, 2025
Mosley et al.	NCT04090281	Single Group Assignment	200	Implementation study of *CYP2C19* genotype and PFT guided antiplatelet therapy in ACS patients.	DAPT with prasugrel 10mg od for 12 months in LOF carriers, clopidogrel 75mg od in noncarriers with further de-escalation based on PFT after 14 days	-	November, 2023
Dan-DAPT	NCT05262803	RCT	2,808	*CYP2C19* genotype guided therapy (both 3 or 6 months) vs. standard DAPT of 6 months in HBR patients	Standard arm: DAPT with ticagrelor 90mg bid/ prasugrel 10mg od in LOF carriers, clopidogrel 75mg od in noncarriers, both for 6 months Short arm: DAPT with ticagrelor 90mg bid/ prasugrel 10mg od in LOF carriers, clopidogrel 75mg od in noncarriers, both for 3 months	DAPT with prasugrel 10mg od /ticagrelor 90mg bid for 6 months	December 2025

Table 4. Continued

Duconge et al.	NCT03419325	Non-randomized	150	*CYP2C19* genotype and PFT guided antiplatelet therapy in patients treated with clopidogrel (CAD/stroke/PAD)	DAPT with ticagrelor 90mg bid/prasugrel 10mg od in patients with HPR or LOF carriers, clopidogrel 75mg od in noncarriers, both for 6 months	-	December, 2023
POPular GUIDE PCI	NCT03823547	Registry	2500	*CYP2C19* genotype guided P2Y12 inhibitor therapy vs. an earlier cohort treated with standard DAPT	DAPT with ticagrelor 90mg bid/prasugrel 10mg od in LOF carriers, clopidogrel 75mg od in noncarriers	DAPT with ticagrelor 90mg bid/prasugrel	December, 2025
ADEN	NCT05577988	RCT	2468	*CYP2C19* genotype guided single antiplatelet therapy in HBR patients one month after ACS	Single APT with aspirin in LOF carriers. Single APT with clopidogrel 75mg od in noncarriers	Single APT with ticagrelor 90mg bid or prasugrel 10mg od	January, 2026

ADEN = Assessment of an Early De-Escalation to a Low-potency Single Antiplatelet Therapy Guided by Genetics Versus a Systematic High-Potency Single Antiplatelet Therapy to Neutralize Bleeding Complications in Patients With High Bleeding Risk Beyond One Month After an Acute Coronary Syndrome; DAN-DAPT = Reduced Antithrombotic Strategy for High Bleeding Risk Patients With Myocardial Infarction; GUARANTEE = Genotyping GUided Antiplatelet theRapy in pAtieNts Treated With Drug Eluting stEnts; APT = antiplatelet therapy; OAC = oral anticoagulation; PFT = platelet function testing; POPular Strategy PD = Pharmacodynamic Outcomes in patients with coronary artery disease undergoing Percutaneous coronary intervention treated with an individualized treatment STRATEGY; other abbreviations as in Tables 1 to 3.

CONCLUSION

At present, genotype-guided antiplatelet therapy is not a standard recommendation in the guidelines due to the perceived absence of adequately powered trials. Nonetheless, based on pharmacological studies and according to numerous RCTs, registries, and meta-analyses, implementing a genotype-guided strategy can indeed offer substantial benefits, particularly in certain patient subgroups. In terms of escalation, these scenarios may involve situations where the risk of thrombosis surpasses the risk of bleeding. As for de-escalation strategies, this encompasses scenarios where patients have an elevated bleeding risk. Thus, when adopting genotype guided antiplatelet therapy, the patient should be central, taking into consideration various clinical, angiographic, and procedural variables before opting for a specific strategy. Ultimately, as evidence on genotype guided therapy continues to increase, with ongoing trials probably further refining the existing evidence, a personalized antiplatelet therapy could become part of the standard of care in patients undergoing PCI in the future.

REFERENCES

1. Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant to the clinical geneticist? Clin Genet [Internet]. 1999 Oct;56(4):247–58.
2. Marín F, González-Conejero R, Capranzano P, Bass TA, Roldán V, Angiolillo DJ. Pharmacogenetics in Cardiovascular Antithrombotic Therapy. J Am Coll Cardiol [Internet]. 2009 Sep;54(12):1041–57.
3. Steen DL, Khan I, Andrade K, Koumas A, Giugliano RP. Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population Representing 239 234 Patients During 2005 to 2018 in the United States. J Am Heart Assoc [Internet]. 2022 May 3;11(9):e022198.
4. Magavern EF, Kaski JC, Turner RM, Drexel H, Janmohamed A, Scourfield A, et al. The role of pharmacogenomics in contemporary cardiovascular therapy: a position statement from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. Eur Hear J - Cardiovasc Pharmacother [Internet]. 2022 Jan 5;8(1):85–99.
5. Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schömig A, et al. Periprocedural Bleeding and 1-Year Outcome After Percutaneous Coronary Interventions. J Am Coll Cardiol. 2008 Feb;51(7):690–7.
6. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J [Internet]. 2016 Nov 13;38(11):804–10.
7. van der Sangen NMR, Rozemeijer R, Chan Pin Yin DRPP, Valgimigli M, Windecker S, James SK, et al. Patient-tailored antithrombotic therapy following percutaneous coronary intervention. Eur Heart J [Internet]. 2021 Mar 7;42(10):1038–46.
8. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. Lancet [Internet]. 2023 Feb;401(10374):347–56.
9. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-thoracic Surg. 2017;53(1):34–78.
10. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Aug;
11. Knuuti J, Wijns W, Flachskampf FA, Gohlke H, Grove EL, James S, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Vol. 41, European Heart Journal. 2020. p. 407–77.
12. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. J Am Coll Cardiol. 2016 Sep;68(10):1116–39.
13. Gurbel PA, Rout A, Tantry US. Pharmacogenetic considerations in antiplatelet therapy. Expert Rev Precis Med Drug Dev [Internet]. 2020 Jul 3;5(4):235–8.
14. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. Drug Metab Dispos. 2010;38(9):1514–21.

15. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation [Internet]. 2009 May 19;119(19):2553–60.
16. Lee CR, Thomas CD, Beitelshees AL, Tuteja S, Empey PE, Lee JC, et al. Impact of the CYP2C19*17 Allele on Outcomes in Patients Receiving Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. Clin Pharmacol Ther. 2021 Mar;109(3):705–15.
17. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. Clin Pharmacol Ther [Internet]. 2022 Feb 8;
18. Fricke-Galindo I, Céspedes-Garro C, Rodrigues-Soares F, Naranjo MEG, Delgado Á, de Andrés F, et al. Interethnic variation of CYP2C19 alleles, 'predicted' phenotypes and 'measured' metabolic phenotypes across world populations. Pharmacogenomics J [Internet]. 2016 Apr 27;16(2):113–23.
19. Nguyen AB, Cavallari LH, Rossi JS, Stouffer GA, Lee CR. Evaluation of race and ethnicity disparities in outcome studies of CYP2C19 genotype-guided antiplatelet therapy. Front Cardiovasc Med. 2022 Aug;9.
20. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: A meta-analysis. JAMA - J Am Med Assoc. 2010;304(16):1821–30.
21. Mega JL, Hochholzer W, Frelinger AL, Kluk MJ, Angiolillo DJ, Kereiakes DJ, et al. Dosing Clopidogrel Based on CYP2C19 Genotype and the Effect on Platelet Reactivity in Patients With Stable Cardiovascular Disease. JAMA. 2011 Nov;306(20).
22. Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, et al. Cytochrome P450 2C19 681G>A Polymorphism and High On-Clopidogrel Platelet Reactivity Associated With Adverse 1-Year Clinical Outcome of Elective Percutaneous Coronary Intervention With Drug-Eluting or Bare-Metal Stents. J Am Coll Cardiol. 2008 May 20;51(20):1925–34.
23. Collet JP, Hulot JS, Pena A, Villard E, Esteve JB, Silvain J, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet (London, England). 2009 Jan;373(9660):309–17.
24. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2007;357(20):2001–15.
25. 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):1045–57.
26. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, et al. Defining Strategies of Modulation of Antiplatelet Therapy in Patients With Coronary Artery Disease: A Consensus Document from the Academic Research Consortium. Circulation. 2023 Jun;147(25):1933–44.
27. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2015;66(9):1036–45.
28. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, et al. Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents. JACC Cardiovasc Interv [Internet]. 2013 Dec;6(12):1267–74.

29. Deiman BALMLM, Tonino PALL, Kouhestani K, Schrover CEMM, Scharnhorst V, Dekker LRCC, et al. Reduced number of cardiovascular events and increased cost-effectiveness by genotype-guided antiplatelet therapy in patients undergoing percutaneous coronary interventions in the Netherlands. Netherlands Hear J [Internet]. 2016 Oct 29;24(10):589–99.
30. 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 [Internet]. 2016 Dec 15;225:289–95.
31. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D, et al. Multisite Investigation of Outcomes With Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2018;11(2):181–91.
32. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet (London, England) [Internet]. 2012 May 5;379(9827):1705–11.
33. Xie X, Ma YT, Yang YN, Li XM, Zheng YY, Ma X, et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. Int J Cardiol [Internet]. 2013 Oct 9;168(4):3736–40.
34. Shen DL, Wang B, Bai J, Han Q, Liu C, Huang XH, et al. Clinical Value of CYP2C19 Genetic Testing for Guiding the Antiplatelet Therapy in a Chinese Population. J Cardiovasc Pharmacol [Internet]. 2016 Mar;67(3):232–6.
35. 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 [Internet]. 2018;71(17):1869–77.
36. Tuteja S, Glick H, Matthai W, Nachamkin I, Nathan A, Monono K, et al. Prospective CYP2C19 Genotyping to Guide Antiplatelet Therapy Following Percutaneous Coronary Intervention: A Pragmatic Randomized Clinical Trial. Circ Genomic Precis Med [Internet]. 2020;13(1):e002640.
37. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes after Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA - J Am Med Assoc. 2020;324(8):761–71.
38. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Van't Hof AWJ, Van Der Harst P, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med. 2019;381(17):1621–31.
39. Ingraham B, Farkoud M, Lennon R, So D, Goodman S, Geller N, et al. Genetic-Guided Oral P2Y12 Inhibitor Selection and Cumulative Ischemic Events After Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2023;
40. Beitelshees AL, Thomas CD, Empey PE, Stouffer GA, Angiolillo DJ, Franchi F, et al. CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention in Diverse Clinical Settings. J Am Heart Assoc [Internet]. 2022 Feb 15 [cited 2022 Mar 14];11(4):e024159.
41. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, et al. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy: A Meta-Analysis. JACC Cardiovasc Interv. 2021;14(7):739–50.

42. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. Lancet [Internet]. 2021 Apr;397(10283):1470–83.
43. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J [Internet]. 2022 Mar 7;43(10):959–67.
44. Ortega-Paz L, Bor W, Franchi F, van de Broek WWA, Rollini F, Giordano S, et al. P2Y12 Inhibition in Patients Requiring Oral Anticoagulation after Percutaneous Coronary Intervention: The SWAP-AC–2 Study. JACC Cardiovasc Interv [Internet]. 2024 Apr;
45. Claassens DMF, van Dorst PWM, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, et al. Cost Effectiveness of a CYP2C19 Genotype-Guided Strategy in Patients with Acute Myocardial Infarction: Results from the POPular Genetics Trial. Am J Cardiovasc Drugs. 2021;
46. Limdi NA, Cavallari LH, Lee CR, Hillegass WB, Holmes AM, Skaar TC, 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(5):724–35.
47. 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;11(1).
48. van den Broek WWA, van Paassen JG, Gimbel ME, Deneer VHM, ten Berg JM, Vreman RA. Cost-effectiveness of clopidogrel versus ticagrelor in patients of 70 years or older with non-ST-elevation acute coronary syndrome. Eur Hear J - Cardiovasc Pharmacother [Internet]. 2022 Jun 20;
49. Ingraham B, Pereira NL. Role For Genotype Testing to Guide Antiplatelet Selection After Percutaneous Coronary Intervention. 2022.
50. Dayoub EJ, Seigerman M, Tuteja S, Kobayashi T, Kolansky DM, Giri J, et al. Trends in Platelet Adenosine Diphosphate P2Y 12 Receptor Inhibitor Use and Adherence Among Antiplatelet-Naive Patients After Percutaneous Coronary Intervention, 2008-2016. JAMA Intern Med. 2018 Jul;178(7):943.
51. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: A genetic substudy of the PLATO trial. Lancet. 2010;376(9749):1320–8.
52. PharmGKB. Annotation of CPIC Guideline for clopidogrel and CYP2C19. 2011.
53. FDA. Table of Pharmacogenetic Associations. 2022.
54. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. Circulation. 2011 Dec;124(23).
55. Collet JP, 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. Eur Heart J [Internet]. 2020 Apr 7;42(14):1289–367.
56. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 Jan;145(3).

57. Luzum JA, Pakyz RE, Elsey AR, Haidar CE, Peterson JF, Whirl-Carrillo M, et al. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: Outcomes and Metrics of Pharmacogenetic Implementations Across Diverse Healthcare Systems. Clin Pharmacol Ther. 2017 Sep;102(3):502–10.
58. Empey PE, Stevenson JM, Tuteja S, Weitzel KW, Angiolillo DJ, Beitelshees AL, et al. Multisite Investigation of Strategies for the Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy. Clin Pharmacol Ther. 2018 Oct;104(4):664–74.
59. Claassens DMF, Bergmeijer TO, Vos GJA, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to CYP2C19 Genotype: A POPular Genetics Subanalysis. Circ Cardiovasc Interv. 2021 Apr;14(4):e009434.
60. Hulot JS, Chevalier B, Belle L, Cayla G, Khalife K, Funck F, et al. Routine CYP2C19 Genotyping to Adjust Thienopyridine Treatment After Primary PCI for STEMI. JACC Cardiovasc Interv. 2020 Mar;13(5):621–30.
61. Azzahhafi J, Broek WWA va. den, Chan Pin Yin DRPP, Harmsze AM, van Schaik RHN, Ten Berg JM. The Clinical Implementation of CYP2C19 Genotyping in Patients with an Acute Coronary Syndrome: Insights From the FORCE-ACS Registry. J Cardiovasc Pharmacol Ther. 2023 Jan;28.
62. Cavallari LH, Franchi F, Rollini F, Been L, Rivas A, Agarwal M, et al. Clinical implementation of rapid CYP2C19 genotyping to guide antiplatelet therapy after percutaneous coronary intervention. J Transl Med. 2018 Dec;16(1):92.
63. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, ten Berg JM, et al. Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC Cardiovasc Interv. 2020;13(5):606–17.
64. Singh M. Bleeding Avoidance Strategies During Percutaneous Coronary Interventions. J Am Coll Cardiol. 2015 May;65(20):2225–38.
65. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med. 2009;360(4):354–62.
66. Fei Y, Lam CK, Cheung BMY. Efficacy and safety of newer P2Y12 inhibitors for acute coronary syndrome: a network meta-analysis. Sci Rep. 2020 Oct;10(1):16794.
67. Rodríguez Vicente AE, Herrero Cervera MJ, Bernal ML, Rojas L, Peiró AM. Personalized medicine into health national services: barriers and potentialities. Drug Metab Pers Ther. 2018 Dec;33(4):159–63.
68. Zhou Y, Koutsilieri S, Eliasson E, Lauschke VM. A paradigm shift in pharmacogenomics: From candidate polymorphisms to comprehensive sequencing. Basic Clin Pharmacol Toxicol. 2022 Dec;131(6):452–64.

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

CHAPTER 4

Is there a benefit for CYP2C19 genotype guided antiplatelet treatment in elderly acute coronary syndrome patients?

W.W.A. van den Broek, J.M. ten Berg

Pharmacogenomics, 22(12), 727–730

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is still the cornerstone for secondary prevention of thrombotic events in patients with an acute coronary syndrome (ACS).[1,2] Since the publication of the TRITON-TIMI 38 trial and the PLATO trial, guidelines recommend the use of ticagrelor or prasugrel over clopidogrel, as ticagrelor and prasugrel showed superiority in reducing cardiovascular death, myocardial infarction (MI) and stroke. However, ticagrelor and prasugrel are more potent platelet inhibitors, making patients treated with ticagrelor or prasugrel more at risk for bleeding compared to patients treated with clopidogrel. [3,4] In patients after percutaneous coronary intervention (PCI) the risk of bleeding and thrombotic events rises with increasing age, though it seems that the risk of bleeding is more related to age than the risk of thrombosis , as age was a significant independent predictor of bleeding, but not of ischemic events.[5] In addition, in older patients there is a higher prevalence of co-morbidities, a lower rate of revascularization and a higher rate of early discontinuation of antiplatelet therapy, especially of ticagrelor. As a result their treatment is often complex and not optimal. The current guidelines do not provide clear guidance in how to treat the elderly population. There are no recommendations based on age, except the recommendation that the dose of prasugrel should be 5mg in patients aged above 75 years.[1,2] Although elderly may be at higher risk of bleeding and could profit of de-escalation of antiplatelet therapy it is important to keep in mind that in cardiovascular conditions a risk-treatment paradox has been described, which is a situation in which patients at high risk for adverse events receive less intensive treatment or less optimal guideline-recommended care than patients at lower risk.[6] With an increasing proportion of ACS patients being of older age, the optimal choice of antithrombotic therapy in elderly patients is a growing challenge and requires thorough contemplation.

Adjustment of antiplatelet therapy by changing P2Y12 inhibitor therapy can be done in different ways: unguided, guided by platelet function testing or guided by *CYP2C19* genotype. The POPular AGE trial showed that unguided de-escalation of ticagrelor to clopidogrel in elderly (>75 years) with non-ST elevation acute coronary syndrome (NSTE-ACS) is a favorable alternative to ticagrelor, leading to fewer bleeding events without an increase in the combined endpoint of all-cause death, MI, stroke, and bleeding.[7] Guided adjustment using platelet function testing (PFT) to adjust antiplatelet therapy was not associated with improved outcomes in elderly ACS patients, as established in the ANTARTIC-trial.[8] In the TROPICAL-ACS a guided de-escalation strategy using PFT was non-inferior to standard treatment in ACS patients managed with PCI, though a sub-analysis showed that the treatment effect was age dependent. In patients younger than 70 years there was a significant reduction in net clinical benefit, while this was not the case in the elderly patients.[9] The question is if *CYP2C19* genotype guided antithrombotic therapy has an additional beneficial effect on outcomes in elderly patients with coronary artery disease in addition to unguided de-escalation to clopidogrel as seen in the POPular AGE trial.

Clopidogrel is a prodrug that has to be transformed to its active metabolite by hepatic cytochrome P450 enzymes, of which *CYP2C19* is the most important. Carriers of *CYP2C19* loss-of-function (LOF) alleles have decreased enzyme function and will create less active metabolite after ingestion of clopidogrel. These patients have lower rates of platelet inhibition as measured with platelet function tests and are at higher risk for developing thrombotic events after PCI. In the POPular GENETICS trial a genotype-guide strategy for selection of oral P2Y12 inhibitor was found to be non-inferior to standard treatment

with ticagrelor or prasugrel with respect to ischemic events, while bleeding events were lower.[10] It is a reasonable hypothesis that also in elderly patients *CYP2C19* genotype influences the balance between benefit and harm when the more potent P2Y12 inhibitors are prescribed in comparison to clopidogrel.

In a pre-specified sub-analysis, containing ACS patients aged 70 years and older derived from the POPular AGE and POPular Genetics trial, the use of clopidogrel in noncarries of *CYPC2C19* LOF-alleles was compared with ticagrelor, irrespective of *CYPC2C19* genotype.[11] The sample size of this analysis depended on the number of patients of 70 years and older included in both trials in whom *CYP2C19* genotype was available, and was therefore not prospectively powered. Of the 1084 patients in this trial (536 patients from the POPular Age trial and 548 patients from the POPular Genetics trial), 590 patients were treated with ticagrelor, 401 noncarriers of LOF-alleles were treated with clopidogrel and 82 carriers of LOF-alleles were treated with clopidogrel. There was no statistically significant difference in net clinical benefit outcome (all-cause death, MI, stroke and PLATO major bleeding) between the patients treated with ticagrelor and the noncarriers of LOF-alleles treated with clopidogrel (17.2% vs. 15.1%, adjusted hazard ratio (adjHR) 1.05, 95%CI 0.77 – 1.44). Also no statistically significant difference was found in the thrombotic (cardiovascular death, MI and stroke) (9.7% vs. 9.2%, adjHR 1.00, 95%CI 0.66 – 1.50) and bleeding outcome (PLATO major and minor bleeding) (17.7% vs. 19.8%, adjHR 0.83, 95%CI 0.62 – 1.12). There were no significant differences in any of these outcomes between the clopidogrel treated noncarriers group and the small clopidogrel treated carriers of loss-of-function alleles group. The numerically lower number of bleeding events, though not statically significant, in the clopidogrel treated patients without a *CYP2C19* LOF-allele combined with a comparable thrombotic event rate can still be interpreted as clinically relevant. Given that the analysis was not prospectively powered, the hypothesized beneficial effect of clopidogrel in noncarriers of a *CYP2C19* LOF-allele may not be reflected in the results, due to the lack of power of the sample size. In conclusion, this analysis suggests that genotyping can be of additional value for clinical decision making in the vulnerable and difficult to treat elderly ACS patients. Testing the *CYP2C19* genotype can provide additional support for prescribing clopidogrel in elderly ACS patients who would otherwise receive ticagrelor. This would also have a beneficial effect on treatment adherence and health care costs.

This said, barring the use of genotyping, the evidence of clopidogrel versus ticagrelor in elderly ACS patients is conflicting. In the elderly subgroup of the PLATO trial (n=2878), ticagrelor use reduced ischemic events, without increasing bleeding events, though fatal bleeding and non-CABG major bleeding were higher in the elderly treated with ticagrelor.[12] The Bremen STEMI Registry (n = 1087 STEMI patients treated with PCI aged 75 years and older) also showed a beneficial effect of ticagrelor compared to clopidogrel on major adverse cardiac and cerebrovascular events without an increase in bleeding events.[13] The national SWEDEHEART registry, reporting 1-year clinical outcomes of ticagrelor versus clopidogrel in elderly MI patients of 80 years and older, found contrasting results, showing no significant reduction in the combined ischemic end point or in net clinical events, though the risk for readmission for bleeding increased with 48% with ticagrelor compared with clopidogrel.[14] The POPular AGE, as the only randomized clinical trial performed specifically in elderly ACS patients comparing ticagrelor with

clopidogrel, provides clarity in this debate, showing that clopidogrel compared to ticagrelor leads to fewer bleeding events without an increase in thrombotic outcomes.[7]

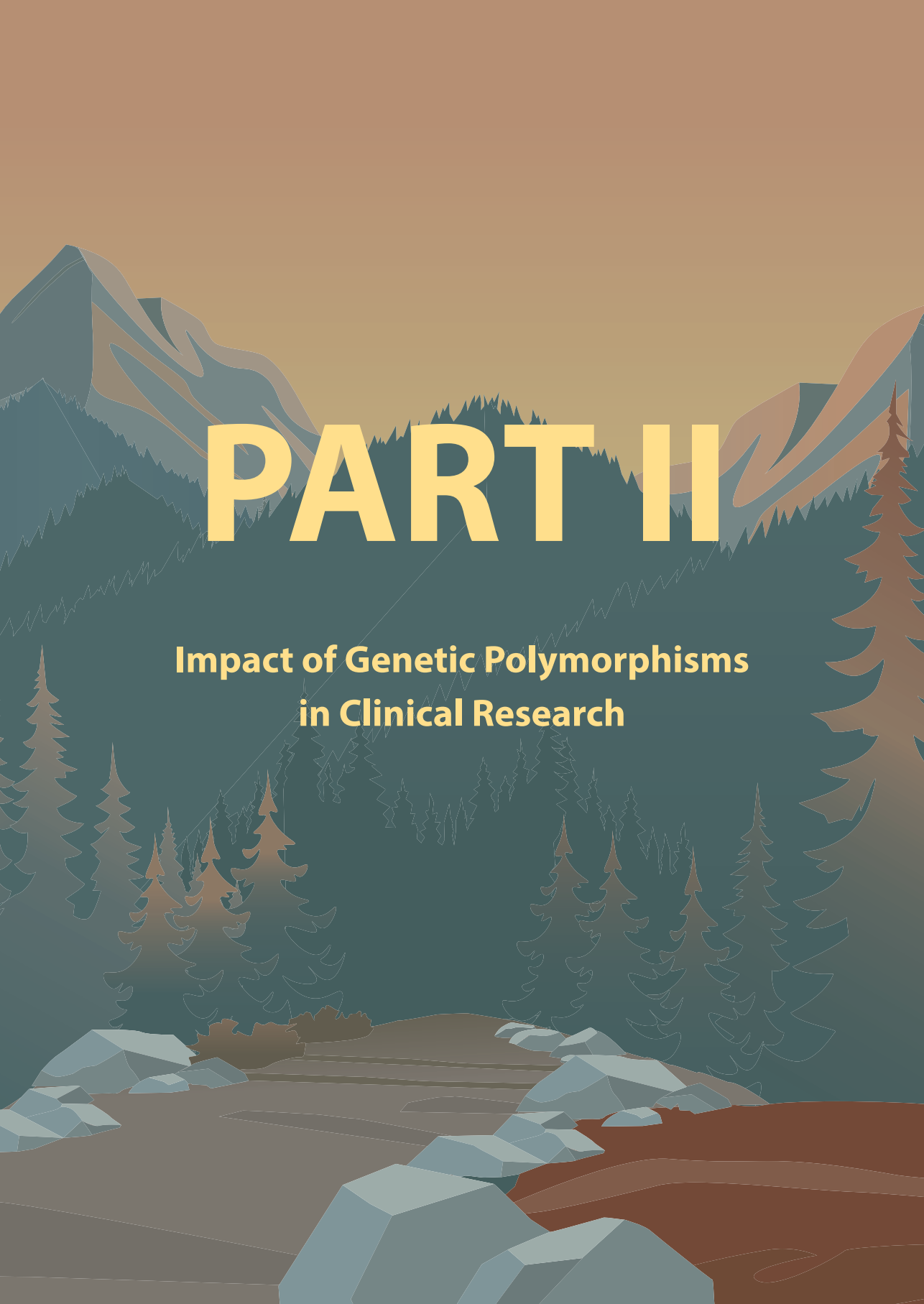
The question remains if *CYP2C19* guided antiplatelet therapy, on top of the results of the POPular AGE, is beneficial in elderly patients. A recent meta-analysis analyzed the effect of *CYP2C19* genotype on treatment outcomes with ticagrelor or prasugrel compared to clopidogrel in patients with coronary artery disease (CAD) undergoing PCI.[15] In total 15949 patients were collected from 7 randomized controlled trials (mean age 62, 77% treated with PCI and 98% presented with an ACS). In patients who carried a *CYP2C19* LOF allele treatment with ticagrelor compared to clopidogrel resulted in a significant reduction of ischemic events (7.0% vs. 10.3%; RR 0.70; 95% CI, 0.59-0.83), whereas no treatment difference was shown in patients who did not carry a *CYPC219* LOF allele (8.8% vs. 9.2%; RR 1.00; 95% CI 0.80-1.2). The test of interaction based on *CYP2C19* genotype status was statistically significant, suggesting that this difference in treatment effect was due to the presence of a *CYP2C19* LOF allele. The authors concluded that these results support genetic testing prior to prescribing P2Y12 inhibitor therapy. Unfortunately, no sub-analysis in elderly patients was performed.

It has to be said that *CYP2C19* genotypes explain only a fraction of the pharmacodynamic response to clopidogrel. In addition to *CYP2C19* genotype status, age, body mass index, kidney function and the presence of diabetes mellitus (DM) also have a contributing role on platelet inhibition by clopidogrel.[16] As stated earlier, comorbidities, like chronic kidney disease and DM, are more common in the elderly ACS patients. It is quite possible that a risk stratification based on, not only genotype, but also clinical variables, is the best way to select the most optimal P2Y12 inhibitor treatment in the elderly population. All things considered it seems very reasonable that in elderly ACS patients, who have increasing risk of bleeding, a de-escalation therapy switching from ticagrelor to clopidogrel using genotyping is beneficial.

REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-thoracic Surg. 2017;53(1):34–78.
2. Collet JP, 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. Eur Heart J [Internet]. 2020 Apr 7;42(14):1289–367.
3. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. TRITON-TIMI 38: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20).
4. 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):1045–57.
5. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SLT, Gershlick AH, Cohen DJ, et al. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention Original Investigation. JAMA [Internet]. 2016;315(16):1735–49.
6. Saar A, Marandi T, Ainla T, Fischer K, Blöndal M, Eha J. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. Int J Cardiol [Internet]. 2018 Dec 1;272:26–32.
7. Gimbel ME, Tavenier AH, Bor W, Hermanides RS, de Vrey E, Heestermans T, et al. Ticagrelor Versus Clopidogrel in Older Patients with NSTE-ACS Using Oral Anticoagulation: A Sub-Analysis of the POPular Age Trial. J Clin Med. 2020;9(10).
8. Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet. 2016;388(10055).
9. Sibbing D, Gross L, Trenk D, Jacobshagen C, Geisler T, Hadamitzky M, et al. Age and outcomes following guided de-escalation of antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: results from the randomized TROPICAL-ACS trial.
10. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. N Engl J Med. 2019;381(17):1621–31.
11. Claassens DMF, Gimbel ME, Bergmeijer TO, Vos GJA, Hermanides RS, van der Harst P, et al. Clopidogrel in noncarriers of CYP2C19 loss-of-function alleles versus ticagrelor in elderly patients with acute coronary syndrome: A pre-specified sub analysis from the POPular Genetics and POPular Age trials CYP2C19 alleles in elderly patients. Int J Cardiol. 2021;334:10–7.
12. Husted S, James S, Becker RC, Horrow J, Katus H, Storey RF, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: A substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes. 2012;5(5):680–8.
13. Schmucker J, Fach A, Luis ; *, Marin AM, Retzlaff T, Osteresch R, et al. Efficacy and Safety of Ticagrelor in Comparison to Clopidogrel in Elderly Patients With ST-Segment-Elevation Myocardial Infarctions.

14. Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, et al. Comparison between Ticagrelor and Clopidogrel in Elderly Patients with an Acute Coronary Syndrome: Insights from the SWEDEHEART Registry. Circulation. 2020;1700–8.
15. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, et al. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy: A Meta-Analysis. JACC Cardiovasc Interv. 2021;14(7):739–50.
16. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, ten Berg JM, et al. Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC Cardiovasc Interv. 2020;13(5):606–17.



PART II

Impact of Genetic Polymorphisms in Clinical Research

CHAPTER 5

CYP2C9 Polymorphisms and the Risk of Cardiovascular Events in Patients Treated with Clopidogrel: Combined Data from the POPular Genetics and POPular AGE Trials

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ABSTRACT

Background

The cytochrome P450 (CYP) 2C9 enzyme plays a role in the metabolization of clopidogrel. Carriage of a *CYP2C9* loss-of-function (LoF) allele has been associated with attenuated pharmacokinetics, leading to a diminished pharmacodynamic response and increased risk for developing stent thrombosis in patients treated with clopidogrel.

Methods

In this study, we aimed to determine the effect of the *CYP2C9*2* and **3* LoF alleles on thrombotic events. Therefore, a post hoc analysis was performed in 878 patients with available CYP2C9 genotype status included in the POPular Genetics and POPular Age trials, which enrolled patients with ST-elevation myocardial infarction and non-ST-elevation myocardial infarction, respectively. The primary thrombotic outcome was a composite of cardiovascular death, myocardial infarction or stroke.

Results

A total of 526 (60%) patients were *CYP2C9* LoF allele noncarriers and 352 (40%) were *CYP2C9* LoF allele (**2* or **3*) carriers. After correction for differences in baseline characteristics, there were no significant differences between *CYP2C9* LoF allele carriers and noncarriers for the combined thrombotic outcome (6.3% vs. 5.9%, hazard ratio 1.16 [0.67–2.0], $p = 0.60$), or the individual thrombotic outcomes. Moreover, no differences were seen in the event rates for clinically relevant bleeding (Bleeding Academic Research Consortium [BARC] 2–5 bleeding) as well as major bleeding (BARC 3 or 5 bleeding).

Conclusions

Carriers of a *CYP2C9 *2* or **3* LoF allele presenting with acute coronary syndrome and treated with clopidogrel did not have an increased risk for thrombotic events compared with noncarriers. Given the limited number of poor metabolizers, no firm conclusions could be drawn with regard to the thrombotic risk for patients carrying two CYP2C9 LoF alleles.

INTRODUCTION

In patients with chronic coronary syndrome (CCS) under-going percutaneous coronary intervention (PCI), dual anti-platelet therapy (DAPT) consisting of aspirin and clopidogrel represents the cornerstone of medical therapy to prevent thrombotic complications.[1] In patients with acute coronary syndrome (ACS), use of the more potent P2Y12 inhibitors prasugrel or ticagrelor is preferred.[2] However, in the current guidelines, guided or unguided de-escalation of potent P2Y12 inhibition, by switching from ticagrelor or prasugrel to clopidogrel, may be considered an alternative DAPT strategy (class IIb, level of evidence A) in patients with ACS deemed unsuitable for potent platelet inhibition (e.g. those with high bleeding risk).[3] Treatment with clopidogrel is subject to large interindividual variability. During the two-step conversion of clopidogrel to its active metabolite, multiple cytochrome P450 (CYP) enzymes play a part (CYP2C19, CYP3A4/5, CYP1A2, CYP2B6 and CYP2C9), however CYP2C19 is the main contributor in this process.[4] As a consequence, carriers of a *CYP2C19* loss-of-function (LoF) allele have a reduced antiplatelet response to clopidogrel and are at higher risk for thrombotic events when compared with noncarriers.[5,6] Therefore, guided de-escalation to clopidogrel can be done by *CYP2C19* genotyping.[7] However, there are other CYP enzyme poly-morphisms involved in the metabolization of clopidogrel that can also affect antiplatelet response to clopidogrel. The CYP2C9 enzyme, which is an important member of the CYP enzyme family, also plays a role in the metabolization of clopidogrel. Of all known variants of the *CYP2C9* gene, *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) are the most common LoF variants with reduced enzymatic activity.[8,9] Carriage of a *CYP2C9* LoF allele has been associated with a lower exposure to clopidogrel active metabolite and a diminished pharmacodynamic response.[10,11] The *CYP2C9*3* LoF variant has even been associated with a 2.4-fold increased risk for developing stent thrombosis (ST) in patients treated with clopidogrel after PCI.[12] Thus, the presence of a *CYP2C9* LoF allele may affect an individual's response to clopidogrel and therefore potentially impact clinical outcomes. However, there is a lack of data regarding the different *CYP2C9* polymorphisms and their prognostic impact in patients treated with clopidogrel. In this post hoc analysis, our aim was to assess the effect of the *CYP2C9* LoF alleles on clopidogrel treatment in ACS patients and investigate whether these alleles influence the risk of occurrence of thrombotic and/or bleeding events using data from two large randomized controlled trials—POPular Genetics and POPular Age.[13,14]

METHODS

Study Design and Population

The design and results of the POPular Genetics and POPular Age trials have been published previously. In brief, the POPular Genetics trial was an open-label, assessor-blinded, randomized controlled trial.[13] Between 2012 and 2018, 2488 patients with ST-elevation myocardial infarction (STEMI) undergoing primary PCI aged 21 years and older were included. Within 48 hours of primary PCI, patients were randomized to either a standard treatment arm (treatment with ticagrelor or prasugrel for 1 year) or

to the genotype-guided arm (treatment adjustment after rapid *CYP2C19* genetic testing). In the genotype-guided arm, patients carrying a *CYP2C19*2* or **3* LoF allele were treated with ticagrelor or prasugrel, while noncarriers (**1/*1*) were treated with clopidogrel. The POPular AGE trial was an open-label, assessor-blinded, randomized controlled trial performed in 12 centers in The Netherlands [14]. Between 2013 and 2018, 1002 patients with non-STEMI (NSTEMI) and unstable angina aged 70 years and older were included. Patients were randomized to either treatment with clopidogrel or treatment with ticagrelor or prasugrel on top of standard care. The follow-up duration was 12 months in both trials. An Institutional Review Board approved the trials and all patients provided written informed consent. This analysis included all patients in whom the CYP2C9 gene was analyzed.

Data Collection

In both studies, *CYP2C9* genotyping was retrospectively performed using blood samples, which were analyzed by LGC Biosearch Technologies (Hoddesdon, UK) using a KASP genotyping assay. In the POPular AGE trial, blood samples were collected in three participating hospitals and were therefore not available for all patients. In the POPular Genetics trial, *CYP2C19* genotyping was performed with the use of the TaqMan StepOnePlus assay at a central laboratory (St. Antonius Hospital, Nieuwegein, The Netherlands) or with an on-site point-of-care Spartan RX device (Spartan Bioscience). In the POPular AGE trial, *CYP2C19* genotyping was performed by LGC Biosearch Technologies using a KASP genotyping assay.

Outcomes and Definitions

Cardiovascular events consisted of all-cause death, cardio-vascular death, myocardial infarction (MI), stroke, ST, target vessel revascularization (TVR), unstable angina, transient ischemic attack (TIA) and any bleeding requiring medical attention classified according to the PLATelet inhibition and patient Outcomes (PLATO) bleeding classification, as well as the Bleeding Academic Research Consortium (BARC) bleeding criteria, at 1-year follow-up. Clinically relevant bleeding was defined as PLATO minor and major bleeding or BARC 2–5 bleeding. The primary thrombotic outcome was a composite of death from cardiovascular causes, MI, or stroke. The outcome definitions were identical to the definitions used in both main trials, in which a blinded event committee adjudicated all adverse clinical events.

Statistical Analysis

This analysis was not prospectively powered and the sample size is based on the number of patients in the original trials of whom the *CYP2C9* genetic profile was available. In this analysis, we compared the thrombotic event rate between carriers and noncarriers of a CYP2C9 LoF allele (**2* or **3*) treated with clopidogrel (dominant model). For survival analyses, patients were also divided into three groups on the basis of their phenotype: extensive metabolizers (*CYP2C9*1/*1* homozygotes), intermediate metabolizers (*CYP2C9*1/*2* and *CYP2C9*1/*3* heterozygotes) and poor metabolizers (*CYP2C9*2/*2*, *CYP2C9*2/*3* and *CYP2C9*3/*3*). Variables are presented as number (percentages) and mean ± standard deviation (SD), or median and interquartile range. Time-to-event curves were constructed using the Kaplan–Meier method. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using

Cox proportional hazard models and adjusted for baseline differences by including all variables with a p value <0.05. p values <0.05 were considered statistically significant. Chi-square analysis was used to test the deviations of genotype distribution from the Hardy–Wein-berg equilibrium.

RESULTS

The POPular Genetics and POPular Age trials included a total of 2488 and 1002 patients, respectively. A flowchart of the selection of patients from these two trials with CYP2C9 status is presented in **Figure 1**.

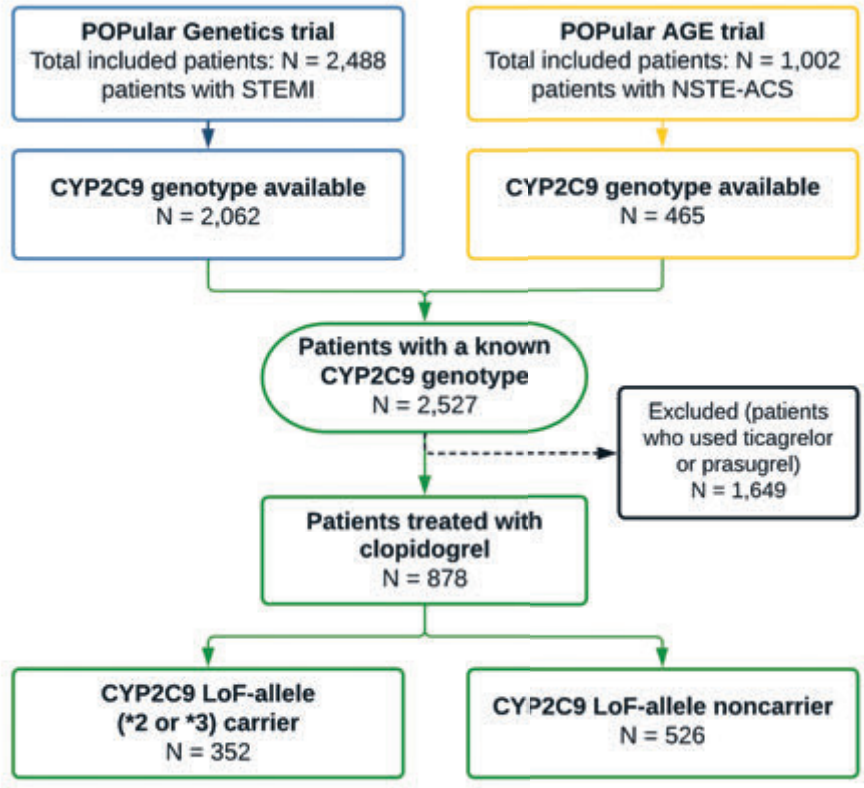

Figure 1. Selection of patients from the POPular Genetics and POPular AGE trials. CYP cytochrome P450, LOF loss-of-function, STEMI ST-elevation myocardial infarction, NSTE-ACS non-ST-elevation acute coronary syndrome

0The *CYP2C9* genotype was available in 2062 (83%) patients in the POPular Genetics trial and 465 (46%) patients in the POPular Age trial, resulting in a total population of 2527 patients with a known *CYP2C9* genotype. From this cohort, 878 (35%) patients were treated with clopidogrel, of whom 526 (60%) were noncarriers of a *CYP2C9* LoF allele and 352 (40%) were *CYP2C9* LoF allele carriers. The baseline characteristics are shown in **Table 1**. Between *CYP2C9* LoF allele carriers and noncarriers, all variables were well balanced, except for a higher frequency of *CYP2C19* LoF carriers (5.1% vs. 11.6%, p = 0.001) and NSTEMI diagnosis at discharge (17.9% vs. 23.6%, p = 0.044) in the *CYP2C19* LoF carrier group. Genotype distributions were in Hardy–Weinberg equilibrium and frequencies were similar to those in other studies of Caucasian participants (**Figure 2**).[10,12]

Table 1. Baseline characteristics in patients treated with clopidogrel, divided between CYP2C9 LoF carriers and CYP2C9 LoF noncarriers

Characteristics	***CYP2C9* LoF carriers *N* = 352**	***CYP2C9* LoF noncarriers *N* = 526**	***p* value**
Age (years, mean ± SD)	66 ± 12	66 ± 12	0.97
Female sex	102 (29.0%)	148 (28.1%)	0.79
Ethnicity			
Caucasian	336 (95.5%)	504 (95.8%)	0.80
Asian	4 (1.1%)	10 (1.9%)	0.38
Arabian	3 (0.9%)	3 (0.6%)	0.69
Latin-American	2 (0.6%)	3 (0.6%)	1.00
African	2 (0.6%)	3 (0.6%)	1.00
Medical history			
Hypertension	161 (45.9%)	259 (49.2%)	0.33
Dyslipidaemia	105 (29.8%)	160 (30.4%)	0.85
Diabetes Mellitus	49 (13.9%)	78 (14.8%)	0.71
Myocardial infarction	51 (14.5%)	69 (13.1%)	0.56
Stroke	21 (6.0%)	24 (4.6%)	0.36
Peripheral arterial disease	18 (5.1%)	26 (4.9%)	0.91
Renal disease	38 (10.9%)	48 (9.2%)	0.42
Bleeding	7 (2.0%)	13 (2.5%)	0.64
CYP2C9 Phenotype			
Intermediate metabolizers *(CYP2C9 *1/*2* or **1/*3* carriers)	310 (35.3%)		
Poor metabolizers (*CYP2C9 *2/*2*, **2/*3* or **3/*3* carriers)	42 (4.8%)		
CYP2C19 genotype			
CYP2C19 LoF carriers	18 (5.1%)	61 (11.6%)	0.001

Table 1. Continued

Diagnosis at discharge			
Unstable angina	8 (2.3%)	13 (2.5%)	0.85
NSTEMI	63 (17.9%)	124 (23.6%)	0.044
STEMI	280 (79.5%)	387 (73.6%)	0.42
Medication at discharge			
Aspirin	326 (92.6%)	489 (93.0%)	0.84
Oral anticoagulation	35 (9.9%)	56 (10.6%)	0.74
Beta blocker	296 (84.1%)	443 (84.2%)	0.96
ACE inhibitor	242 (68.8%)	369 (70.2%)	0.66
Statin	341 (96.9%)	500 (95.1%)	0.47
CAG performed	334 (94.9%)	503 (95.6%)	0.61
Radial access site	209 (62.6%)	339 (67.9%)	0.14
PCI	309 (87.8%)	562 (87.8%)	0.98

ACE angiotensin-converting enzyme, CAG coronary angiography, CYP cytochrome P450, LoF loss-of-function, NSTEMI non-ST-elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-elevation myocardial infarction, SD standard deviation

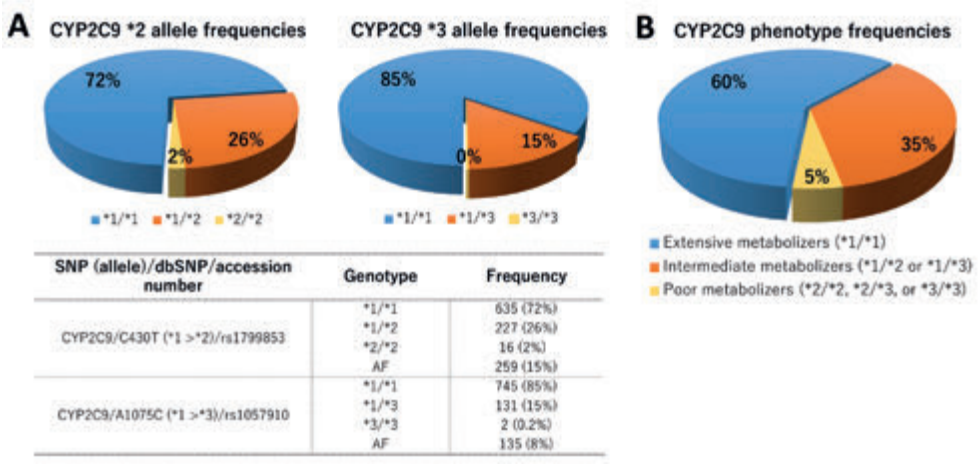

Figure 2. Oversight of the different allele frequencies of both the CYP2C9 *2 and *3 genotypes.

A. Allele frequencies separated for the CYP2C9 *2 and *3 LoF alleles. The table shows the total allele frequencies for both the CYP2C9 *2 and *3 LoF alleles. B. CYP2C9 frequencies according to their phenotype (extensive metabolizers, intermediate metabolizers or poor metabolizers). AF allele frequency, CYP cytochrome P450, LoF loss-of-function, SNP single nucleotide polymorphism

ACE angiotensin-converting enzyme, CAG coronary angiography, CYP cytochrome P450, LoF loss-of-function, NSTEMI non-ST-elevation myocardial infarction, PCI percutaneous coronary intervention, STEMI ST-elevation myocardial infarction, SD standard deviation

The occurrence of cardiovascular events was comparable in both carriers and noncarriers of a *CYP2C9* LoF allele (**Figure 3a**; **Table 2**). No significant differences were seen between carriers and noncarriers of a CYP2C9 LoF allele for the combined thrombotic outcome (6.3% vs. 5.9%, HR 1.16 [0.67–2.02], p = 0.60) or the individual thrombotic outcomes, after correction for *CYP2C19* LoF allele carrier status and diagnosis at discharge. Event rates for thrombotic outcomes were numerically higher in poor metabolizers compared with extensive metabolizers (9.5% vs. 5.9%, HR 1.93 [0.67–5.54], p = 0.22). Unfortunately, the number of poor metabolizers was very low (n = 42). When specifically assessing the different *CYP2C9* polymorphisms, there was no statistically significant difference in the thrombotic outcome between *CYP2C9 *3* carriers and noncarriers (7.5% vs. 5.8%, HR 1.42 [0.71–2.84], p = 0.32) or between *CYP2C9 *2* carriers and noncarriers (6.2% vs. 6.0%, HR 1.13 [0.62–2.07], p = 0.68). No differences were seen in the event rates for clinically relevant bleeding (BARC 2–5 bleeding: 12.5% vs. 14.8%, HR 0.90 [0.62–1.30], p = 0.57; PLATO minor and major bleeding: 11.4% vs. 13.9%, HR 0.86 [0.58–1.27], p = 0.45), or for major bleeding (BARC 3 or 5 bleeding: 3.7% vs. 3.8%, HR 1.08 [0.53–2.19], p = 0.83; PLATO major bleeding: 2.8% vs. 3.2%, HR 0.93 [0.42–2.05], p = 0.86) (**Figure 3b**; **Table 2**).

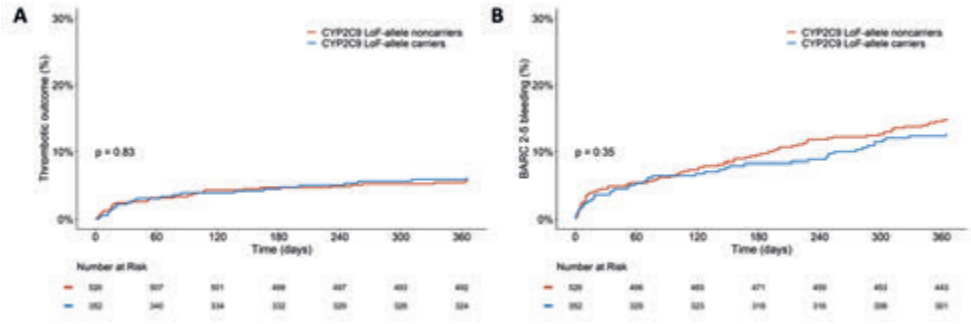

Figure 3. Outcomes of clopidogrel-treated patients with regard to the composite thrombotic and bleeding outcome in CYP2C9 LoF carriers compared with noncarriers.

Kaplan–Meier curves for a the thrombotic outcome, consisting of cardiovascular death, myocardial infarction and stroke, and b BARC 2–5 bleeding. BARC Bleeding Academic Research Consortium, CYP cytochrome P450, LoF loss-of-function

Table 2. Occurrence of thrombotic and bleeding events in CYP2C9 LoF carriers and noncarriers treated with clopidogrel

Event	*CYP2C9* LoF carriers (N = 352) (%)	Poor metabolizers (N = 42) (%)	Intermediate metabolizers (N = 310) (%)	*CYP2C9* LoF non-carriers (N = 526) (%)	HR 95% CI)[a]	p value
Composite of thrombotic outcomes	22 (6.3)	4 (9.5)	18 (5.8)	31 (5.9)	1.16 (0.67–2.02)	0.60
All-cause death	13 (3.7)	1 (2.4)	12 (3.9)	12 (2.3)	1.82 (0.82–4.03)	0.14
Cardiovascular death	5 (1.4)	0 (0.0)	5 (1.6)	6 (1.1)	1.36 (0.41–4.51)	0.61
MI	14 (4.0)	4 (9.5)	10 (3.2)	22 (4.2)	1.05 (0.53–2.06)	0.90
TVR	4 (1.1)	1 (2.4)	3 (1.0)	4 (0.8)	1.58 (0.39–6.40)	0.53
ST	1 (0.3)	1 (2.4)	0 (0.0)	1 (0.2)	1.35 (0.09–21.65)	0.83
Stroke	4 (1.1)	0 (0.0)	4 (1.3)	4 (0.8)	1.61 (0.40–6.56)	0.51
Bleeding outcomes						
BARC 2–5 bleeding	44 (12.5)	5 (11.9)	39 (12.6)	78 (14.8)	0.90 (0.62–1.30)	0.57
BARC 3 or 5 bleeding	13 (3.7)	1 (2.4)	12 (3.9)	20 (3.8)	1.08 (0.53–2.19)	0.83
PLATO minor or major bleeding	40 (11.4)	5 (11.9)	35 (11.3)	73 (13.9)	0.86 (0.58–1.27)	0.45
PLATO major bleeding	10 (2.8)	1 (2.4)	9 (2.9)	17 (3.2)	0.93 (0.42–2.05)	0.86

The event rates for poor (**2/*2, *2/*3* or **3/*3*) and intermediate (**1/*2* or **1/*3*) metabolizers are also shown. Differences in event rates for both poor and intermediate metabolizers were compared with *CYP2C9* LoF noncarriers using Cox proportional hazard models. All comparisons were not statistically different (*p* value > 0.05). *BARC* Bleeding Academic Research Consortium, *CI* confidence interval, *CYP* cytochrome P450, *HR* hazard ratio, *LoF* loss-of-function, *MI* myocardial infarction, *PLATO* PLATelet inhibition and patient Outcomes, *ST* stent thrombosis, *TVR* target vessel revascularization

[a]HRs are calculated by comparing *CYP2C9* LoF carriers with noncarriers. The composite of thrombotic outcomes consists of cardiovascular death, MI and stroke. HRs were adjusted for *CYP2C19* LoF allele carrier status and diagnosis at discharge

DISCUSSION

In this post hoc analysis investigating the prognostic impact of the *CYP2C9* polymorphisms on cardiovascular outcomes in patients treated with clopidogrel for ACS (POPular Genetics and POPular Age trials), the main finding is that there were no differences in the risk for thrombotic events between *CYP2C9* LoF carriers and noncarriers. This was also the case when specifically assessing the impact of the *CYP2C9 *3* allele on thrombotic events.

The CYP2C9 enzyme plays an important role in the metabolization of about 15% of clinically administered drugs. Several studies have shown that the presence of a *CYP2C9* polymorphism can

have clinical implications in different antithrombotic treatments. One of the most significant clinical impacts of *CYP2C9* polymorphisms is the metabolism of Vitamin K antagonists (VKA, such as warfarin and acenocoumarol), with an approximately five-fold stronger anticoagulant effect. Poor metabolizers with a *CYP2C9* LOF variant need lower doses of VKA to attain an adequate response and are more prone to adverse effects such as bleeding.[15,16] Next to VKAs, *CYP2C9* also plays a role in the metabolization of aspirin and *CYP2C9* polymorphisms have been associated with a higher risk for adverse effects and aspirin intolerance.[17,18]

CYP2C9 only plays a role in the second metabolization step in the activation of clopidogrel.[5] In addition, the presence of a CYP2C9 LoF allele has been associated with decreased exposure to the active metabolite of clopidogrel and a diminished pharmacodynamic response. In the study by Harmsze et al. regarding patients undergoing elective coronary stent implantation, carriers of the *CYP2C9 *3* LoF allele showed overall higher on-clopidogrel platelet reactivity and an increased risk for a poor response to clopidogrel, indicating that the genetic variant *CYP2C9 *3* plays an important role in response to clopidogrel.[11] However, in healthy subjects, there is more controversy between the association of the *CYP2C9* LoF alleles and the effect of clopidogrel. While Brandt et al. showed that carriers of the *CYP2C9 *2* or *3* allele had decreased exposure to the active metabolite of clopidogrel and were more often poor responders, Mega et al. did not find any association with CYP2C9 LoF alleles and the pharmacokinetic and pharmacodynamic response to clopidogrel.[5,10] Moreover, in line with our results, Mega et al. observed no significant associations between the *CYP2C9* genotype and thrombotic events in a cohort of 1477 patients treated with clopidogrel; however, they assessed neither poor responder status nor the effect of the individual *CYP2C9 *2* and *3* polymorphisms in their analysis. Compared with the population in the study by Mega et al., the number of carriers of a *CYP2C9* LoF allele was higher in our study population, although our overall population was slightly smaller. In contrast to their analysis, we did assess the impact of the different *CYP2C9* LoF alleles separately. Numerically, the thrombotic event rates were higher in carriers of a *CYP2C9 *3* allele (7.5% vs. 5.8%), while this was not the case in carriers of the CYP2C9 *2 allele (6.2% vs. 6.0%). As these differences were not statistically significant, no firm conclusions can be drawn from these results. However, this observation is in line with a previous case-control study by Harmsze et al. showing that the *CYP2C9 *3* LoF allele in particular was associated with an increased risk for ST, while the *CYP2C9 *2* LoF allele was not.[12]

As previous studies have shown that *CYP2C9* LoF allele carriers have decreased exposure to the active metabolite of clopidogrel, it can be hypothesized that this could lead to a lower risk for adverse effects such as bleeding. Nonetheless, we found no differences in bleeding rates between the two groups that could substantiate this hypothesis.

Overall, our results suggest that there is no increased risk for thrombotic events in patients who carry a *CYP2C9 *2* or *CYP2C9 *3* LoF allele. This is reassuring as it implicates that it is not necessary to test for the *CYP2C9* polymorphisms when starting treatment with clopidogrel. Currently, CYP2C19 remains

the most important CYP enzyme in the metabolization of clopidogrel, affecting the pharmacokinetics, pharmacodynamic response and risk on thrombotic events in patients with a *CYP2C19* LoF allele. In recent years, there has been growing evidence in favor of a *CYP2C19* genotype-guided treatment strategy when prescribing DAPT in patients with ACS, implicating that tailoring the P2Y12 inhibitor based on a patient's *CYP2C19* genotype can improve cardiovascular outcomes.[13,19,20] In particular, the POPular Genetics trial showed that by applying a genotype-guided de-escalation strategy, 61% of patients could be treated with clopidogrel instead of ticagrelor, which resulted in a substantially lower risk of bleeding events without any evidence for an increase in ischemic events.[13]

Limitations

There are limitations in this study. First, this post hoc analysis was dependent on the available *CYP2C9* genotype data of the POPular Genetics and POPular Age trial. As a result, it was not prospectively powered to detect a difference in the cardio-vascular outcomes. Our results should therefore be interpreted in light of the limited sample size. Second, in the POPular Genetics trial, patients were randomized between a *CYP2C19* genotype-guided treatment strategy versus conventional treatment. Therefore, the *CYP2C19* genotype was not normally distributed over the patients treated with clopidogrel, which is also reflected in the baseline table. However, in our analyses, we adjusted for the carrier status of the *CYP2C19* LoF allele to account for this unequal distribution. Finally, due to the low prevalence of the poor metabolizer phenotype, we used a dominant model in our primary analysis, assuming that having one or more copies of the *CYP2C9*2* or **3* allele increased the thrombotic risk compared with the **1/*1* genotype. Therefore, a possible effect limited to *CYP2C9* poor metabolizers might have been underestimated or missed.

CONCLUSION

Carriage of the *CYP2C9 *2* or **3* LoF alleles did not increase the risk for thrombotic events in patients presenting with ACS treated with clopidogrel. Due to the limited number of poor metabolizers, further studies should be conducted in a larger cohort treated with clopidogrel to be able to definitely rule out an association between *CYP2C9* poor metabolizers and thrombotic risk.

REFERENCES

1. Knuuti J, Wijns W, Flachskampf FA, Gohlke H, Grove EL, James S, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.
2. Valgimigli M, Bueno H, Byrne RA, Collet J-P, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European. Eur Heart J. 2018;39:213–60.
3. Collet J-P, 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. Eur Heart J. 2020;42:1289–367. https://acade mic.oup.com/eurheartj/article/42/14/1289/5898842
4. Kazui M, Nishiya Y, Ishizuka T, Hagihara K, Farid NA, Okazaki O, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopi-dogrel to its pharmacologically active metabolite. Drug Metab Dispos. 2010;38:92–9.
5. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P-450 polymorphisms and response to clopi-dogrel. N Engl J Med. 2009;360:354–62.
6. Mega JL, Simon T, Collet JP, Anderson JL, Antman EM, Bliden K, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel pre-dominantly for PCI: a meta-analysis. JAMA. 2010;304:1821–30.
7. Ancrenaz V, Daali Y, Fontana P, Besson M, Samer C, Dayer P, et al. Impact of genetic polymorphisms and drug–drug interac-tions on clopidogrel and prasugrel response variability. Curr Drug Metab. 2010;11:667–77.
8. Xie HG, Prasad HC, Kim RB, Stein CM. CYP2C9 allelic variants: ethnic distribution and functional significance. Adv Drug Deliv Rev. 2002;54:1257–70.
9. Kirchheiner J, Brockmöller J. Clinical consequences of cytochrome P450 2C9 polymorphisms. Clin Pharmacol Ther. 2005;77(1):1–16.
10. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopi-dogrel but not prasugrel. J Thromb Haemost. 2007;5:2429–36.
11. Harmsze A, Van Werkum JW, Bouman HJ, Ruven HJ, Breet NJ, Ten Berg JM, et al. Besides CYP2C19*2, the variant allele CYP2C9*3 is associated with higher on-clopidogrel platelet reactivity in patients on dual antiplatelet therapy undergoing elective coronary stent implantation. Pharmacogenet Genom. 2010;20:18–25.
12. Harmsze AM, Van Werkum JW, Ten Berg JM, Zwart B, Bou-man HJ, Breet NJ, et al. CYP2C19*2 and CYP2C9*3 alleles are associated with stent thrombosis: a case-control study. Eur Heart J. 2010;31:3046–53.
13. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Van't Hof AWJ, Van Der Harst P, et al. A genotype-guided strat-egy for oral P2Y12 inhibitors in primary PCI. N Engl J Med. 2019;381:1621–31.
14. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, 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.

15. Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnetTM systematic review and meta-analysis. Genet Med. 2005;7(2):97–104.
16. Schalekamp T, Oosterhof M, Van Meegen E, Van Der Meer FJM, Conemans J, Hermans M, et al. Effects of cytochrome P450 2C9 polymorphisms on phenprocoumon anticoagulation status. Clin Pharmacol Ther. 2004;76:409–17.
17. Agundez J, Martinez C, Perez-Sala D, Carballo M, Torres M, Garcia-Martin E. Pharmacogenomics in aspirin intolerance. Curr Drug Metab. 2010;10:998–1008.
18. Palikhe NS, Kim SH, Nam YH, Ye YM, Park HS. Polymorphisms of aspirin-metabolizing enzymes CYP2C9, NAT2 and UGT1A6 in aspirin-intolerant urticaria. Allergy Asthma Immunol Res. 2011;3:273–6.
19. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral P2Y12 inhibitor therapy: a meta-analysis. JACC Car-diovasc Interv. 2021;14:739–50.
20. Beitelshees AL, Thomas CD, Empey PE, Stouffer GA, Angio-lillo DJ, Franchi F, et al. CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention in diverse clini-cal settings. J Am Heart Assoc. 2022;11:e024159. https://doi.org/ 10.1161/JAHA.121.024159

CHAPTER 6

Effects of CYP3A4*22 and CYP3A5 on clinical outcome in patients treated with ticagrelor for ST-segment elevation myocardial infarction: POPular Genetics sub-study

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ABSTRACT

Aims

To determine the clinical efficacy,adverse events and side-effect dyspnea of CYP3A4*22 and CYP3A5 expressor status in ticagrelor treated patients.

Methods and results

Ticagrelor treated patients from the POPular Genetics randomized controlled trial were genotyped for CYP3A4*22 and CYP3A5*3 alleles. Patients were divided based on their genotype. In total 1,281 patients with ST-segment elevation myocardial infarction (STEMI) were included. CYP3A4*22 carriers (n = 152) versus CYP3A4*22 non-carrier status (n = 1,129) were not found to have a significant correlation with the primary thrombotic endpoint: cardiovascular death, myocardial infarction, definite stent thrombosis and stroke [1.3% vs. 2.5%, adjusted hazard ratio 1.81 (0.43–7.62) p = 0.42], or the primary bleeding endpoint: PLATO major and minor bleeding [13.2% vs. 11.3%, adjusted hazard ratio 0.93 (0.58–1.50) p = 0.77]. Among the CYP3A4*1/*1 patients, CYP3A5 expressors (n = 196) versus non-expressors (n = 926) did not show a significant difference for the primary thrombotic [2.6% vs. 2.5%, adjusted hazard ratio 1.03 (0.39–2.71) p = 0.95], or the primary bleeding endpoint [12.8% vs. 10.9%, adjusted hazard ratio 1.13 (0.73–1.76) p = 0.58]. With respect to dyspnea, no significant difference was observed between CYP3A4*22 carriers versus CYP3A4*22 non-carriers [44.0% vs. 45.0%, odds ratio 1.04 (0.45–2.42) p = 0.93], or in the CYP3A4*1/*1 group, CYP3A5 expressors versus CYP3A5 non-expressors [35.3% vs. 47.8%, odds ratio 0.60 (0.27–1.30) p = 0.20].

Conclusion

In STEMI patients treated with ticagrelor, neither the CYP3A4*22 carriers, nor the CYP3A5 expressor status had a statistical significant effect on thrombotic and bleeding event rates nor on dyspnea.

INTRODUCTION

Patients with acute coronary syndrome (ACS) are treated with dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, according to the current guidelines. It is estimated that, in 2015, the number of patients requiring DAPT has increased to approximately 1.4–2.2 million patients per year worldwide. Current ACS guidelines recommend the use of the stronger antiplatelet drugs ticagrelor or prasugrel over clopidogrel in combination with aspirin. The use of clopidogrel in patients with ACS is currently limited to the situation when ticagrelor or prasugrel are not available, cannot be tolerated, or are contraindicated.[1,2]

Ticagrelor is a direct acting oral, reversible antiplatelet agent with a plasma half-life of approximately 7–12 h. Unlike clopidogrel, which has to be metabolized into its active variant by hepatic CYP450 enzymes in order to gain its therapeutic effect, ticagrelor does not require metabolic activation. However, ticagrelor is extensively metabolized and eliminated by primarily CYP3A4, and, to a lesser extent, by CYP3A5 (as shown in vitro studies) into the metabolites C124910XX and C133913XX.[3] Therefore, it is not recommended to combine ticagrelor with strong CYP3A4 inhibitors or inducers. For example, concomitant use of ketoconazole increases the Cmax of ticagrelor 2.4 times and the Area Under the Curve (AUC) 7.3 times.[4] The C124910XX compound exhibits almost the same potency in antiplatelet effect as the parent drug and is present at approximately 30%–40% of the levels of ticagrelor. C124910XX is further metabolized by UDP-glucuronosyltransferase, or via hydroxylation to a minor hydroxylated derivative and then excreted in the urine.[3]

A recent study showed that gene polymorphisms in the *CYP3A4* and *CYP3A5* genes influence the biological availability of ticagrelor. The *CYP3A4* intron six single-nucleotide polymorphism (SNP) (*rs35599367C>T*, *CYP3A4*22*), which has an allele frequency of 3%–8% in the Caucasian population and less than 1% in the African and Asian population, reduces the hepatic expression of *CYP3A4*, explaining ~12% of *CYP3A4* enzyme activity variability.[5,6] Previous research has shown that *CYP3A4* (*CYP3A4*22*) genotype correlate with the pharmacodynamics (PD) and pharmacokinetics (PK) of ticagrelor, resulting in more platelet inhibition 24 h after ticagrelor administration, consistent with a decreased metabolism and thus higher plasma concentrations.[7] As a consequence, being carrier of the *CYP3A4*22* allele could lead to an increased risk of ticagrelor-related side-effects, such as bleedings and dyspnea. To date, the effects of *CYP3A4* and *CYP3A5* genetic polymorphisms have only been studied in trials with a small sample size and with regards to PD and PK. Little is known about the clinical effects of *CYP3A4* and *CYP3A5* polymorphisms with respect to ticagrelor efficacy. Our study aims to assess the effects of the *CYP3A4*22* allele and *CYP3A5* expressor status in ticagrelor treated patients with a myocardial infarction, with respect to clinical endpoints and the most common side-effect dyspnea.

METHODS

Study design and patient population

The rationale and design of the POPular Genetics trial have been described previously.[8] In brief, the POPular Genetics was a randomized, open-label, multicenter controlled trial involving 2,488 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). Patients were randomized to *CYP2C19* genotyping or routine ticagrelor or prasugrel treatment. In the genotyping group, patients carrying a *CYP2C19*2* or **3* loss-of-function allele were prescribed ticagrelor or prasugrel, and patients without a *CYP2C19*2* or **3* allele received clopidogrel. Patients were followed until 1 year after admission and all endpoints were adjudicated by a blinded event committee. The aim of the study was to compare *CYP2C19* genotype-guided antiplatelet therapy to a non-tailored strategy in terms of net clinical benefit, safety and cost-effectiveness.[9] An additional blood sample was collected and stored for further (genetic) analysis. Written informed consent was obtained from each patient. The institutional review boards of all participating centers approved the protocol of the POPular Genetics study. The current study complies with the principles of the Declaration of Helsinki.

DNA sampling

Blood samples were collected during the POPular Genetics trial from the majority of patients in both treatment groups. After completion of the trial, *CYP3A4*22* (*rs35599367*) and *CYP3A5*3* (*rs776746*) genotyping was performed by LGC Biosearch Technologies (Hoddesdon, United Kingdom) using a kompetitive allele specific (KASP) genotyping assay. *CYP2C19*2* and *3 genotyping was already performed during the initial study.[10]

Analyses

Each patient was classified into *CYP3A4*22* carrier (carrying at least one *CYP3A4*22* allele) and *CYP3A4*22* non-carrier, and *CYP3A5* non-expressor (homozygous for the *CYP3A5*3* allele) versus *CYP3A5* expressor (*CYP3A5*1/*1* or **1/*3*). Patients without blood sample or incomplete genotyping results were excluded from the analyses. In addition, patients treated with clopidogrel or prasugrel were excluded.

Three different analyses were performed. Because of the previous studies showing a significant effect on platelet inhibition in CYP3A4*22 carriers we first compared CYP3A4*22 carriers with *CYP3A4*22* non-carriers, irrespective of *CYP3A5* or *CYP2C19* status. In order to gain knowledge regarding the sole function of *CYP3A5* the second analysis was performed in patients not carrying a *CYP3A4*22* allele (*CYP3A4*1/*1*), comparing *CYP3A5* non-expressors with *CYP3A5* expressors. Third, we compared fast *CYP3A* metabolizers (defined as patients being both *CYP3A4*22* non-carrier and *CYP3A5* expressor) with *CYP3A* reduced metabolizers (*CYP3A4*22* carriers and *CYP3A5* non-expressors).

Clinical endpoints

The number of patients available for analysis was not prospectively powered and was based on the number of patients in the original trial of whom the *CYP3A4* and *CYP3A5* genotyping results were available. There were two primary endpoints: a combined thrombotic endpoint, consisting of

cardiovascular death, myocardial infarction, definite stent thrombosis and stroke, and a bleeding endpoint, consisting of Platelet Inhibition and Patient Outcomes (PLATO) major and minor bleeding. Furthermore, the individual components of the thrombotic and bleeding endpoint were analyzed as secondary endpoints. The secondary endpoint was the cessation or switching of ticagrelor to a different P2Y12 inhibitor due to dyspnea.

Statistical methods

Continuous variables are presented as mean and standard deviation (SD), or median and interquartile range (IQR), based on distribution pattern. Discrete variables are presented as frequencies and percentages (%). The Mann-Whitney or student's t-test and Chi-square test were used to compare continuous and categorical variables, respectively. A p-value below 0.05 was considered statistically significant. Kaplan Meier curves were estimated and used to graphically assess the primary endpoints and the log-rank test was used to calculated the p-values. Cox proportional hazard models were used to calculate crude and adjusted hazard ratio's (HR) and the 95% confidence interval (CI). Logistic regression analyses were used to calculate crude and adjusted odds ratio's (OR) and the 95% CI. To adjust for baseline differences, all baseline differences with a p-value <0.15 were candidate for univariate regression. If there was a significant correlation ($p < 0.10$) in the univariate analysis, these baseline characteristics were selected for the multivariate regression analysis. All variables with a remaining $p < 0.10$ in the multivariate regression analysis were considered as confounders in the regression model. All analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, United States).

RESULTS

Patient characteristics

The initial POPular Genetics study cohort, recruiting patients from May 2012 until April 2018, consisted of 2,488 patients (100%). Using additional genotyping after study completion, *CYP3A4*22* and *CYP3A5*3* were successfully genotyped in 1,974 patients (79.3%). Genotypes for *CYP3A4* and *CYP3A5* could not be obtained in 514 patients (21.7%) due to assay failure or lack of a blood sample. From this cohort, a total of 1,281 patients (64.8%) were treated with ticagrelor. This patient cohort had a complete follow-up and was used for the current analyses (flowchart is presented in **Figure 1**). The mean age was 61.4 ± 11.4 years; 23.4% of patients were female. A total of 147 patients (11.5%) had the *CYP3A4*1/ *22* genotype, five (0.4%) had the *CYP3A4*22/*22* genotype. The remaining 1,129 patients (88.1%) were classified as *CYP3A4*1/*1* (wild type) genotype. Furthermore, in *CYP3A4*1/*1* patients, 178 patients (15.7%) had the *CYP3A5*1/*3* genotype, 17 patients (1.5%) the *CYP3A5*1/*1* genotype, and 926 (82.0%) patients the *CYP3A5*3/*3* genotype.

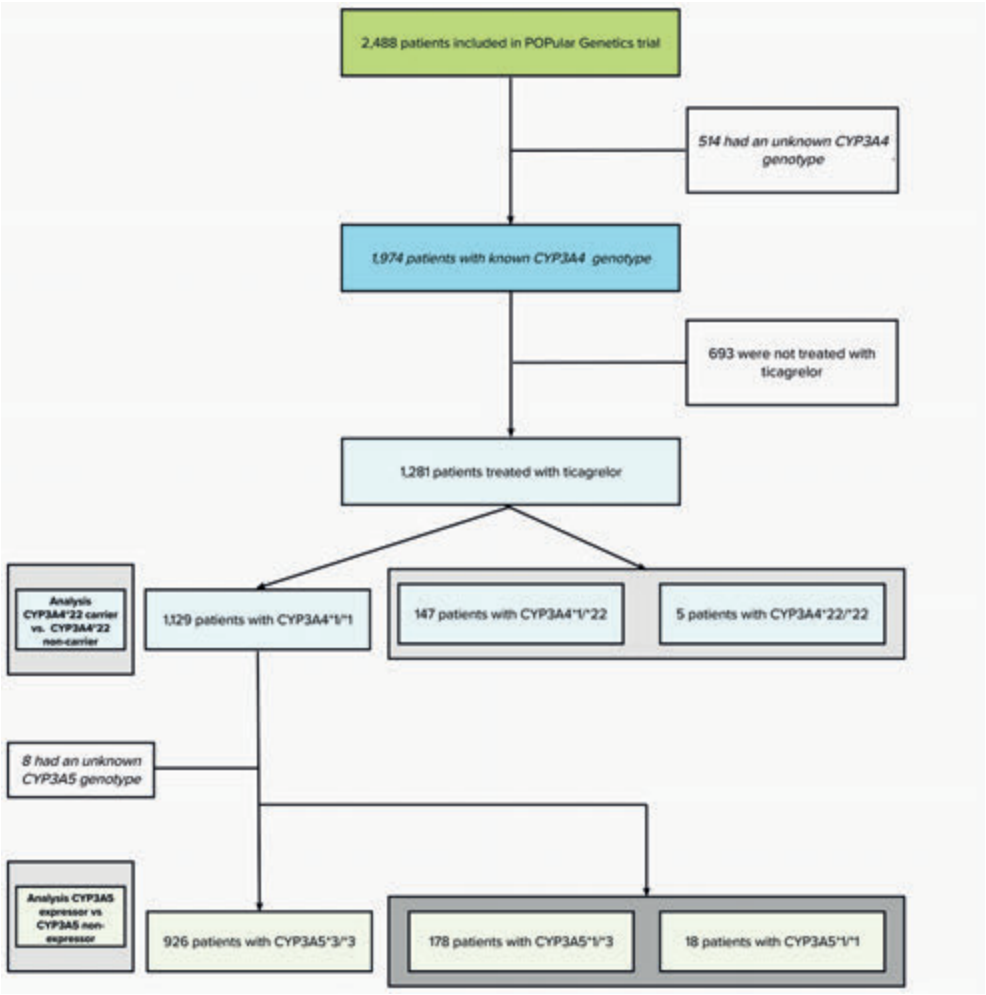

Figure 1. Flowchart of the POPular Genetics CYP3A4 and CYP3A5 sub study.

In **Table 1** the baseline characteristics of *CYP3A4*22* carriers versus non-carriers are presented. In the *CYP3A4*22* groups, all variables were balanced in baseline characteristics, except for a significant higher frequency of females (30.3% vs. 22.5%; p = 0.03), prior stroke or TIA (5.3% vs. 2.6%; p = 0.06), more common use of AT-II antagonists (13.2% vs. 9.0%; p = 0.10), and statin use (98.7% vs. 96.5%; p = 0.15). Furthermore, the *CYP3A4*22* carriers more often had bifurcation lesions when compared to *CYP3A4*22* non-carriers, (9.9% vs. 19.4%; p = 0.01) (**Supplementary Table S1**). **Supplementary Table S2** and **Supplementary Table S3** present the variables used in the univariate and multivariate regression analysis based on the *CYP3A4* status with regards to the bleeding endpoint.

In the *CYP3A5* groups, all variables were balanced in baseline characteristics, except for a significant higher prevalence of prior CABG (3.1% vs. 0.9%; p = 0.01). *CYP3A5* expressors had a numerically higher BMI (28.1 vs. 27.1; p = 0.10) and a numerically higher prevalence of prior stroke or TIA (4.1% vs. 2.2%; p = 0.10). The baseline characteristics of the *CYP3A5* expressor versus non-expressor patients can be found in Supplementary **Table S1A**. **Supplementary Table S4** and **Supplementary Table S5** present the variables used in the univariate and multivariate regression analysis based on the *CYP3A5* status with regards to the bleeding endpoint.

Table 1. Baseline characteristics of ticagrelor treated patients according to CYP3A4 status.

	All patients N = 1281	**CYP3A4*22 non carriers[a] N = 1129**	**CYP3A4*22 carriers N = 152**	**p-value**
Age (yrs.), mean ± SD	61.4 ± 11.4	61.3 ± 11.4	62.1 ± (11.2)	0.41
Body mass index (kg/m2), mean ± SD	27.3 ± 6.7	27.4 ± 7.0	26.8 ± 3.8	0.33
Female sex, n (%)	300 (23.4)	254 (22.5)	46 (30.3)	0.03*
Medical history, n (%)				
Current or former smoker (%)	573 (44.7)	502 (44.4)	71 (46.7)	0.43
Hypertension (%)	502 (39.2)	445 (39.4)	57 (37.5)	0.65
Hyperlipidemia (%)	260 (20.3)	235 (20.8)	25 (16.4)	0.21
Diabetes mellitus (%)	139 (10.9)	120 (10.6)	19 (12.5)	0.49
Chronic kidney disease (%)[b]	106 (8.3)	94 (8.3)	12 (7.9)	0.75
Peripheral arterial disease	28 (2.2)	22 (1.9)	6 (3.9)	0.11
Coronary artery disease[c]	131 (10.2)	119 (10.5)	12 (7.9)	0.31
Relevant bleeding	29 (2.3)	26 (2.3)	3 (2.0)	0.80
Prior stroke or TIA	37 (2.9)	29 (2.6)	8 (5.3)	0.06*
Prior myocardial infarction	99 (7.7)	91 (8.1)	8 (5.3)	0.23
Prior PCI	99 (7.7)	90 (8.0)	9 (5.9)	0.37
Prior CABG	15 (1.2)	14 (1.2)	1 (0.7)	0.53
Clinical presentation				
Heart rate (bpm), mean ± SD	73.4 ± 14.6	73.2 ± 14.6	74.8 ± 13.2	0.20
Systolic BP (mmHg), mean ± SD	132.5 ± 20.4	132.6 ± 20.5	132.2 ± 19.9	0.82
Serum creatinine (µmol/L), mean ± SD	79.7 ± 20.4	79.9 ± 20.6	78.1 ± 18.5	0.29
Killip class, n (%)II-IV	9 (0.7)	8 (0.7)	1 (0.7)	0.98
Length of hospital stay (days), mean ± SD	3.2 ± 2.4	3.2 ± 2.5	3.1 ± 1.9	0.73
Discharge medication, n (%)				
Aspirin	1255 (98.0)	1104 (97.8)	151 (99.3)	0.20
Ticagrelor	1281 (100.0)	1129 (100.0)	152 (100.0)	—
Vitamin K antagonist	0 (0.0)	0 (0.0)	0 (0.0)	—
Novel oral anticoagulant	3 (0.2)	3 (0.3)	0 (0.0)	0.53

Table 1. Continued

ACE inhibitor	1006 (78.5)	888 (78.7)	118 (77.6)	0.77
AT-II antagonist	122 (9.5)	102 (9.0)	20 (13.2)	0.10*
Beta blocker	1134 (88.5)	996 (88.2)	138 (90.8)	0.35
Statin	1239 (96.7)	1089 (96.5)	150 (98.7)	0.15
Proton Pump Inhibitor	958 (74.8)	840 (74.4)	118 (77.6)	0.39
CYP2C19 LoF carrier[d]	321 (68.6)	294 (68.9)	27 (65.9)	0.69
CYP3A4 genotype (n, %)				
*1/*1	1129 (88.1)	1129 (100.0)	0 (0.0)	—
*1/*22	147 (11.5)	0 (0.0)	147 (96.7)	—
*22/*22	5 (0.4)	0 (0.0)	5 (3.3)	—
CYP3A5 genotype (n,%)				
*3/*3	1065 (83.1)	926 (82.0)	139 (91.4)	—
*1/*3	189 (14.8)	178 (15.8)	11 (7.2)	—
*1/*1	18 (1.4)	17 (1.5)	1 (0.7)	—

TIA, transient ischemic attack; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; bpm, beats per minute; BP, blood pressure; ACE, indicates angiotensin-converting enzyme; AT II, angiotensin II; BMI, body mass index; creatinine clearance was calculated with the use of the CKD-EPI, formula. [a]CYP3A4*22 non-carriers exists out of patients with the CYP3A4*1/*1 genotype, CYP3A4*22 carriers exists out of patients with the CYP3A4*1/*22 and CYP3A4*22/*22 genotype. [b]Chronic kidney disease are patients with an estimated glomerular filtration rate <60 ml/min/1.73 m2 [c]Coronary artery disease is defined as an obstruction of >50% in the epicardial coronary arteries. [d]CYP2C19 LOF, carrier indicates the presence of CYP2C19*2 or CYP2C19*3 alleles, this was known in 427 CYP3A4*22 non-carriers and 41 carriers. *Variables with a p-value <0.10 which are used for the multivariate analysis.

Clinical impact of CYP3A4*22 carrier status

For this analysis, 152 patients carrying a *CYP3A4*22* allele and 1,129 patients with a *CYP3A4*1/*1* genotype were compared (**Table 2**). No significant differences were observed between the two groups for the combined thrombotic endpoint [1.3% vs. 2.5%, adjusted HR 1.81 (0.43–7.62), p = 0.42; **2B**], or the combined bleeding endpoint [13.2% vs. 11.3%, adjusted HR 0.93(0.58–1.50), p = 0.77; **Figure 2A**]. With regards to dyspnea, 194 patients switched from ticagrelor to another P2Y12 inhibitor or discontinued P2Y12-therapy. We observed no significant differences between the groups with respect to the occurrence of dyspnea: 44.0% in *CYP3A4*22* carriers, and 45.0% in *CYP3A4*22* non-carriers [OR 1.04 (0.45–2.42), p = 0.93, **Supplementary Figure S6** and **Supplementary Figure S7**]. No multivariate analysis was performed, because no significant confounders were presented by the univariate analysis.

Table 2. Clinical endpoint for CYP3A4 in patients treated with ticagrelor.

	CYP3A4*22 carriers (N=152)	CYP3A4*22 non-carriers (N=1129)	Unadjusted Hazard ratio (95% CI)	Adjusted Hazard ratio (95% CI)¥	Adjusted p-value
Thrombotic endpoint No. of patients (%)	**Cumulative incidence**	**Cumulative incidence**			
Cardiovascular death, MI, definite ST, and stroke	2 (1.3)	28 (2.5)	1.87 [0.45-7.8]	1.81 [0.43-7.62]	0.42
Cardiovascular death	0 (0.0)	6 (0.5)			0.99
Stroke	2 (1.3)	8 (0.7)			0.36
Myocardial infarction					
Spontaneous MI	2 (1.3)	41 (3.6)			0.17
Definite ST	2 (1.3)	7 (0.6)			0.99
Bleeding endpoint					
PLATO major and minor bleeding	20 (13.2)	128 (11.3)	0.85 [0.53-1.36]	0.93 [0.58 – 1.50]	0.77
PLATO major	4 (2.6)	16 (1.4)			0.89
PLATO minor	16 (10.5)	112 (9.9)			0.91
Side effect - No. of patients (%)	**Cumulative incidence**	**Cumulative incidence**	**Unadjusted Odds Ratio**	**Unadjusted p-value**	
Dyspnea[a]	11 (44.0)	76 (45.0)	1.04 [0.45-2.42]	0.93	

ST, stent thrombosis; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes

¥ Significant variables are shown in Supplementary Table 2 and 3, adjustments were made for the covariate statins as confounder for the thrombotic endpoints. With regards to the bleeding endpoint adjustments were made for prior stroke and peripheral arterial disease. [a] The total percentages were calculated based on all 194 patients who switched from ticagrelor to another P2Y12 inhibitor or discontinued treatment. No multivariate analysis was performed, because no significant confounders were presented by the univariate analysis.

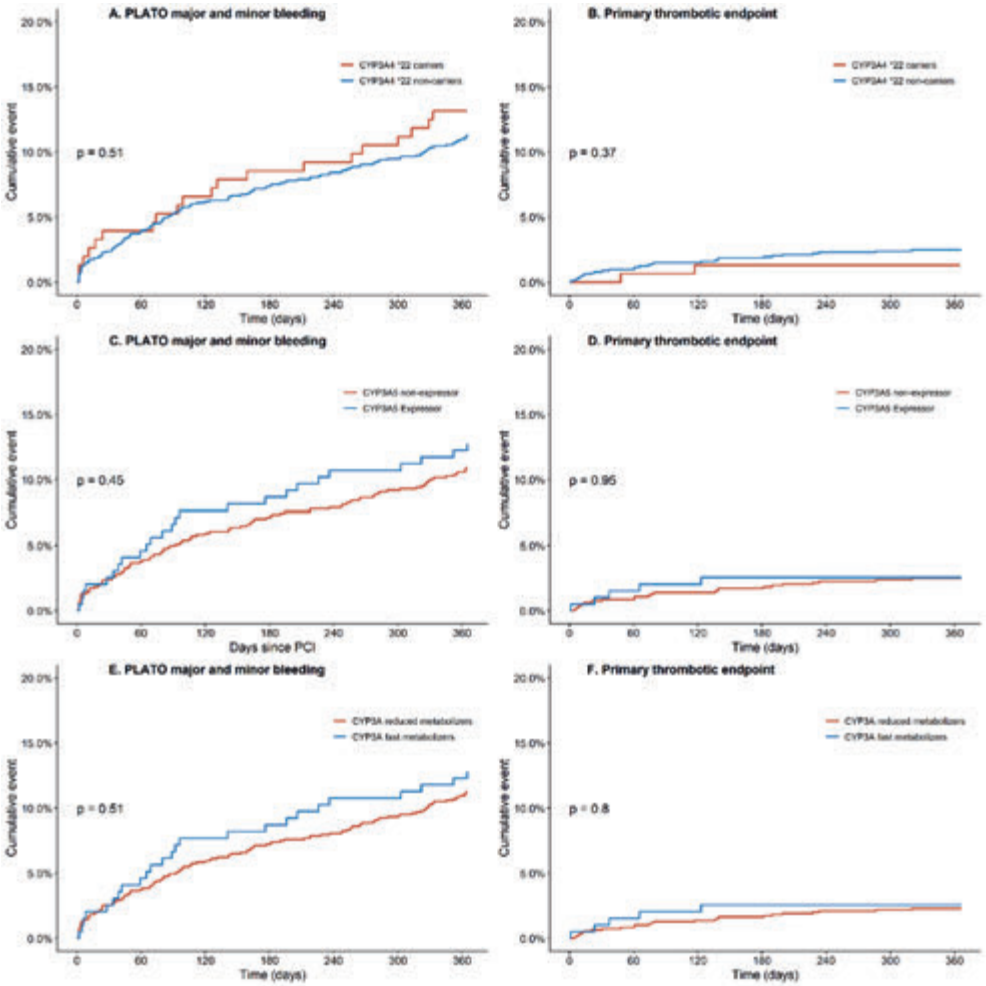

Figure 2. Endpoints of ticagrelor treated patients with regards to the combined thrombotic and bleeding endpoint for CYP3A, CYP3A4 and CYP3A5 status.

Kaplan-Meier curves for (A) the combined bleeding endpoint, defined as PLATO major and minor bleeding in CYP3A4*22 carriers versus non-carriers, for (B) the combined thrombotic endpoint, defined as cardiovascular death, myocardial infarction, definite stent thrombosis, and stroke in CYP3A4*; 22 carriers versus non carriers, for (C) the combined bleeding endpoint in CYP3A5 expressors versus non-expressors, for (D) the combined thrombotic endpoint in CYP3A5 expressors versus non-expressors, for (E) the combined bleeding endpoint in CYP3A fast metabolizers versus reduced metabolizers and for (F) the combined thrombotic endpoint in CYP3A fast metabolizers versus reduced metabolizers.

Clinical effect of CYP3A5 expressor

In this analysis, 196 *CYP3A5* expressors (with a *CYP3A5*1/1* or *CYP3A5*1/*3* genotype) and 926 CYP3A5 non-expressors (patients with a *CYP3A5*3/*3* genotype) were compared (**Table 3**). No significant differences were found between the two groups for the combined thrombotic endpoint [2.6% vs. 2.5%, adjusted HR 1.03 (0.39–2.71), p = 0.95; **Figure 2D**], or the combined bleeding endpoint [12.8% vs. 10.9%, adjusted HR 1.13 (0.73–1.76), p = 0.58; **Figure 2C**]. With respect to dyspnea, 168 patients switched from ticagrelor to another P2Y12 inhibitor or discontinued P2Y12-therapy. No significant differences were found between *CYP3A5* non-expressors versus expressors [47.8% versus 35.3% OR 0.60 (0.27–1.30), p = 0.20; **Supplementary Figure S8** and **Supplementary Figure S9**].

Table 3. Clinical Endpoint for *CYP3A5* in patients treated with ticagrelor

Ticagrelor treated patients with *CYP3A422 non-carriers**					
Endpoint	**CYP3A5 non-expressors[a] (N=926)**	**CYP3A5 expressors[a] (N=196)**	**Unadjusted Hazard ratio (95% CI) ¥**	**Unadjusted p-value**	**Adjusted p-value**
Thrombotic endpoints - No. of patients (%)	**Cumulative incidence**	**Cumulative incidence**			
Cardiovascular death, MI, definite ST, and stroke	23 (2.5)	5 (2.6)	1.03 [0.39-2.71]	0.95	
Cardiovascular death	6 (0.6)	0 (0.0)		0.48	
Stroke	7 (0.8)	0 (0.0)		0.44	
Myocardial infarction					
Spontaneous MI	30 (3.2)	10 (5.1)		0.20	
Definite ST	6 (0.6)	1 (0.5)		0.88	
Bleeding endpoints - No. of patients (%)	**CYP3A5 non-expressors (N=926)**	**CYP3A5 expressors N=196**	**Unadjusted Hazard ratio (95% CI)**	**Adjusted Hazard ratio (95% CI)¥**	**Adjusted p-value**
PLATO major and minor bleeding	101 (10.9)	25 (12.8)	1.15 [0.74-1.77]	1.13 [0.73-1.76]	0.58
PLATO major	16 (1.7)	0 (0.0)			
PLATO minor	85 (9.2)	25 (12.8)	1.45 [0.92-2.30]	0.45 [0.92-2.29]	0.11
Side-effects - No. of patients (%)	**Cumulative incidence**	**Cumulative incidence**	**Unadjusted Odds Ratio**	**Unadjusted p-value**	
Dyspnea[b]	64 (47.8)	12 (35.3)	0.60 [0.27-1.30]	0.20	

ST, stent thrombosis; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes ¥ No confounders were chosen based on the univariate and multivariable cox regression models for the individual trombotic endpoints. For the bleeding endpoints the covariate prior stroke or TIA was used to adjust for confounders, see table 4 and 5 from the supplementary. [a]*CYP3A5* non-expressors are patients with the genotype *CYP3A5*3/*3*. [b] The total percentages were calculated based on all 168 patients who switched from ticagrelor to another P2Y12 inhibitor or discontinued treatment.

Clinical effect of CYP3A fast metabolizers

In this analysis, 195 *CYP3A* fast metabolizers (with both a *CYP3A4*1/*1* and *CYP3A5*1/1* or *CYP3A5*1/*3* genotype) and 1,094 CYP3A reduced metabolizers (patients with a *CYP3A4*1/*22* or *CYP3A4*22/*22* and *CYP3A5*3/*3* genotype) were compared (**Table 4**). No significant differences were found between the two groups for the combined thrombotic endpoint [2.6% vs. 2.3%, HR 1.13 (0.43–2.95), p = 0.81; **Figure 2F**], or the combined bleeding endpoint [12.8% vs. 11.2%, adjusted HR 1.13 (0.73–1.73), p = 0.59; **Figure 2E**]. With respect to dyspnea, 195 patients switched from ticagrelor to another P2Y12 inhibitor or discontinued P2Y12-therapy. No significant differences were found between *CYP3A* fast metabolizers versus reduced metabolizers [35.3% versus 47.2%, OR 0.60 (0.28–1.32), p = 0.21; **Table 4**].

Table 4. Clinical endpoint for CYP3A fast metabolizers *versus* CYP3A reduced metabolizers in patients treated with ticagrelor

	CYP3A fast metabolizers[a] (N=195)	**CYP3A reduced metabolizers[a] (N=1094)**	**Hazard ratio (95% CI)**	**P-value**
Thrombotic endpoint No. of patients (%)	**Cumulative incidence**	**Cumulative incidence**		
Cardiovascular death, MI, definite ST, and stroke	5 (2.6)	25 (2.3)	1.13 [0.43-2.95]	0.81
Cardiovascular death	0 (0.0)	6 (0.6)		0.17
Stroke	0 (0.0)	9 (0.8)		0.09
Myocardial infarction				
Spontaneous MI	5 (2.6)	13 (1.2)		0.17
Definite ST	1 (0.5)	8 (0.7)		0.99
Thrombotic endpoint No. of patients (%)				
PLATO major and minor bleeding	25 (12.8)	123 (11.2)	1.13 [0.73-1.73]	0.59
PLATO major	0 (0.0)	20 (1.8)		0.06
PLATO minor	25 (12.8)	103 (9.4)		0.15
	Cumulative incidence	**Cumulative incidence**	**Unadjusted Odds Ratio**	
Dyspnea[b]	12 (35.3)	76 (47.2)	0.61 [0.28-1.32]	0.21

ST, stent thrombosis; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes. [a]CYP3A fast metabolizers is defined by *CYP3A4*22* non-carriers and CYP3A5 non-expressors. CYP3A4 reduced metabolizers is defined by *CYP3A4*22* carriers and CYP3A5 expressors. [b]The total percentages were calculated based on all 195 patients who switched from ticagrelor to another P2Y12 inhibitor or discontinued treatment.

DISCUSSION

In this analysis, STEMI patients treated with ticagrelor who were carrier of a *CYP3A4*22* allele showed no statistical significant difference in thrombotic or bleeding rates compared to *CYP3A4*22* non-carriers. The same holds true for patients who were *CYP3A5* expressor versus *CYP3A5* non-expressor, adjusted for *CYP3A4*22* genotype (as only *CYP3A4*22* non-carriers were considered), and for CYP3A fast metabolizer versus CYP3A reduced metabolizer patients. Additionally, there was no significant difference in the rate of dyspnea in relation to the SNP's mentioned. Nevertheless, the number of patients with a thrombotic event was numerically higher in the *CYP3A4*22* non-carrier group, while bleeding was numerically lower. While no definite conclusions can be drawn based on a numerical trend, our data shows a direction of effect as was expected based on the rationale of the study analysis. Although our study population was relatively large, the number of patients carrying a *CYP3A4*22* allele was low, and therefore a recessive model had to be used (comparing *CYP3A4*1/*1* to **1/*22* plus **22/*22*), diluting a possible effect of the *CYP3A4*22* polymorphism. Analysis in a much larger patient cohort, using a dominant gene model, will be necessary to achieve adequate statistical power to draw definite conclusion.

CYP3A4*22 carriers

Earlier pharmacodynamic studies demonstrated a significant increase in ticagrelor concentration in *CYP3A4*22* carriers; however, these studies did not evaluate clinical endpoints for the CYP3A4*22 allele and GYP3A5 expressor statu.[11,12] For example, a study performed by Holmberg et al. in 19 healthy volunteers with the *CYP3A4*1/*1* genotype and six with the *CYP3A4*1/*22* genotype found that the AUG of ticagrelor was 89% higher in *CYP3A4*22* carriers than in **22* non-carriers, and **22* carriers showed more pronounced platelet inhibition (antiplatelet activity was tested with turbidimetric optical detection using the VerifyNow) 24 h after administration of a single dose of ticagrelor (43% vs. 21%, p = 0.029).[7] They concluded that the *CYP3A4*22* allele markedly impairs ticagrelor elimination, enhancing its antiplatelet effect, which could potentially lead to a higher risk for bleeding.

CYP3A5 expressor status

Liu et al. studied the effect of *CYP3A5*3* on platelet reactivity.[3] Only a minor impact of *CYP3A5*3* on platelet reactivity was found, which led the authors to conclude that there should be no dosage adjustment based on this allele.

Other genetic influences on ticagrelor

Varenhorst et al. performed a genome-wide association study (GWAS) with patients treated with ticagrelor in the PLATO trial, which was the landmark trial demonstrating the clinical effect of ticagrelor in AGS patients.[12,13] Using a discovery cohort (n = 1,812) and a replication cohort (n = 1,941), three genetic loci were found to be of genome wide significance (*CYP3A4*, *SLC O 1B1*, *UGT2B7*) for ticagrelor pharmacokinetics in this AGS patient cohort. The modest effects of these loci on ticagrelor plasma levels did not translate into any detectable effect on the primary composite endpoints, non-GABG-

related bleeding, or patient-reported dyspnea. The *CYP3A4* SNP included in the GWAS, however, was the *CYP3A4*7* allele (*rs56324128*), while the *CYP3A4*22* allele was not included.[14] The *CYP3A4*22* (*rs35593367G>T*) polymorphism results in an amino acid substitution and has been shown to impair the enzymatic function of *GYP3A4*, which result in a reduction in the elimination of ticagrelor; the function of the *CYP3A4*7* allele is unkown.[6,15] In this study *GYP3A4*7* was not determined, and therefore was not taken into account. There are currently no other studies known to the authors that evaluated the influence of *CYP3A4*22* or *CYP3A5*3* on clinical endpoints in patients using ticagrelor.[6]

Clinical relevance

Treatment regimens based on pharmacogenetic data are used more often in clinical practice, and have been shown to be important in STEMI patients treated with clopidogrel, based on *CYP2C19* genotype.[9] While treatment with antiplatelet drugs is a constant balancing act between efficacy (preventing thrombotic events) and safety (preventing bleeding events), any new factors influencing this balance might help to find the optimal balance for the individual patient.[12]

Limitations

This study has several important limitations. First, this was a sub study of a larger randomized trial; therefore, it was not powered for the primary endpoints. As mentioned above with respect to *CYP3A4*22* analysis, the low number of patients being homozygous for the *CYP3A4*22* allele led to the use of a recessive model (comparing *CYP3A4*1/*1* to **1/*22* and **22/*22*) instead of a dominant model. Therefore, a possible effect limited to patients homozygous for the *CYP3A4*22* allele or *GYP3A5* expressor status might have been underestimated or missed. Second, the use of strong *GYP3A4* inhibitors or inducers, other than statins, could not be accounted for, and could potentially have influenced the results. Finally, Varenhorst et al. found an association between other genetic loci, such as *UGT2B7* and *SLCO1B1*, and plasma ticagrelor levels, although there is no direct evidence for whether *UGT2B7* or *SLCO1B1* is involved in ticagrelor metabolism.[12] Those SNP's were not available for analysis in our patient cohort. In addition, the POPular Genetics trial randomized patients to genotyping versus conventional treatment. Therefore, *CYP2C19* genotype is not normally distributed over this study group, supposing that *CYP2C19* has no clinically relevant effect on ticagrelor there could still be a possible effect on *CYP3A4* or *CYP3A5*. The baseline shows that there is no significant difference between the two groups. Therefore, no further adjustments were made and the clinical effect is expected to be minimal.

Although the above limitations are clear, we feel that the unique nature of these data on SNP's in relation to clinical endpoints in ticagrelor treated ACS patients contributes to the understanding of the genetic influences of the *CYP3A* locus on ticagrelor metabolism and their impact on clinical endpoints.

CONCLUSION

The *CYP3A4*22* polymorphisms and *CYP3A5* expressor status in ticagrelor treated patients presenting with STEMI did not show a statistical significant association with bleeding or thrombotic events in this analysis. In addition, no association was found between *CYP3A4* or *CYP3A5* genotypes and dyspnea.

REFERENCES

1. Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., et al. (2017). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* 39 (2), 119–177. doi:10.1093/eurheartj/ehx393
2. Collet, J-P., Thiele, H., Barbato, E., Barthelemy, O., Bauersachs, J., Bhatt, D. L., et al. (2020). 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* 2020, 1289–1367. doi:10.1093/eurheartj/ehaa575
3. Liu, S., Shi, X., Tian, X., Zhang, X., Sun, Z., and Miao, L. (2017). Effect of CYP3A*41G and CYP3A5*3 polymorphisms on pharmacokinetics and pharmacodynamics of ticagrelor in healthy Chinese subjects. *Front. Pharmacol.* 8, 176–178. doi:10.3389/fphar.2017.00176
4. Teng, R., and Butler, K. (2013). Effect of the CYP3A inhibitors, diltiazem and ketoconazole, on ticagrelor pharmacokinetics in healthy volunteers. *J. Drug Assess.* 2 (1), 30–39. doi:10.3109/21556660.2013.785413
5. Wang, D., Guo, Y., Wrighton, S. A., Cooke, G. E., and Sadee, W. (2011). Intronic polymorphism in CYP3A4 affects hepatic expression and response to statin drugs. *Pharmacogenomics J.* 11, 274–286. doi:10.1038/tpj.2010.28
6. Mulder, T. A. M., van Eerden, R. A. G., de With, M., Elens, L., Hesselink, D. A., Matic, M., et al. (2021). CYP3A4*22 genotyping in clinical practice: Ready for implementation? *Front. Genet.* 12. doi:10.3389/fgene.2021.711943
7. Holmberg, M. T., Tornio, A., Paile-Hyvärinen, M., Tarkiainen, E. K., Neuvonen, M., Neuvonen, P. J., et al. (2019). CYP3A4*22 impairs the elimination of ticagrelor, but has no significant effect on the bioactivation of clopidogrel or prasugrel. *Clin. Pharmacol. Ther.* 105 (2), 448–457. doi:10.1002/cpt.1177
8. Bergmeijer, T. O., Janssen, P. W. A., Schipper, J. C., Qaderdan, K., Ishak, M., Ruitenbeek, R. S., et al. (2014). CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients. *Am. Heart J.* 168 (1), 16–22. doi:10.1016/j.ahj.2014.03.006
9. Claassens, D. M. F., Vos, G. J. A., Bergmeijer, T. O., Hermanides, R. S., van 't Hof, A. W. J., van der Harst, P., et al. (2019). A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N. Engl. J. Med.* 381 (17), 1621–1631. doi:10.1056/NEJMoa1907096
10. KASP thermal cycling. Available at: https://biosearch-cdn.azureedge.net/assetsv6/KASP-thermal-cycling-61-55 (Accessed November 21, 2022).
11. Kreutz, R. P., Owens, J., Jin, Y., Nystrom, P., Desta, Z., Kreutz, Y., et al. (2013). Cytochrome P450 3A4*22, PPAR-α, and ARNT polymorphisms and clopidogrel response. *Clin. Pharmacol.* 5, 185–192. doi:10.2147/CPAA.S53151
12. Varenhorst, C., Eriksson, N., Johansson, Å., Barratt, B. J., Hagstrom, E., Akerblom, A., et al. (2015). Effect of genetic variations on ticagrelor plasma levels and clinical outcomes. *Eur. Heart J.* 36 (29), 1901–1912a. doi:10.1093/eurheartj/ehv116
13. James, S. K., Roe, M. T., Cannon, C. P., Cornel, J. H., Horrow, J., Husted, S., et al. (2011). Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management. *BMJ* 342 (7812), 1–11. doi:10.1136/bmj.d3527
14. Eiselt, R., Domanski, T. L., Zibat, A., Mueller, R., Presecan-Siedel, E., Hustert, E., et al. (2001). Identification and functional characterization of eight CYP3A4 protein variants. *Pharmacogenetics* 11 (5), 447–458. doi:10.1097/00008571-200107000-00008
21. Nieuweboer, A., Clarke, S. J., and Charles, K. A. (2012). Lower CYP3A4 activity in cancer patients, as measured with probes midazolam and erythromycin. *Research Article*, 137–149.

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

CHAPTER 7

Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis

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ABSTRACT

Aims

Dual-antiplatelet therapy (DAPT) with aspirin and a potent P2Y12 inhibitor is the standard treatment for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). De-escalation of the potent P2Y12 inhibitor is an appealing concept to balance the ischaemic and bleeding risks after PCI. An individual patient data meta-analysis was performed to compare de-escalation versus standard DAPT in patients with ACS.

Methods and results

Electronic databases, including PubMed, Embase, and the Cochrane database, were searched to identify randomised clinical trials (RCTs) comparing the de-escalation strategy with the standard DAPT after PCI in patients with ACS. Individual patient-level data were collected from the relevant trials. The co-primary endpoints of interest were the ischaemic composite endpoint (a composite of cardiac death, myocardial infarction, and cerebrovascular events) and bleeding endpoint (any bleeding) at 1-year post-PCI. Four RCTs (the TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS, and TALOS-AMI trials) including 10 133 patients were analysed. The ischaemic endpoint was significantly lower in the patients assigned to the de-escalation strategy than in those assigned to the standard strategy (2.3% vs. 3.0%, hazard ratio [HR] 0.761, 95% confidence interval [CI] 0.597-0.972, log rank P = 0.029). Bleeding was also significantly lower in the de-escalation strategy group (6.5% vs. 9.1%, HR 0.701, 95% CI 0.606¬0.811, log rank P < 0.001). No significant intergroup differences were observed in terms of all-cause death and major bleeding events. Subgroup analyses revealed that compared to guided de-escalation, unguided de-escalation had a significantly larger impact on bleeding endpoint reduction (P for interaction = 0.007); no intergroup differences were observed for the ischaemic endpoints.

Conclusion

In this individual patient data meta-analysis, DAPT-based de-escalation was associated with both decreased ischaemic and bleeding endpoints. Reduction in bleeding endpoints was more prominent for the unguided than the guided de-escalation.

INTRODUCTION

Dual antiplatelet therapy (DAPT), consisting of aspirin and a potent P2Y12 inhibitor, is the standard treatment strategy after percutaneous coronary intervention (PCI) for patients with acute coronary syndrome (ACS).[1] Platelet inhibition for reducing thrombotic complications is essential within the first year after PCI, especially in those with high thrombotic risk such as ACS. Although potent P2Y12 inhibitors have proven beneficial for reducing the ischaemic outcomes, they are inherently associated with an increased risk of bleeding. Bleeding complications in these patients are not benign, because they have been associated with higher mortality and morbidity.[2] The increased bleeding risk can particularly outweigh the thrombotic risk after the acute phase when thrombotic risk significantly decreases.[3] Various antiplatelet strategies have been studied to reduce adverse outcomes by taking into account the change over time in the thrombotic and bleeding risks and balance the relative trade-off.[3] Among these, DAPT de-escalation, which is defined as switching be-tween oral P2Y12 inhibitors from a more potent to a less potent agent, may be a promising method and has been evaluated in various trials.[4] Such de-escalation strategies, including both guided and un-guided, have been included in the recent guidelines.[1,5] Previous study-level meta-analyses of randomized clinical trials (RCTs) have reported the outcomes of de-escalation strategies. However, these analyses focused on vastly heterogeneous strategies, wherein obtaining meaningful insights into the individual strategies was prohibitive.[6-8] Because of the inherent limitation of study-level analyses, investigators could not account for the time-dependent risk of de-escalation nor could they assess heterogeneity among studies for various outcomes. The absence of patient-level data prohibits the assessment of various characteristics that are related to safety and efficacy outcomes, including the individual ischaemic and bleeding risk profile.[9,10] The availability of individual data would allow the investigation of the association of these factors with de-escalation on adverse events and identification of those who could benefit the most from de-escalation.[11] A patient-level analysis based on a large cohort is needed to provide more in-sights into the impact of de-escalation strategies on thrombotic and bleeding risks. Given the clinical importance of understanding the potential benefits and safety of de-escalation strategies in patients with ACS, we aimed to conduct an individual patient meta-analysis of RCTs evaluating a DAPT de-escalation strategy in patients with ACS. We also performed landmark analyses of the de-escalation time points and subgroup analyses to compare different de-escalation methods, including guided and unguided de-escalation.

METHODS

Search strategy and selection criteria

This individual patient data meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was prospectively registered in the PROSPERO registry (ID: CRD42021245477). We searched the PubMed, Embase, and Cochrane databases to identify RCTs that evaluated the efficacy and safety of de-escalation strategies which were

published before 31 December 2021. We used the following search terms: ('acute coronary syndrome' OR 'ACS' OR 'myocardial infarction') AND ('primary' OR 'percutaneous coronary intervention' OR 'PCI') AND ('de-escalation' OR 'guided' OR 'guide') AND ('antiplatelet' OR 'P2Y12 inhibitor' OR 'P2Y12' OR 'dual antiplatelet therapy' OR 'DAPT'). Multicentre RCTs that included more than 1000 patients were included, while there were no language restrictions. Two authors (J.K. and J.C.) independently identified the studies that met the search criteria. Only published studies were included in the analysis; abstracts or conference presentations were not included. Conflicts over inclusion were resolved by consensus with a third author (K.W.P.). All studies were reviewed to identify any irrelevant duplicated studies. Four trials met the search criteria, and individual patient-level data were obtained from them. The search strategy is provided in the Supplementary Appendix. These data were reviewed by each trial investigator and com-pared with the data from previously published trials.

Study Endpoints

The co-primary endpoints for this analysis were ischaemic and bleeding endpoints at 12 months post-PCI. The ischaemic endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, and cerebrovascular events. The bleeding endpoint comprised type 2 or higher bleeding events (according to the Bleeding Academic Research Consortium [BARC] criteria) or major or minor bleeding events (according to the Platelet Inhibition and Patient Outcomes [PLATO] criteria). The secondary endpoints were the individual components of the primary endpoints, such as all-cause death, myocardial infarction, stent thrombosis, repeat revascularization, stroke, major bleeding (type 3 or 5 [according to the BARC criteria] or major [according to the PLATO criteria]). The endpoints in each trial were defined according to the definitions used in the original trials and are provided in Supplementary Appendix.

Landmark analyses were pre-specified and performed to consider the potential impact of specific de-escalation time points on the clinical endpoints. Subgroup analyses of the primary endpoint were performed for key pre-specified clinical subgroups, which included those classified by age, sex, renal function, diabetes status, and angiographic vessel disease. The interactions between the subgroup status and the treatment effect were tested.

Data-analysis

An individual participant data meta-analysis was planned with comparisons performed on an intention-to-treat basis. All patients received PCI for the treatment of ACS, and the time point 0 for the analysis was the point of randomization (after index PCI but before discharge), except for the TALOS-AMI trial in which randomization occurred 30±7 days post-PCI. For the TALOS-AMI trial, we used the time of PCI as time point 0 because the trial reported all events that occurred after PCI but before randomization. Continuous variables are presented as mean ± standard deviation, while categorical variables are expressed as counts and percentages. Continuous variables were compared using Student's t-test, while categorical variables were compared using the $\chi 2$ test. Adjustment for multiple hypothesis testing was not performed. Event rates were calculated using the Kaplan–Meier method, and a Cox proportional

hazard regression model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). The HRs, 95% CIs and P-values were calculated by the competing risk analysis based on the Fine and Gray method. The 95% CIs for secondary endpoints were not adjusted for multiple testing. The primary analysis was based on a one-stage approach, which simultaneously included all data from the trials using a fixed-effect and random-effect Cox regression model stratified by each trial. Subsequently, a two-stage analysis of the primary endpoints was performed through a trial-level approach with an inverse-variance method, based on the DerSimonian–Laird estimator for combining the trial-level estimates. A heterogeneity analysis was performed across the included trials by testing for an interaction between the trial and the treatment effect of the primary endpoint; this analysis was performed using the two-stage fixed-effects model with the I2 statistic and Cochran's Q test.

A Bayesian analysis of the co-primary endpoints at the time point of 12 months after randomization was also performed, assuming a non-informative prior with a uniform distribution of 0 to 1. The probabilities of absolute risk differences of 0.0%, at least 1.0%, and 2.5% in the primary endpoints between the two treatment arms were determined through Bayesian analysis. A two-sided P-value of <0.05 was considered significant for all tests. All analyses were performed using CRAN R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Our initial search yielded 1143 results; after applying the selection criteria, four RCTs (the TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS, and TALOS-AMI trials) were finally included in our meta-analysis (**Figure 1**). The detailed data for each trial are provided in Supplementary Appendix. Individual patient-level data were collected from all four RCTs. Among these RCTs, two evaluated guided de-escalation (the TROPICAL-ACS and POPular Genetics trials), while two evaluated unguided de-escalation (the HOST-REDUCE-POLYTECH-ACS and TALOS-AMI trials). All studies were considered to have a low bias risk (Supplementary Appendix).

The baseline characteristics of the pooled total population are presented in **Table 1**. A total of 10 133 patients were analysed, among which 5065 and 5068 patients were included in the de-escalation group (de-escalation DAPT strategy implemented) and the standard group (standard DAPT strategy implemented), respectively. During the 1-year follow-up period, 140 patients (2.8%) and 146 patients (2.9%) were lost to follow-up in the de-escalation group and the standard group, respectively. Adherence to the allocated medication was marginally higher in the de-escalation group (93.1% vs. 92.1%, P = 0.049). The median age of the total population was 57.8 years, and 86.0%.

Clinical endpoints

During the median follow-up duration of 365 days (interquartile range [IQR]: 351–365 days), the cumulative incidence of the ischaemic endpoint was 2.3% (95% CI 1.9%–2.8%) in the de-escalation group and 3.0% (95% CI 2.6%–3.5%) in the standard group (HR 0.761, 95% CI 0.597–0.972; log-rank P =

0.029; **Figure 2A**). Two-stage approaches yielded very similar results with no inter-trial heterogeneity observed (I2 = 0%, τ2 = 0%, Cochran's Q = 0.30, and P = 0.959; Supplementary Appendix). The cumulative incidence of the bleeding endpoint was 6.5% (95% CI 5.8%–7.1%) in the de-escalation group and 9.1% (95% CI 8.3%–9.9%) in the standard group (HR 0.701, 95% CI 0.606– 0.811; log-rank P < 0.001; **Figure 2B**).

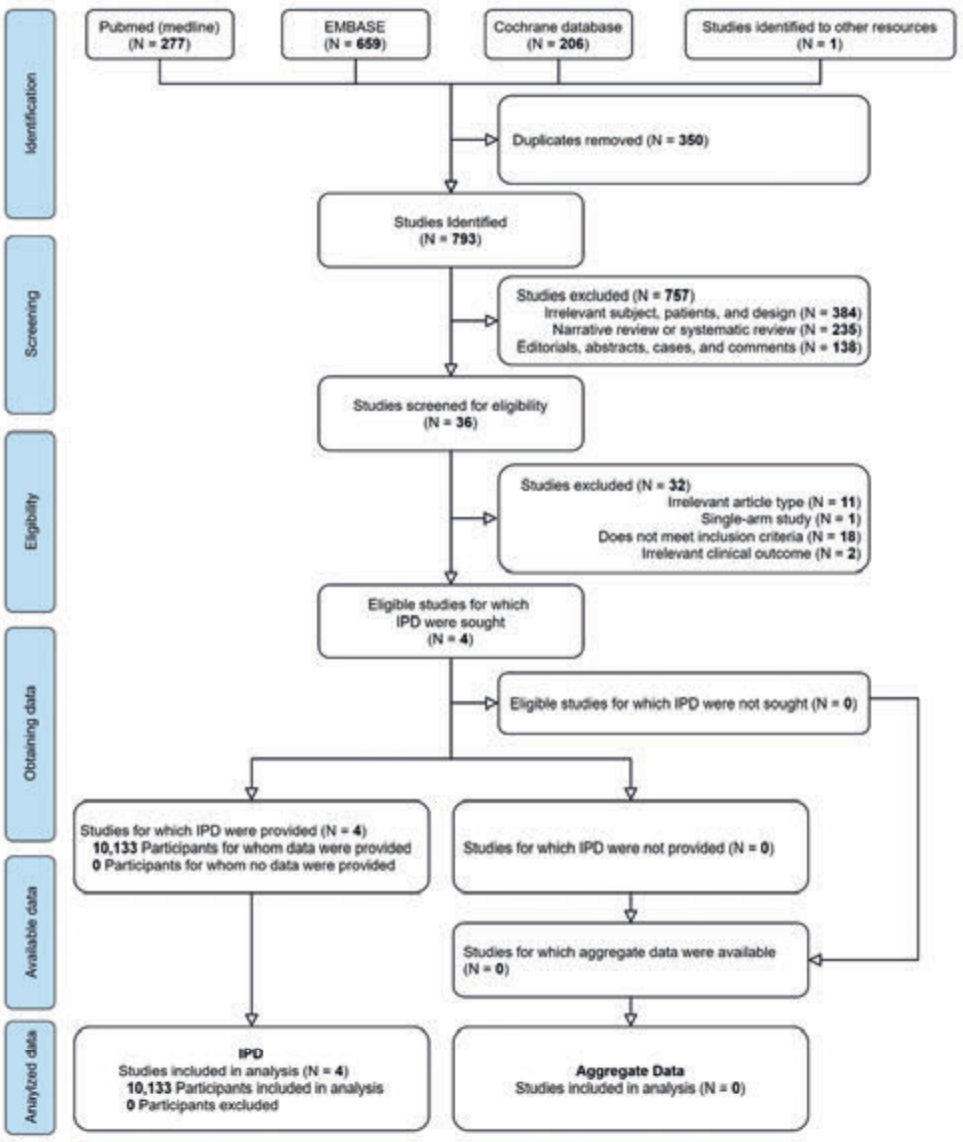

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1. Baseline characteristics of the total population

Characteristic	De-escalation (n = 5065)	Standard (N = 5068)
Demographics and comorbidities		
Age, years	59.9 ± 10.5	59.7 ± 10.7
Male sex	4136 (81.7%)	4108 (81.1%)
Ethnicity		
Caucasian	2486 (49.1%)	2488 (49.1%)
African	4 (0.1%)	3 (0.1%)
Arabian	14 (0.3%)	7 (0.1%)
Asian	2531 (50.0%)	2530 (49.9%)
Latin	11 (0.2%)	14 (0.3%)
Others	19 (0.4%)	26 (0.5%)
Height, cm	172 ± 9	172 ± 9
Body weight, kg	80.7 ± 14.9	80.6 ± 15.1
Body surface area, m^2	1.96 ± 0.21	1.96 ± 0.21
Diabetes mellitus	1264 (25.0%)	1272 (25.1%)
Hypertension	2702 (53.4%)	2723 (53.7%)
Dyslipidaemia	2351 (46.4%)	2356 (46.5%)
Current smoking	1168 (23.1%)	1155 (22.9%)
Chronic kidney disease	857 (16.9%)	818 (16.2%)
Previous PCI	440 (8.7%)	480 (9.5%)
Previous CABG	65 (1.3%)	79 (1.6%)
Clinical indication of PCI		
Unstable angina	689 (13.6%)	732 (14.4%)
NSTEMI	1496 (29.5%)	1494 (29.5%)
STEMI	2880 (56.9%)	2862 (56.1%)
Laboratory results		
Haemoglobin, g/dl	13.1 ± 2.8	13.0 ± 2.8
Creatinine, mg/dl	0.95 ± 0.52	0.95 ± 0.48
Antiplatelet agent at discharge		
Aspirin	5010 (99.2%)	5012 (99.2%)
P2Y12 inhibitor		
Clopidogrel	718 (14.2%)	114 (2.2%)
Prasugrel	2449 (48.4%)	2467 (48.7%)
Ticagrelor	1888 (37.3%)	2477 (48.9%)

Table 1. Continued

Antiplatelet agent at the de-escalation period		
Aspirin	4980 (98.3%)	5010 (98.9%)
P2Y12 inhibitor		
Clopidogrel	2835 (56.0%)	205 (4.0%)
Prasugrel	1611 (31.8%)	2345 (46.3%)
Ticagrelor	542 (10.7%)	2486 (49.1%)
Angiographic data per patient		
Extent of CAD		
1-vessel disease	2222 (58.4%)	2220 (58.2%)
2-vessel disease	1013 (26.5%)	1004 (26.3%)
3-vessel disease	582 (15.2%)	591 (15.5%)
Left main disease	121 (2.4%)	108 (2.1%)
Total number of implanted stents	1.0 [IQR 1.0–2.0]	1.0 [1.0–2.0]
Implanted stents ≥3	1545 (30.5%)	1
PCI-treated coronary artery		
Left main	90 (1.8%)	83 (1.8%)
Left anterior descending artery	2341 (46.2%)	2297 (45.3%)
Left circumflex artery	887 (17.5%)	965 (19.0%)
Right coronary artery	1740 (34.4%)	1695 (33.4%)

CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction. Data are presented as mean ± standard deviation, n (%), or median [interquartile range].

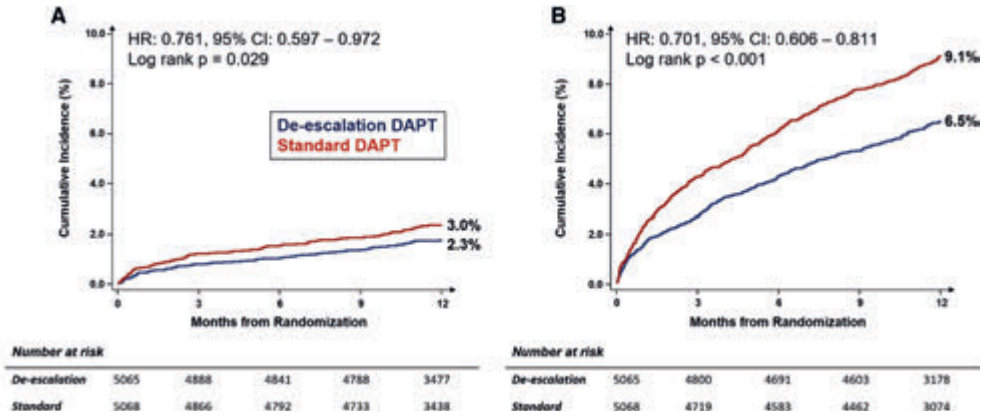

Figure 2. Cumulative analysis of the ischaemic endpoint and bleeding endpoint.

The Kaplan–Meier analysis curves of patients who received de-escalation strategy and standard strategy are shown for the ischaemic endpoint (A) and bleeding endpoint (B).

There was a trend for inter-trial heterogeneity, which did not reach the level of statistical significance (I2 = 56.6%, Cochran's Q = 6.91, and P = 0.075; **Supplementary Appendix**). The absolute risk differences at 12 months were 0.7% (95% CI 0.3%–1.1%) for the ischaemic endpoint and 2.6% (95% CI 1.9%–3.3%) for the bleeding endpoint. The cumulative incidences of the secondary endpoints are shown in **Table 2**, along with the competing risk for all endpoints except for mortality. The 1-year mortality rate was similar between the de-escalation and standard groups (1.0% [51/5065] vs. 1.1% [55/5068]; HR 0.925, 95% CI 0.632–1.354, log-rank P = 0.687). The incidence of ischaemic endpoints, including non-fatal myocardial infarction, cerebrovascular events, repeat revascularisation and stent thrombosis, were also similar between the de-escalation and standard groups. For major bleeding events, the incidence was numerically lower in the de-escalation group, but the difference did not reach statistical significance. No significant inter-trial heterogeneity was observed for the secondary endpoints in a two-staged approach (**Supplementary Appendix**).

As a sensitivity analysis, a landmark analysis was performed at the specific time point of de-escalation, which was unique for each study. Overall, the results were consistent with the original analysis. The risks of the ischaemic endpoint (HR 0.768, 95% CI 0.595–0.991; log-rank P = 0.041) and the bleeding endpoint (HR 0.693, 95% CI 0.596–0.807; logrank P < 0.001) were significantly lower in the de-escalation group than in the standard group (**Supplementary Appendix**).

Bayesian analysis revealed that the absolute risk difference for the bleeding events between the two groups was 2.48% (95% credible interval: 1.47%–3.51%). The probability that the bleeding events were more common in the standard group was 99.9%. More specifically, there was a 99.8% probability that the absolute risk difference in the bleeding events was at least 1.0%, and a 48.3% probability that the absolute risk difference for the bleeding events was at least 2.5%. Furthermore, the absolute risk difference for the ischaemic events between the two groups was 0.69% (95% credible interval: 0.07%–1.31%). The probability that the ischaemic events were more common in the standard group was 98.5%, with a 16.2% probability that the absolute risk difference was at least 1.0% (**Figure 3**).

Table 2. Clinical outcomes of the intention-to-treat population

	De-escalation (N = 5065)	Standard (N = 5068)	P-value[a]	Hazard ratio[b] (95% confidence interval)	P-value[b]
	% (No. of patients)*				
Primary endpoints					
Ischaemic endpoint[c]	2.3% (114)	3.0% (149)	0.029	0.76 (0.60–0.97)	0.029
Bleeding endpoint[d]	6.5% (312)	9.1% (438)	<0.001	0.70 (0.61–0.81)	<0.001
All-cause death	1.0% (51)	1.1% (55)	0.698	0.92 (0.63–1.35)	0.687
Cardiovascular death	0.5% (26)	0.7% (38)	0.133	0.68 (0.41–1.12)	0.132
Non-cardiovascular death	0.5% (25)	0.3% (17)	0.215	1.46 (0.79–2.71)	0.222
Non-fatal myocardial infarction	1.2% (62)	1.6% (82)	0.094	0.75 (0.54–1.05)	0.089
Cerebrovascular events	0.6% (30)	0.8% (39)	0.278	0.77 (0.48–1.24)	0.273
Major bleeding[e]	1.2% (60)	1.4% (71)	0.335	0.84 (0.60–1.19)	0.314
Any revascularization	2.4% (121)	2.3% (119)	0.892	1.01 (0.79–1.31)	0.914
Stent thrombosis	0.2% (8)	0.2% (11)	0.492	0.73 (0.29–1.80)	0.486

[a]The P value in the fourth column are the values form the $\chi 2$ test. [b]The hazard ratio and P-values in the sixth column were calculated by the competing risk analysis based on the Fine and Gray method. The 95% confidence intervals for secondary end points have not been adjusted for multiple testing. [c]Primary ischaemic endpoint is defined as a composite of cardiac death, non-fatal myocardial infarction, cerebrovascular events, and major bleeding events (BARC type ≥3). [d]Primary bleeding endpoint was defined as type 2, 3, or 5 bleeding events according to the BARC criteria or minor and major bleeding according to the PLATO criteria. [e]Major bleeding was defined as bleeding events defined as type 3 or 5 according to the BARC criteria or major bleeding according to the PLATO criteria. *Clinical endpoints were evaluated in the intention-to-treat population at 12 months after index PCI. The percentages shown are Kaplan–Meier estimates.

Subgroup analyses

Results of a comparison of the treatment effects between the de-escalation strategy and the standard therapy for key subgroups are presented in **Figure 4**. No statistically significant heterogeneity was observed for the ischaemic and bleeding endpoints across the clinical sub-groups, including those classified by age, diabetes, hypertension, renal function, smoking, clinical presentation as ST-elevation myocardial infarction, angiographic vessel disease, stent number, and the initial P2Y12 inhibitor usage. However, the impact of bleeding risk reduction by de-escalation was numerically larger when de-escalation was per-formed from ticagrelor to clopidogrel as compared to de-escalation from prasugrel to clopidogrel. Also, a significant interaction was found between the bleeding endpoints and the type of de-escalation strategy used (i.e. guided or unguided; P for interaction = 0.007). Unguided de-escalation and guided de-escalation reduced the bleeding events by 50% (HR 0.50, 95% CI 0.38–0.67, P < 0.001) and 21% (HR 0.79, 95% CI 0.67–0.94, P = 0.008) of the patients, respectively.

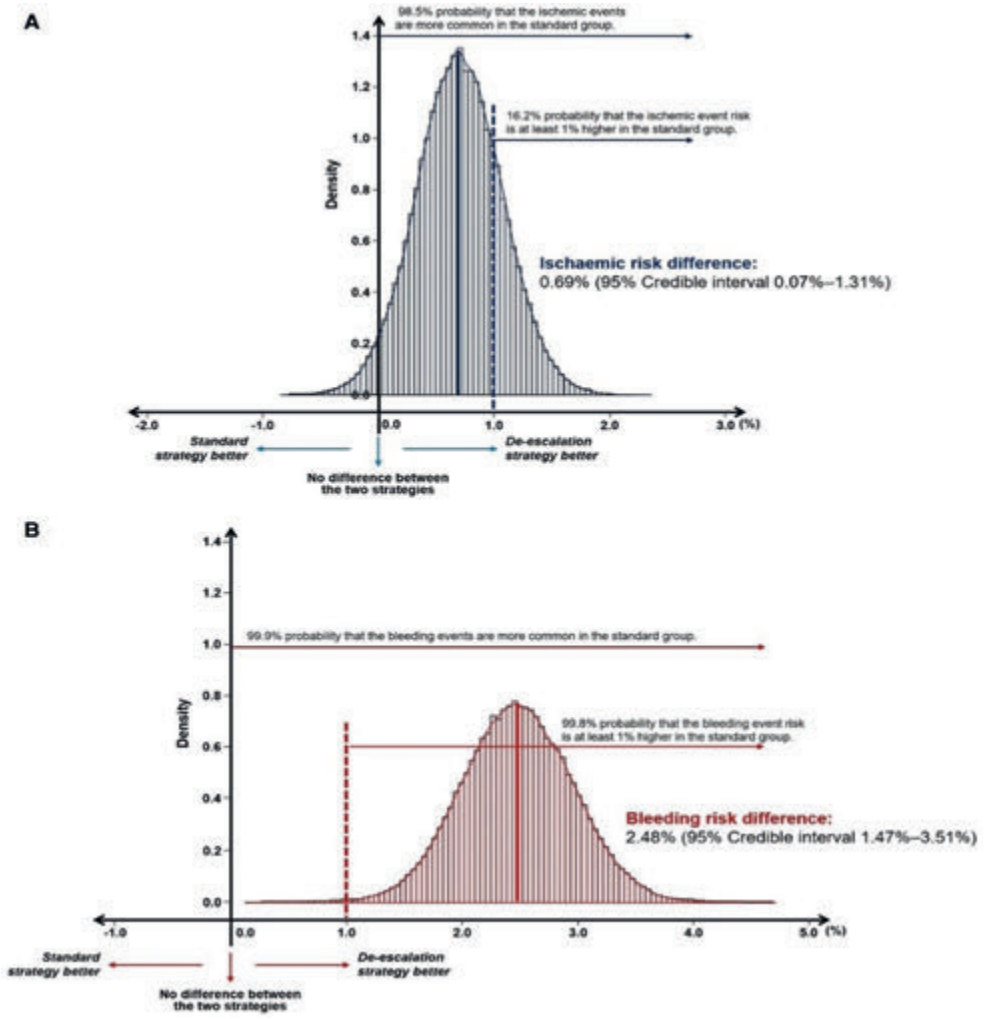

Figure 3. Density plot of the risk difference of ischaemic and bleeding endpoints.

The absolute risk difference of (A) ischaemic risk and (B) bleeding risk between the two strategies was calculated using the Bayesian analysis. The risk difference for endpoints were calculated at the timepoint of 12 months post-randomization between the two treatment arms.

A

	De-escalation	Standard	HR (95% CI)	p-value	P for interaction
Age					
< 65	61/3327	81/3349	0.75 (0.54-1.05)	0.094	0.935
≥ 65	53/1738	68/1719	0.77 (0.54-1.10)	0.151	
Gender					
Male	93/4136	115/4108	0.80 (0.61-1.05)	0.107	0.464
Female	21/929	34/960	0.64 (0.37-1.10)	0.103	
Hypertension					
No	43/2362	58/2344	0.73 (0.49-1.09)	0.121	0.530
Yes	71/2702	91/2723	0.78 (0.57-1.07)	0.121	
Diabetes					
No	73/3801	100/3795	0.73 (0.54-0.98)	0.037	0.585
Yes	41/1264	49/1272	0.84 (0.55-1.27)	0.400	
Chronic kidney disease					
No	81/4201	111/4244	0.73 (0.55-0.98)	0.033	0.988
Yes	33/857	38/818	0.83 (0.52-1.32)	0.430	
Current smoker					
No	71/2972	99/2962	0.71 (0.52-0.96)	0.028	0.644
Yes	40/2079	50/2092	0.80 (0.53-1.22)	0.297	
Clinical Diagnosis					
non-STE ACS	54/2185	57/2226	0.96 (0.66-1.39)	0.810	0.115
STEMI	60/2880	92/2642	0.64 (0.46-0.89)	0.008	
Angiographic disease					
1 vessel disease	35/2222	50/2220	0.69 (0.45-1.06)	0.093	0.700
Multivessel disease	45/1595	58/1595	0.78 (0.53-1.14)	0.199	
Stent number > 3					
No	74/3520	92/3497	0.79 (0.59-1.08)	0.141	0.654
Yes	40/1545	57/1571	0.71 (0.47-1.06)	0.095	
Initial P2Y12 inhibitor					
Ticagrelor	27/1349	38/1310	0.76 (0.53-1.08)	0.123	0.800
Prasugrel	53/2474	70/2474	0.69 (0.42-1.13)	0.144	
De-escalation guidance					
Unguided	48/2519	66/2516	0.72 (0.50-1.04)	0.080	0.688
Guided	66/2546	83/2552	0.80 (0.58-1.10)	0.168	

B

	De-escalation	Standard	HR (95% CI)	p-value	P for interaction
Age					
< 65	165/3327	238/3349	0.69 (0.56-0.84)	<0.001	0.819
≥ 65	147/1738	200/1719	0.71 (0.58-0.88)	0.002	
Gender					
Male	233/4136	328/4108	0.69 (0.59-0.82)	<0.001	0.761
Female	79/929	110/960	0.73 (0.55-0.98)	0.034	
Hypertension					
No	132/2362	198/2344	0.65 (0.52-0.81)	<0.001	0.342
Yes	180/2702	240/2723	0.75 (0.62-0.91)	0.003	
Diabetes					
No	255/3801	350/3795	0.72 (0.61-0.84)	<0.001	0.542
Yes	57/1264	88/1272	0.64 (0.46-0.89)	0.009	
Chronic kidney disease					
No	239/4201	349/4244	0.68 (0.58-0.80)	<0.001	0.505
Yes	71/857	87/818	0.77 (0.56-1.05)	0.097	
Current smoker					
No	188/2972	289/2962	0.64 (0.53-0.76)	<0.001	0.078
Yes	123/2079	147/2092	0.83 (0.66-1.06)	0.136	
Clinical Diagnosis					
non-STE ACS	107/2185	165/2226	0.65 (0.51-0.83)	<0.001	0.433
STEMI	205/2880	273/2842	0.73 (0.61-0.88)	0.001	
Angiographic disease					
1 vessel disease	108/2222	159/2220	0.67 (0.52-0.85)	0.001	0.966
Multivessel disease	76/1595	114/1586	0.66 (0.50-0.89)	0.005	
Stent number >3					
No	175/3520	253/3497	0.68 (0.56-0.82)	<0.001	0.618
Yes	137/1545	185/1571	0.73 (0.59-0.91)	0.006	
Initial P2Y12 inhibitor					
Ticagrelor	38/1349	71/1348	0.52 (0.35-0.77)	0.001	0.178
Prasugrel	146/2474	203/2474	0.71 (0.58-0.88)	0.002	
De-escalation guidance					
Unguided	71/2519	138/2516	0.50 (0.38-0.67)	<0.001	0.007
Guided	241/2546	300/2552	0.79 (0.67-0.94)	0.008	

Figure 4. Subgroup analysis.

Comparison of the treatment effects for the ischaemic endpoint (A) and the bleeding endpoint (B) between the de-escalation strategy and the standard therapy for the key subgroups.

DISCUSSION

In this meta-analysis, we analysed individual patient-level data from four RCTs. The analysis included 10 133 patients who were randomised to either the de-escalation DAPT strategy or the standard DAPT strategy after PCI for ACS. The main findings of the current study are as follows: (i) de-escalation was associated with a significant reduction in both the ischaemic and bleeding events, (ii) there was no significant difference in mortality between the two strategies, (iii) in a landmark analysis per-formed from the actual timepoint of de-escalation, which was unique for each trial, the beneficial effect of de-escalation for the ischaemic and bleeding events was consistent, and (iv) compared to guided DAPT de-escalation, unguided universal DAPT de-escalation was associated with a significantly larger reduction in bleeding (Structured Graphical Abstract).

In patients with ACS receiving PCI, the combination of aspirin and a potent P2Y12 receptor inhibitor is one of the key components of medical therapy. Due to the heightened thrombotic risk in ACS, potent P2Y12 inhibitors, such as prasugrel and ticagrelor, are recommended due to their enhanced potency and decreased variability of platelet inhibition.[12] Although the use of potent agents significantly reduced the ischaemic events, this came at the cost of increased bleeding. Moreover, previous studies have shown that the impact of major bleeding on mortality after PCI is comparable to that of recurrent thrombotic events, further supporting the clinical necessity to reduce both ischaemic and bleeding risks.[13,14] Therefore, there is a need for novel antithrombotic strategies, where the combined risk of ischaemia and bleeding can be minimized.[15] In this regard, de-escalation of the potent P2Y12 inhibitor may be a potential solution. The concept of de-escalation is based on the hypothesis that there is a temporal change in the risk of ischaemia and bleeding after PCI over time. The risk of thrombosis is the greatest immediately after PCI. However, it rapidly decreases along with the stabilization of the patient and the lesion.[16] However, the bleeding risk is maintained or does not decline at the rate that the ischaemic risk declines. Therefore, the relative impact of the bleeding risk increases, justifying a de-escalation strategy.[17,18] The interindividual variability in the response to clopidogrel also serves to justify the requirement of de-escalation.17 Numerous modifiable and unmodifiable factors (including the genetic polymorphisms of *CYP2C19*) may reduce the response to clopidogrel, which is associated with an increased risk of ischaemic events. These carriers of *CYP2C19* loss-of-function alleles may be the patients that need potent P2Y12 inhibitors. However, for patients that may achieve sufficient platelet inhibition with clopidogrel, pre-scribing a potent P2Y12 inhibitor may expose them to unnecessary bleeding risk.

Multiple RCTs have shown promising results supporting de-escalation and such a strategy is commonly adopted in clinical practice.[19] Consequently, de-escalation is backed by recent guidelines, which state that de-escalation may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition.1,5 A few study-level analyses have addressed the outcomes of de-escalation but until now, there has been no individual patient-level analysis of de-escalation. A well-designed patient-level analysis has several advantages, such as using common definitions and time-to-event data for estimating the survival of multiple studies.[20]

In the current analysis, we obtained patient-level data from four RCTs; each RCT compared a de-escalation DAPT strategy with a standard DAPT strategy. The TROPICAL-ACS trial was the first study to evaluate the safety and efficacy of guided de-escalation. In that study, de-escalation was guided by platelet function testing (PFT); all patients were started on prasugrel for 1 week and then switched to clopidogrel. Prasugrel was re-prescribed only in those with a high platelet reactivity to clopidogrel.[21] The study showed that PFT-guided de-escalation of P2Y12 inhibitor therapy was non-inferior to standard prasugrel therapy for preventing thrombotic events, with a similar rate of bleeding. The POPular Genetics trial evaluated a *CYP2C19* genotype-guided de-escalation strategy in patients with ST-elevation myocardial infarction. In the genotype-guided strategy group, *CYP2C19* genotyping was per-formed; the carriers of the *CYP2C19* loss-of-function allele were treated with ticagrelor or prasugrel, while non-carriers (C*YP2C19*1/*1*) were treated with clopidogrel.[22] No significant intergroup difference was observed in the ischaemic outcome, while the bleeding outcome was significantly decreased by 22% in the genotype-guided de-escalation group. The HOST-REDUCE-POLYTECH-ACS trial evaluated an unguided prasugrel-based dose de-escalation strategy.[23] One month after the index PCI, the de-escalation group received a prasugrel daily dose de-escalated from 10 to 5 mg. The rate of ischaemic out-comes was similar between the prasugrel-based de-escalation strategy and standard strategy groups, while the de-escalation group experienced a 52% bleeding risk reduction. Finally, the TALOS-AMI trial evaluated an unguided ticagrelor-based de-escalation strategy.[24] At 1-month post-PCI, ticagrelor was switched to clopidogrel in the de-escalation group. Between the de-escalation strategy group and the standard strategy group, there was no significant difference in the composite ischaemic outcome, while bleeding occurred less frequently in the de-escalation group (relative risk reduction of 48%). Collectively, all trials showed no difference in ischaemic outcomes; however, the bleeding complications were reduced by the de-escalation strategy in three trials. Of note, the TOPIC trial also evaluated unguided de-escalation.[25] The results in this trial were mostly in line with the current analysis, reporting that switching a potent P2Y12 inhibitor to clopidogrel at 1 month after PCI reduced bleeding without a significant increase in ischaemic outcomes in ACS patients. However, the trial was a single centre study with only 646 patients en-rolled and therefore was not included in the current analysis. Further, the TOPIC trial lacked data regarding clinical events that occurred within the first month after PCI.

According to the concept of de-escalation, it would seem appropriate that de-escalation would only reduce the bleeding complications and may have adverse effects on the ischaemic endpoints. However, previous RCTs did not show that the de-escalation strategy has a hazardous effect on the ischaemic risk, while a comprehensive evaluation of the true effect of de-escalation was difficult due to the distinct definition of ischaemic endpoints. In the current analysis, to evaluate the impact of platelet-centric ischaemic endpoints, we defined ischaemic endpoints as a composite of cardiac death, myocardial infarction, and cerebrovascular events. Our analysis showed that de-escalation was associated with a significantly reduced risk of platelet-centric ischaemic endpoints. A reduction in both the bleeding and ischaemic endpoints, which seems counterintuitive theoretically, is a phenomenon that has been observed in other trials.[26,27] This can be explained in several ways. First, compliance with antiplatelet agents can be poor in those who experience bleeding events, leading to increased

ischaemic endpoints. Second, various clinical factors (such as old age and chronic kidney disease) are associated with increased ischaemic and bleeding risks, therefore patients with these risk factors are at risk for various adverse events. Meticulous medical treatment in these patients would reduce both ischaemic and bleeding events. Third, cardiac death, by definition, is an ischaemic endpoint that may originate from a bleeding complication. Therefore, reducing the risk of bleeding may be associated with a reduction in cardiac death events.

In subgroup analysis, the treatment effect was consistent between various subgroups, with no significant interaction. However, the impact of bleeding risk reduction by unguided universal DAPT de-escalation was significantly larger compared to guided DAPT de-escalation. This may be due to the fact that in the guided studies, the bleeding reduction benefit of patients that received guided de-escalation is offset by those who are deemed to be poor clopidogrel responders and continue to receive potent P2Y12 inhibitors. Also, because the two universal de-escalation studies were both conducted in Asians, who have a lower ischaemic risk, the better efficacy needs to be interpreted with caution and cannot be extrapolated to other ethnicities or to those with high ischaemic risk. Additionally, the timing of de-escalation should be considered in interpreting the results. For guided de-escalation trials, the de-escalation timing was 48 h post-PCI (POPular Genetics) and 2 weeks post-PCI (TROPICAL-ACS), while that for unguided de-escalation trials were both 1-month post-PCI (HOST-REDUCE-POLYTECH-ACS, TALOS-AMI). Although subgroup analysis showed no significant inter-action between guided vs. unguided de-escalation and the ischaemic endpoint, an early unguided de-escalation may be harmful, especially in the early period after ACS, when the high ischaemic risk persists. Interestingly, bleeding risk reduction by de-escalation was numerically larger when de-escalation was performed from ticagrelor to clopidogrel as compared to de-escalation from prasugrel to clopidogrel. Such observation is in line with results from a previous trial which showed that prasugrel was associated with a lower bleeding risk than ticagrelor.[28]

Although guided and unguided de-escalation were similar with regard to ischaemic endpoints, significant improvements in the selection of patients in the guided approach could lead to better clinical out-comes. In particular, if early de-escalation is considered in patients at higher ischaemic risk, unguided de-escalation has the potential risk of increasing the risk of ischaemic adverse events. A previous study has shown that integrating clinical risk factors with genotyping could predict high on-treatment platelet reactivity, which may be used to increase the precision of selecting patients for guided de-escalation.[29]

Collectively, our findings show that compared to the standard DAPT strategy, de-escalation of the potent P2Y12 inhibitor provides clinical benefit where both ischaemic and bleeding events are decreased.

Limitations

There are important limitations that should be noted in the current study. First, our study only focused on DAPT de-escalation during the first year after index PCI. Recently, some studies have focused on potent P2Y12 inhibitor monotherapy after ultra-short-term DAPT within the first year after PCI, the so-called 'early P2Y12 monotherapy'.[26] The safety and efficacy of early P2Y12 monotherapy, with respect to those

of the DAPT de-escalation therapy, are beyond the scope of the current study. Second, the definition of clinical outcomes may differ between the trials; however, the endpoints that we analysed were hard endpoints that were free from such bias. Periprocedural myocardial infarction was excluded from the primary ischaemic endpoint, and we performed a landmark analysis as a sensitivity analysis to confirm the consistency of our findings. Third, we could not analyse the impact of the procedural complexity of PCI. It is well known that patients who receive complex PCI might require a stronger antiplatelet strategy. Our database lacked specific procedural information; there-fore, we could not analyse the impact of the de-escalation DAPT strategy in the complex PCI subgroup. Furthermore, we could not observe interactions between the complex PCI factors, including patients who received left main stenting, those with three-vessel disease, or those in whom more than two stents were implanted. Fourth, guided de-escalation RCTs were performed in Europe, while unguided de-escalation RCTs were performed in East Asia. Because the relative ischaemia–bleeding trade-off may be slightly different according to ethnicity, such differences may have affected the results of the analysis. As such, the generalizability of the current findings may be limited. Finally, although the concepts of guided and unguided de-escalation could be compared in the current study, a conclusion on which is the optimal de-escalation strategy cannot be drawn from the current data. This is because the individual trials used different P2Y12 inhibitors, and the timing of de-escalation was not the same. Guiding still seems to be potentially a safer strategy, particularly if considering early de-escalation or even if later in a population at higher ischaemic risk.

CONCLUSION

In conclusion, the de-escalation DAPT strategy compared with a standard DAPT strategy was associated with reductions in both the ischaemic and bleeding endpoints in patients with ACS who underwent PCI.

REFERENCES

1. Collet JP, Thiele H, Barbato E, Barthelemy 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. Eur Heart J 2021;42:1289–1367. https://doi. org/10.1093/eurheartj/ehaa575
2. Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coron-ary intervention. J Am Coll Cardiol 2015;66:1036–1045. https://doi.org/10.1016/j.jacc. 2015.06.1323
3. Kupka D, Sibbing D. De-escalation of P2Y12 receptor inhibitor therapy after acute cor-onary syndromes in patients undergoing percutaneous coronary intervention. Korean Circ J 2018;48:863–872. https://doi. org/10.4070/kcj.2018.0255
4. Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, et al. International expert consensus on switching platelet P2Y12 receptor-inhibiting therapies. Circulation 2017;136:1955–1975. https://doi.org/10.1161/ CIRCULATIONAHA.117. 031164
5. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87–165. https://doi.org/10.1093/eurheartj/ehy394
6. Shoji S, Kuno T, Fujisaki T, Takagi H, Briasoulis A, Deharo P, et al. De-escalation of dual antiplatelet therapy in patients with acute coronary syndromes. J Am Coll Cardiol 2021; 78:763–777. https://doi.org/10.1016/j. jacc.2021.06.012
7. Angiolillo DJ, Patti G, Chan KT, Han Y, Huang WC, Yakovlev A, et al. De-escalation from ticagrelor to clopidogrel in acute coronary syndrome patients: a systematic review and meta-analysis. J Thromb Thrombolysis 2019;48:1–10. https://doi.org/10.1007/s11239-019-01860-7
8. Khan SU, Khan MZ, Khan MS, Mahmood A, Kalra A, Kaluski E, et al. De-escalation of antiplatelets after percutaneous coronary intervention: a Bayesian network meta-analysis of various de-escalation strategies. Eur Heart J Cardiovasc Pharmacother 2021;7:209–215. https://doi.org/10.1093/ehjcvp/pvaa025
9. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Comparative effects of guided vs. Potent P2Y12 inhibitor therapy in acute coronary syn-drome: a network meta-analysis of 61 898 patients from 15 randomized trials. Eur Heart J 2022;43:959–967. https://doi.org/10.1093/eurheartj/ehab836
10. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary interven-tion: a systematic review and meta-analysis. Lancet 2021;397:1470–1483. https://doi. org/10.1016/S0140-6736(21)00533-X
11. Tavenier AH, Mehran R, Chiarito M, Cao D, Pivato CA, Nicolas J, et al. Guided and un-guided de-escalation from potent P2Y12 inhibitors among patients with acute coronary syndrome: a meta-analysis. Eur HeartJ Cardiovasc Pharmacother 2022;8:492–502. https:// doi.org/10.1093/ehjcvp/pvab068
12. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collabor-ation with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European society of cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–260. https://doi.org/10. 1093/eurheartj/ehx419

13. Corrigendum to: 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:3096. https://doi.org/10.1093/eurheartj/ehz507
14. Vranckx P, Leonardi S, Tebaldi M, Biscaglia S, Parrinello G, Rao SV, et al. Prospective val-idation of the bleeding academic research consortium classification in the all-comer PRODIGY trial. Eur Heart J 2014;35:2524–2529. https://doi.org/10.1093/eurheartj/ ehu161
15. Chhatriwalla AK, Amin AP, Kennedy KF, House JA, Cohen DJ, Rao SV, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary inter-vention. JAMA 2013;309:1022–1029. https://doi.org/10.1001/jama.2013.1556
16. Gallone G, Baldetti L, Pagnesi M, Latib A, Colombo A, Libby P, et al. Medical therapy for long-term prevention of atherothrombosis following an acute coronary syndrome: JACC state-of-the-art review. J Am Coll Cardiol 2018;72:2886–2903. https://doi.org/ 10.1016/j.jacc.2018.09.052
17. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in percutaneous coronary intervention. JACC Cardiovasc !nterv 2019;12:1521–1537. https://doi.org/10.1016/j.jcin.2019.03.034
18. Sinnaeve PR, Adriaenssens T. Dual antiplatelet therapy de-escalation strategies. Am J Cardiol 2021;144:S23–S31. https://doi.org/10.1016/j.amjcard.2020.12.020
19. Bagai A, Peterson ED, Honeycutt E, Effron MB, Cohen DJ, Goodman SG, et al. In-hospital switching between adenosine diphosphate receptor inhibitors in patients with acute myocardial infarction treated with percutaneous coronary intervention: in-sights into contemporary practice from the TRANSLATE-ACS study. Eur Heart J Acute Cardiovasc Care 2015;4:499–508. https://doi.org/10.1177/2048872614564082
20. Lyman GH, Kuderer NM. The strengths and limitations of meta-analyses based on aggregate data. BMC Med Res Methodol 2005;5:14. https://doi.org/10.1186/1471-2288-5-14
21. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergo-ing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747–1757. https://doi.org/10.1016/S0140-6736(17)32155-4
22. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van't Hof AWJ, van der Harst P, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med 2019;381:1621–1631. https://doi.org/10.1056/NEJMoa1907096
23. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, et al. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in pa-tients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. Lancet 2020;396:1079–1089. https://doi.org/10.1016/S0140-6736(20)31791-8
24. Kim CJ, Park MW, Kim MC, Choo EH, Hwang BH, Lee KY, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. Lancet 2021;398: 1305–1316. https://doi.org/10.1016/S0140-6736(21)01445-8

25. Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet in-hibition after acute coronary syndrome) randomized study. Eur HeartJ 2017;38:3070–3078. https:/doi.org/10.1093/eurheartj/ehx175
26. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–2042. https://doi.org/10.1056/NEJMoa1908419
27. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicen-tre trial. Lancet 2021;397:2487–2496. https://doi.org/10.1016/S0140-6736(21)01063-1
28. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381: 1524–1534.
29. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, Ten Berg JM, et al. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clo-pidogrel: the ABCD-GENE score. JACC Cardiovasc Interv 2020;13:606–617. https://doi. org/10.1016/j.jcin.2020.01.226

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

CHAPTER 8

Genotype-Guided vs. Conventional Oral P2Y12 inhibitors in Acute Coronary Syndrome: a combined analysis of TAILOR-PCI and POPular Genetics Genotype-Guided P2Y12 Therapy in ACS

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ABSTRACT

Background

Genetic testing has been proposed as a tool to guide the selection of an oral P2Y12 inhibitor in patients with acute coronary syndrome (ACS) or in those undergoing percutaneous coronary interventions (PCI). This genotype-guided approach may lead to either de-escalation or escalation of antiplatelet therapy, each carrying distinct implications for clinical outcomes.

Methods

We performed a systematic review and an individual participant data meta-analysis of randomized controlled trials (RCTs) comparing guided therapy using *CYP2C19* genetic testing vs. conventional therapy among patients with ACS undergoing PCI. The primary safety endpoint was time to first type 2, 3 or 5 BARC bleeding at 12 months. The primary efficacy endpoint was time to first major adverse cardiovascular event (MACE) at 12 months. Secondary endpoints included net adverse cardiovascular events (NACE) and the individual components of the primary outcomes. Pre-specified analysis considering guided escalation and de-escalation as separate strategies was conducted.

Results

Two RCTs met the search criteria and individual participant-level data were obtained. A total of 6,734 participants were available for analysis. After 1 year, there were no differences in the primary safety (adjusted Hazard Ratio [$_{adj}$HR] 0.88; 95% CI 0.72,1.06) or efficacy endpoints (0.83; 95% CI 0.63,1.09) in with overall guided vs. conventional therapy. However, guided therapy reduced myocardial infarction (0.68; 95% CI 0.48,0.97) and NACE (0.85; 95% CI 0.73,1.00) compared with conventional therapy. Guided de-escalation reduced the primary safety endpoint (0.77; 95% CI 0.62,0.97) and NACE (0.77; 95% CI 0.62,0.94) with no significant difference in MACE, compared to the conventional therapy. The primary safety and efficacy endpoints were similar between patients undergoing guided escalation and conventional therapy groups. Time-dependent covariate analyses showed that overall guided and de-escalation strategies reduced bleeding and NACE prior to 90 days, compared to conventional therapy.

Conclusion

These findings highlight the need to evaluate the clinical impact of genotype-guided therapy by separately assessing de-escalation and escalation strategies. Among ACS patients undergoing PCI, genotype-guided de-escalation reduces bleeding and NACE without increasing MACE compared to conventional therapy. The benefits of genotype-guided therapy were greater within the first 3 months after PCI.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is recommended for the prevention of thrombotic events in patients with an acute coronary syndrome (ACS) or those undergoing percutaneous coronary intervention (PCI).[1,2] In ACS patients undergoing PCI, P2Y12 inhibition with prasugrel or ticagrelor is preferred over clopidogrel given their enhanced efficacy.[2,3] However, such ischemic benefit comes at the expense of an increased risk of bleeding.[4,5] Studies suggest that the superior efficacy of prasugrel and ticagrelor occurs because of pharmacologic variability in clopidogrel response, whereas they achieve limited ischemic benefit and increased bleeding in patients with adequate clopidogrel-induced platelet inhibition or in *CYP2C19* loss-of-function (LoF) genetic variant non-carriers.[6-9] These observations have set the foundations for a guided selection of P2Y12 inhibiting therapy (i.e., genetic testing) with the aim of optimizing the balance between bleeding and ischemic risks[9,10]. Clopidogrel, but not prasugrel or ticagrelor, is activated primarily after being metabolized by a highly polymorphic hepatic cytochrome (CYP)2C19 enzyme.[11,12] LoF genetic variants in *CYP2C19* alleles (i.e., **2* and **3*) result in decreased clopidogrel metabolism leading to decreased active metabolite levels, increased rates of high platelet reactivity (HPR) and thrombotic complications while on clopidogrel therapy.[13-16] Therefore, genetic testing can identify these patients and guide the personalized selection of LoF carriers to be treated with prasugrel or ticagrelor and LoF non-carriers to be treated with clopidogrel as opposed to the universal use of prasugrel or ticagrelor which results in increased bleeding and limited ischemic benefit.[9,10] However, the expected outcomes of a guided selection of P2Y12 inhibiting therapy depends on whether it leads to a strategy of de-escalation (i.e., reduction in potency) or escalation (i.e., increase in potency) of platelet inhibition relative to the standard therapy.[9] This distinction is crucial to best define the benefits associated with a specific genotype-guided strategy instead of combining the outcomes of approaches with converse intended benefits which may conceal its true impact.[9] To date, randomized clinical trials (RCTs) assessing the clinical benefits of a genotype-guided vs. standard selection of P2Y12 inhibitor therapy are limited by heterogeneity in the approaches as well as the sample size to have the statistical power to assess for differences in ischemic and bleeding endpoints.[9,10] We conducted a systematic review and an individual participant data meta-analysis (IPD-MA) of RCTs to determine whether a genotype-guided de-escalation or escalation of oral P2Y12 inhibiting therapy may improve outcomes compared to standard therapy in patients with ACS undergoing PCI.

METHODS

Search strategy and eligibility criteria

This systematic review was reported in accordance with the Guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (**Table S1**). The protocol was prospectively registered in PROSPERO and is available online (www.crd.york.ac.uk/prospero, CRD42024580431). An updated version of the study protocol is provided as supplementary appendix.

From database inception to November 2023 we searched MEDLINE with PubMed interface, the Cochrane Central Register of Controlled Trials, Embase and the Web of Science databases. Search terms included: "acute coronary syndrome", "myocardial infarction", "percutaneous coronary intervention", "genotype", "guided", "guide", "P2Y12 inhibitor", "antiplatelet", as well as combinations of these terms. The full search strategy is provided in **Table S2**. Citations were screened on the basis of title and abstract by two independent reviewers. Potentially eligible reports were retrieved and scrutinized for eligibility in full-article. Reference lists of the eligible reports were reviewed for any eligible reports not captured initially. Only full-text published studies were included in the analysis, with no language restrictions. The inclusion criteria were: (i) randomized clinical trial, (ii) inclusion of patients presenting with ACS and treated with PCI, (iii) comparison between genotype-guided vs. conventional therapy among the totality of patients undergoing PCI, (iv) reporting clinical outcomes at a follow-up ≥12 months. The exclusion criteria were: (i) non-randomized studies, (ii) selective inclusion of patients presenting with chronic coronary syndrome (CCS), (iii) studies using a genetic testing panel different from that currently recommended (i.e., inclusive of *CYP2C19 *2* and *3* LoF alleles), (iv) use of antiplatelet therapy different from that currently recommended (i.e., cilostazol or high- dose clopidogrel), and (v) inadequate use of alternative antiplatelet therapy in *CYP2C19* LoF carriers in the guided group (i.e. use of prasugrel or ticagrelor <90%).[2,3,17] Studies in which P2Y12 inhibitor selection was guided by platelet function testing were also excluded. Two investigators (M.G. and D.J.A.) independently determined whether the studies met the pre-specified eligibility criteria. Disagreements were resolved by consensus. Our initial search yielded 966 unique citations; after applying the pre-specified eligibility criteria, two RCTs were deemed eligible after full text review (**Figure S1** for study selection flow-chart): Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPular Genetics) and Tailored Antiplatelet Therapy Following PCI (TAILOR- PCI)[18,19]. The principal investigators of these trials agreed to provide their data for this IPD-MA. In June 2024, an updated search was conducted using the exact same search strategy that did not identify other eligible RCTs.

Study Endpoints

The pre-specified co-primary endpoints were a safety endpoint of minor and major bleeding at 12 months post-PCI and an efficacy endpoint of major adverse cardiovascular events (MACE). The primary safety endpoint included time to first type 2, 3 or 5 Bleeding Academic Research Consortium (BARC) bleeding events. The primary efficacy endpoint of time to first MACE was a composite of cardiovascular (CV) death, non-fatal myocardial infarction (MI), definite or probable stent thrombosis (ST), and stroke. Secondary endpoints included time to first individual components of the primary endpoints, including CV death, MI, stroke, and ST as well as BARC 3 or 5 bleeding and net adverse clinical events (NACE; a composite of CV death, MI, ST, stroke and BARC 2, 3 or 5 bleeding) at 12 months. **Table S3** reports the detailed definitions of outcomes in the RCTs that were included.

Data extraction and quality assessment

After obtaining electronic datasets of anonymized individual participant data, all data were reviewed for completeness and consistency and compared with the results from the previously published reports. Details about the inclusion and exclusion criteria as well as of baseline and procedural characteristics of included studies are reported in **Table S4** and **S5**, respectively. Clinical outcomes among included trials are reported in **Table S6**.

Two investigators (M.G. and D.J.A) independently assessed the risk of bias by using the Cochrane Risk-of-Bias tool 2 (**Figure S2**). Disagreements were solved by discussion. To maintain a homogeneous cohort of patients, we excluded from the TAILOR-PCI dataset patients with CCS (n= 972) and patients with concomitant oral anticoagulant use (n= 115). Similarly, we excluded from the POPular Genetics dataset patients with concomitant oral anticoagulant use (n= 122). Moreover, we included patients from the POPular Genetics dataset who were enrolled prior to the major protocol revision who shifted from an escalation to de-escalation strategy, as well as those who experienced events within the first 24 hours after PCI (n= 179). A flow-diagram of the study is reported in **Figure S3**.[18]

Data analysis

All individual level data from both trials were available and were combined into a single data set for analysis (one-stage approach). Categorical variables were expressed as frequencies and percentages and continuous variables were presented as mean (SD). Baseline variables were compared using standardized differences given the randomization into the 2 groups, with values greater than 0.1 indicating substantial imbalance. Post-randomization variables were tested using Pearson's chi-squared test for discrete variables, the Wilcoxon rank-sum test for continuous variables and a log-rank test for time-to-event variables. Kaplan-Meier curves were estimated for time-to-first first event by treatment group, both overall and within treatment strategy, and these estimates are used when reporting percentage of events at 12 months.

Endpoints were modeled as time-to-first event using a Cox proportional hazards model, adjusted for pre-specified covariates which were used in stratified randomization (age, gender, ST- segment elevation myocardial infarction [STEMI] and site) as well as with interaction terms between trial and covariate[20]. Differing event rates per trial were handled by using separate baseline hazards per trial. Proportional hazard ratios (HR) over time were reported with 95% confidence intervals (CI). A two-sided P-value of <0.05 was considered significant for all tests. Enrolling site was modeled as a random effect.

All the analyses were run according to the pre-specified sensitivity analysis considering escalation and de-escalation as separate strategies. Escalation and de-escalation were defined according to the P2Y12 inhibitor used in the conventional therapy group. In particular, in line with Academic Research Consortium definitions, "de-escalation" was defined as a decrease in intensity of platelet inhibition (i.e., switching from prasugrel or ticagrelor to clopidogrel) and "escalation" was defined as an increase in intensity of platelet inhibition (i.e., switching from clopidogrel to prasugrel or ticagrelor).[21] Pre-specified sensitivity analyses included modeling recurrent events using an Andersen-Gill approach, and time-

dependent effects to determine if the treatment effect was different in the first 90 days after PCI compared to the effect from 91 days to 12 months post- PCI.

Subgroups were analyzed using an extension of the primary models with an interaction approach for one-stage meta-analysis models.[22] A sensitivity analysis using two-stage meta-models was also performed. Terms for both the across-site and within-site interactions were included, using site covariate means and within-site centered covariates, respectively to avoid ecological bias. Pre- specified subgroup analyses of the primary endpoints included the following variables: age (≥75 vs. <75 years), sex (male vs. female), ethnicity (Asian vs. Caucasian vs. other), clinical presentation 11 (STEMI vs. non-ST segment elevation MI [NSTEMI] or unstable angina [UA]), renal function (estimated glomerular filtration rate ≥60 mL/min vs. <60 mL/min), diabetes mellitus status (yes vs. no), body weight (body mass index ≥30 vs. <30), complexity of PCT (yes vs. no), use of proton pump inhibitor (yes vs. no), *CYP2C19* carrier status (homozygotes vs. heterozygotes). The within- site variables were used to estimate subgroup hazard ratios for these patient level risk factors and to calculate the interaction p-value. Interaction tests for strategy (de-escalation/escalation) were based on across site effects. Six patients were missing STEMI at presentation and were excluded from modeling. Sensitivity analyses included an analysis selectively in STEMI patients and an extended analysis encompassing all patients from the original datasets, including those with CCS or concomitant anticoagulant use. All analyses were conducted with SAS software, version 9.4 (SAS Institute Inc).

RESULTS

A total of 6,734 patients were analyzed, with 3,358 participants assigned to the genotype- guided group and 3,376 to the conventional therapy group. The baseline characteristics of the pooled total population are presented in **Table 1**. Clopidogrel (63.6%) and ticagrelor (35.5%) were the most commonly used oral P2Y12 inhibitors at discharge, with only 1.2% of patients being prescribed prasugrel. All included patients underwent PCI. Nearly 30% of patients were carriers of one (heterozygous) and 5% carriers of two (homozygous) *CYP2C19* LoF alleles. Approximately 35% of participants in the genotype-guided arms underwent a strategy of de-escalation (n=1,191) and 65% (n=2,167) of escalation, compared with conventional therapy. Baseline characteristics according to de-escalation or escalation strategies are reported in **Tables S7** and **S8**. Baseline characteristics in STEMI patients are reported in **Table S9**. Both studies were assessed as having a low risk of bias (**Figure S2**).

Table 1. Baseline and procedural characteristics of conventional vs. guided therapy.

Variable	Conventional Therapy (N=3376)	Genotype-guided Therapy (N=3358)	Absolute Std. Diff.
Age			1.7%
Mean, SD	61.6 (11.3)	61.7 (11.0)	
Median (Q1, Q3)	61 (54, 69)	62 (54, 69)	
Age, y, n (%)			
<50	496 (14.7%)	471 (14.0%)	1.9%
50-59	976 (28.9%)	977 (29.1%)	0.4%
60-69	1065 (31.5%)	1082 (32.2%)	1.4%
70-74	375 (11.1%)	364 (10.8%)	0.9%
75-79	267 (7.9%)	266 (7.9%)	0.0%
80+	197 (5.8%)	198 (5.9%)	0.3%
Sex, n (%)			
Male	2543 (75.3%)	2516 (74.9%)	0.9%
Female	833 (24.7%)	842 (25.1%)	0.9%
Race/ethnicity, n (%)			
African/Black	52 (1.5%)	53 (1.6%)	0.2%
Asian	707 (20.9%)	728 (21.7%)	1.8%
Caucasian	2448 (72.5%)	2411 (71.8%)	1.6%
Hispanic/Latino	73 (2.2%)	76 (2.3%)	0.6%
Other/Unknown	96 (2.8%)	90 (2.7%)	1.0%
Strategy, n (%)			
de-escalation	1192 (35.3%)	1191 (35.5%)	0.3%
escalation	2184 (64.7%)	2167 (64.5%)	0.3%
CYP2C19*2/*3, n (%)			
Non-carrier	1971 (64.9%)	2034 (64.5%)	0.9%
Heterozygous	915 (30.1%)	967 (30.7%)	1.2%
Homozygous	149 (4.9%)	151 (4.8%)	0.6%
Trial population, n (%)			
POPular	1272 (37.7%)	1273 (37.9%)	0.5%
TAILOR-PCI	2104 (62.3%)	2085 (62.1%)	0.5%
Presentation, n (%)			
ACS/NSTEMI	1573 (46.6%)	1555 (46.4%)	0.5%
STEMI	1801 (53.4%)	1799 (53.6%)	0.5%
Body Mass Index			3.1%
Mean, SD	28.0 (5.4)	28.2 (5.5)	
Median (Q1, Q3)	27 (25, 30)	27 (25, 31)	

Table 1. Continued

Diabetes, n (%)	678 (20.1%)	730 (21.7%)	4.1%
Dyslipidemia, n (%)	1268 (37.6%)	1237 (36.9%)	1.5%
Hypertension, n (%)	1779 (52.8%)	1792 (53.4%)	1.3%
PAD, n (%)	75 (2.2%)	86 (2.6%)	2.2%
History of MI, n (%)	358 (10.6%)	382 (11.4%)	2.5%
History of CABG, n (%)	140 (4.1%)	130 (3.9%)	1.4%
Stroke/TIA, n (%)	84 (2.5%)	83 (2.5%)	0.1%
History of PCI, n (%)	501 (14.8%)	518 (15.4%)	1.6%
Family History of CAD, n (%)	1229 (37.1%)	1237 (37.7%)	1.1%
Smoking status, n (%)			
Current smoker	1223 (36.8%)	1207 (36.4%)	0.8%
Former smoker	820 (24.7%)	809 (24.4%)	0.6%
Never smoker	1278 (38.5%)	1297 (39.1%)	1.4%
Baseline LVEF, n (%)			
Severly reduced (<30%)	15 (0.4%)	17 (0.5%)	0.4%
Reduced	213 (6.3%)	193 (5.7%)	2.4%
Preserved (>50%)	944 (28.0%)	974 (29.0%)	2.3%
Unknown	2204 (65.3%)	2174 (64.7%)	1.1%
Estimated GFR			4.5%
Mean, SD	87.0 (23.7)	88.1 (26.6)	
Median (Q1, Q3)	87 (73, 100)	88 (73, 100)	
Vascular access site, n (%)			
Femoral	968 (28.7%)	1028 (30.6%)	4.3%
Radial	2369 (70.2%)	2293 (68.3%)	4.1%
Other/unknown	39 (1.2%)	37 (1.1%)	0.3%
BMS Stent, n (%)	188 (5.6%)	198 (5.9%)	1.4%
DES Stent, n (%)	3155 (93.5%)	3143 (93.6%)	0.6%
Any PCI in graft, n (%)	64 (1.9%)	50 (1.5%)	2.6%
PCI in LAD, n (%)	1581 (46.8%)	1575 (46.9%)	0.1%
PCI in LMCA, n (%)	52 (1.5%)	57 (1.7%)	1.0%
PCI in RCA, n (%)	1278 (37.9%)	1298 (38.7%)	1.6%
PCI in LCX, n (%)	818 (24.2%)	770 (22.9%)	3.1%
Complex PCI | High/C lesion, n (%)	1254 (37.1%)	1246 (37.1%)	0.1%
Clopidogrel at discharge, n (%)	2192 (64.9%)	2089 (62.2%)	2.0%
Ticagrelor at discharge, n (%)	1152 (34.1%)	1239 (36.9%)	1.8%
Prasugrel at discharge, n (%)	34 (1.0%)	50 (1.5%)	8%
Statin at discharge, n (%)	3232 (95.9%)	3241 (96.6%)	12%

Table 1. Continued

PPI at discharge, n (%)	1549 (46.0%)	1545 (46.1%)	93%
Beta-blocker at discharge, n (%)	2834 (84.1%)	2846 (84.9%)	39%
ACE inhibitor at discharge, n (%)	1932 (57.3%)	1900 (56.6%)	57%
CCB at discharge, n (%)	455 (13.5%)	444 (13.2%)	75%

Abbreviations: SD: standard deviation; CYP: cytochrome; ACS: acute coronary syndrome; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; PAD: peripheral artery disease; MI: myocardial infarction; CABG: coronary artery bypass grafting; TIA: transient ischemic attack; PCI: percutaneous coronary intervention; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; GFR: glomerular filtration rate; BMS: bare metal stent; DES: drug eluting stent; LAD: left anterior descending artery; LMAC: left main coronary artery; RCA: right coronary artery; LCX: left circumflex artery; PPI: proton pump inhibitors; ACE: angiotensin-converting enzyme; CCB: calcium channel block

Clinical outcomes -Guided strategy in the overall study population

The primary safety endpoint occurred in 203 patients (6.2%) in the genotype-guided group and in 225 patients (6.9%) in the conventional therapy group at 12 months. There was no difference in the primary safety endpoint between groups ($_{adj}$HR 0.88; 95% CI 0.72, 1.06; p=0.17) (**Figure 1** and **Table 2**). The primary efficacy endpoint occurred in 94 patients (2.8%) in the genotype-guided group and in 114 patients (3.5%) in the conventional therapy group at 12 months. There was no difference in the primary efficacy endpoint between groups ($_{adj}$HR 0.83; 95% CI 0.63, 1.09; p=0.17) (**Figure 2** and **Table 2**). There was a reduction in MI ($_{adj}$HR 0.68; 95% CI 0.48, 0.97) and NACE ($_{adj}$HR 0.85; 95% CI 0.73, 1.00) with guided vs. conventional therapy at 12 months (**Figure 3** and **Table 2**). There was no difference between treatment groups in the other secondary endpoints at 12 months (**Table 2**). Results from the sensitivity analyses using recurrent events (**Figure S4**), using different statistical methods (**Table S10**), in STEMI patients (**Table S11** and **Figure S5**) and including patients with CCS or concomitant anticoagulant use (**Figure S6**) were consistent with the main analysis. Analyses of a priori subgroups did not find any significant interactions between treatment groups and subgroups for the primary safety or efficacy endpoints (**Table S7**).

De-escalation strategy

The primary safety endpoint occurred in 145 patients (12.2%) in the genotype-guided de- escalation group and in 177 patients (15.0%) in the conventional therapy group at 12 months. There was a significant reduction in the primary safety endpoint in the genotype-guided de-escalation vs. conventional therapy groups ($_{adj}$HR 0.77; 95% CI 0.62, 0.97; p=0.030) (**Figure 1** and **Table 2**). The primary efficacy endpoint occurred in 37 patients (3.1%) in the genotype-guided de-escalation group and in 42 patients (3.5%) in the conventional therapy group at 12 months. There was no difference in the primary efficacy endpoint between groups ($_{adj}$HR 0.87; 95% CI 0.56, 1.36; 13 p=0.54) (**Figure 2** and **Table 2**). NACE was reduced at 12 months ($_{adj}$HR 0.77; 95% CI 0.63, 0.94) (**Figure 3** and **Table 2**). There was no difference between treatment groups in individual ischemic or bleeding endpoints at 12 months (**Table 2**). Results

were consistent with sensitivity analyses using recurrent events (**Figure S4**), using different statistical methods (**Table S10**), in STEMI patients (**Table S11** and **Figure S5**) or including patients with CCS or concomitant anticoagulant (**Figure S6**). Analyses of a priori subgroups did not find any significant interactions between treatment groups and subgroups for the primary safety or efficacy endpoints (**Figure S8**).

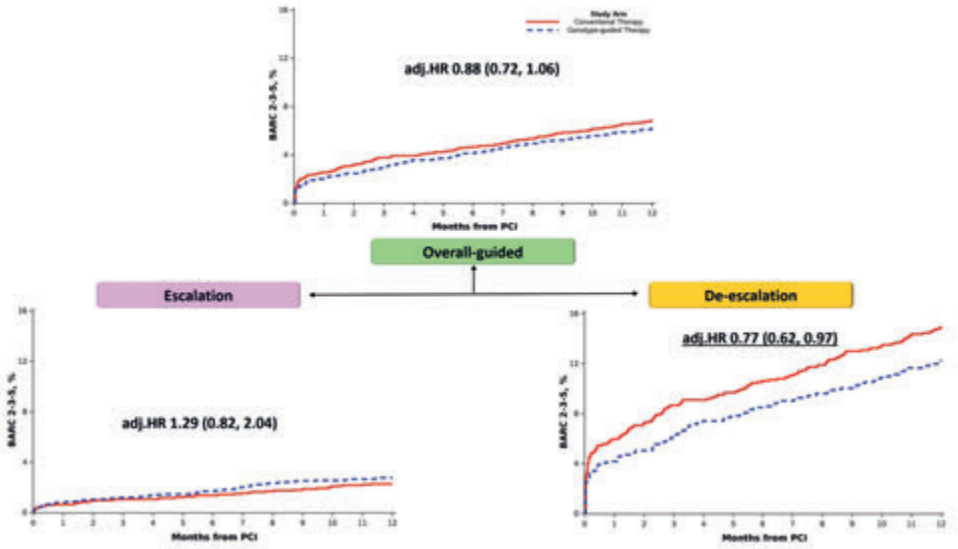

Figure 1. 12-month Kaplan-Meier curves for the primary safety endpoint.

Overall genotype-guided vs. conventional therapy (up), genotype-guided de-escalation vs. conventional therapy (left) and genotype-guided escalation vs. conventional therapy (right). Genotype-guided de-escalation was associated with a reduction in BARC 2-5 bleeding while overall genotype-guided and genotype-guided escalation did not show any difference compared with conventional therapy. Abbreviations: BARC= Bleeding Academic Research Consortium, PCI= percutaneous coronary intervention, HR= Hazard ratio, adj= adjusted.

Escalation strategy

The primary safety endpoint occurred in 58 patients (2.8%) in the genotype-guided escalation group and in 48 patients (2.3%) in the conventional therapy at 12 months. There was no difference in the primary safety endpoints between groups ($_{adj}$HR 1.22; 95% CI 0.83, 1.79; p=0.31) (**Figure 1** and **Table 2**). The primary efficacy endpoint occurred in 57 patients (2.7%) in the genotype-guided escalation group and in 72 patients (3.5%) in the conventional therapy at 12 months. There was no difference in the primary efficacy endpoint between subgroups ($_{adj}$HR 0.79; 95% CI 0.56, 1.12; p=0.19) (**Figure 2** and **Table 2**). Compared with conventional therapy, genotype-guided escalation was not associated with any difference in NACE or individual ischemic or bleeding endpoints at 12 months (**Figure 3** and **Table 2**). Results were consistent with sensitivity analyses using recurrent events (**Figure S4**), using

different statistical methods (**Table S10**), in STEMI patients (**Table S11** and **Figure S5**) or including patients with CCS or concomitant anticoagulant (**Figure S6**). Analyses of a priori subgroups did not find any significant interactions between treatment groups and subgroups for the primary safety or efficacy endpoints (**Figure S9**).

Table 2. Number of patients with events and 12-month Kaplan-Meier event rates and adjusted hazard ratios by overall-guided, guided de-escalation or guided escalation vs. conventional therapy.

Endpoint	Genotype-guided therapy N (%)	Conventional therapy N (%)	Adj. Hazard Ratio (95% CI)	P-value
Overall-guided vs. conventional therapy				
MACE (primary efficacy)	94 (2.8)	114 (3.5)	0.83 (0.63, 1.09)	0.17
BARC 2-3-5 (primary safety)	203 (6.2)	225 (6.9)	0.88 (0.72, 1.06)	0.17
NACE	282 (8.6)	324 (9.8)	0.85 (0.73, 1.00)	0.048
CV mortality	27 (0.8)	23 (0.7)	1.18 (0.68, 2.07)	0.55
Myocardial infarction	51 (1.6)	75 (2.3)	0.68 (0.48, 0.97)	0.035
Stroke	16 (0.5)	21 (0.6)	0.76 (0.40, 1.46)	0.41
Stent thrombosis	25 (0.8)	29 (0.9)	0.86 (0.50, 1.47)	0.32
BARC 3-5	60 (1.8)	49 (1.5)	1.23 (0.84, 1.79)	0.29
Guided de-escalation vs. conventional strategy				
MACE (primary efficacy)	37 (3.1)	42 (3.5)	0.87 (0.56, 1.36)	0.54
BARC 2-3-5 (primary safety)	145 (12.2)	177 (15.0)	0.78 (0.63, 0.98)	0.030
NACE	171 (14.4)	212 (17.8)	0.77 (0.63, 0.94)	0.012
CV mortality	8 (0.7)	9 (0.8)	0.87 (0.33, 2.24)	0.77
Myocardial infarction	20 (1.7)	27 (2.3)	0.74 (0.41, 1.31)	0.30
Stroke	10 (0.8)	10 (0.8)	0.97 (0.41, 2.34)	0.95
Stent thrombosis	8 (0.7)	9 (0.8)	0.89 (0.34, 2.30)	0.80
BARC 3-5	27 (2.3)	23 (1.9)	1.16 (0.66, 2.02)	0.60
Guided escalation vs. conventional strategy				
MACE (primary efficacy)	57 (2.7)	72 (3.5)	0.79 (0.56, 1.12)	0.19
BARC 2-3-5 (primary safety)	58 (2.8)	48 (2.3)	1.22 (0.83, 1.79)	0.31
NACE	111 (5.3)	112 (5.3)	1 (0.77, 1.30)	0.99
CV mortality	19 (0.9)	14 (0.7)	1.38 (0.69, 2.75)	0.36
Myocardial infarction	31 (1.5)	48 (2.4)	0.65 (0.41, 1.02)	0.062
Stroke	6 (0.3)	11 (0.5)	0.55 (0.20, 1.49)	0.24
Stent thrombosis	17 (0.8)	20 (1.0)	0.85 (0.45, 1.63)	0.63
BARC 3-5	33 (1.6)	26 (1.2)	1.28 (0.76, 2.14)	0.35

Abbreviations: CV: Cardiovascular; BARC: Bleeding Academic Research Consortium; MACE: major adverse cardiovascular events; NACE: net adverse clinical events.

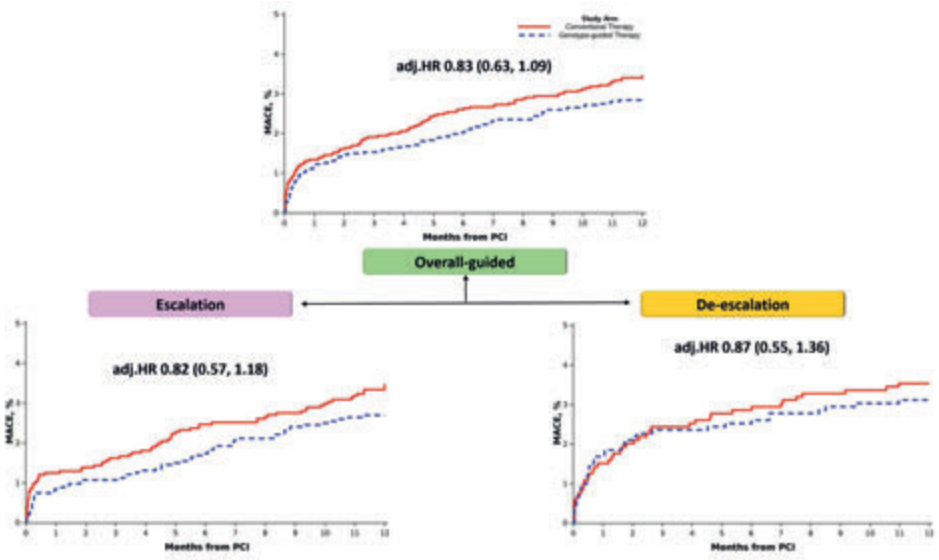

Figure 2. 12-month Kaplan-Meier curves for the primary efficacy endpoint.

Overall genotype guided vs. conventional therapy (up), genotype-guided de-escalation vs. conventional therapy (left) and genotype-guided escalation vs. conventional therapy (right). None of the tested strategies reduced the primary efficacy endpoint of MACE compared with conventional therapy. Abbreviations: MACE= Major adverse cardiovascular events, PCI= percutaneous coronary intervention, adj= adjusted.

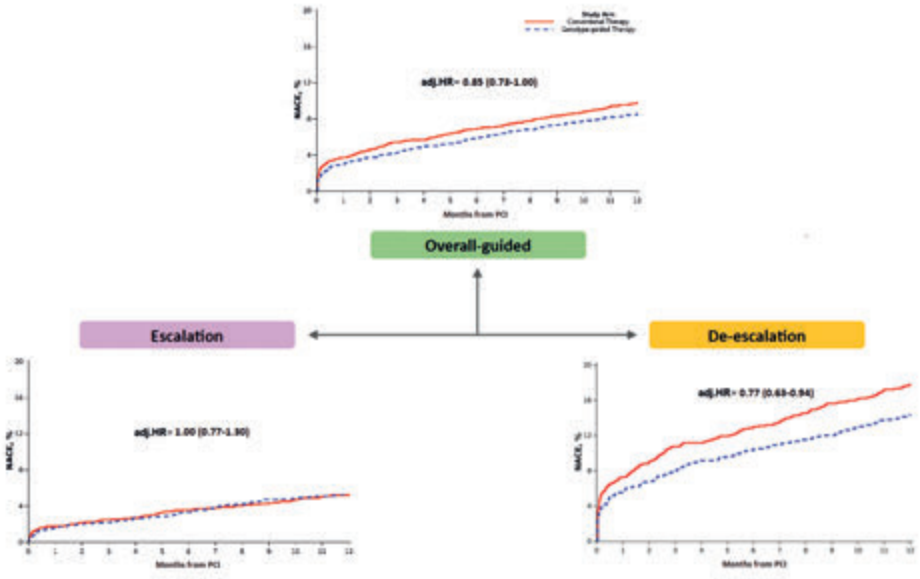

Figure 3. 12-month Kaplan-Meier curves for NACE.

Overall genotype-guided vs. conventional therapy (up), genotype-guided de-escalation vs. conventional therapy (left) and genotype-guided escalation vs. conventional therapy (right). Overall genotype-guided and genotype-guided de-escalation, but not genotype-guided escalation, reduced NACE compared with conventional therapy. Abbreviations: NACE= net adverse cardiovascular events, PCI= percutaneous coronary intervention, HR= Hazard ratio, adj= adjusted.

3.3 Time-dependent covariate analysis - Guided strategy in the overall study population

Analyses with time-dependent treatment effects showed that the primary safety endpoint was lower in the first 90 days in the genotype-guided group ($_{adj}$HR 0.76, 95% CI 0.58, 0.99), 14 while there was no difference between groups after 90 days ($_{adj}$HR 1.02, 95% CI 0.78, 1.35) from PCI. Guided strategy did not reduce the risk of the primary efficacy endpoint prior to 90 days ($_{adj}$HR 0.80, 95% CI 0.55, 1.16) or after 90 days ($_{adj}$HR 0.86, 95% CI 0.57, 1.29) from PCI, compared to conventional therapy (**Table S12** and **Figure S10**). NACE was lower in the first 90 days in the genotype-guided group ($_{adj}$HR 0.77, 95% CI 0.62, 0.95;), while there was no difference between groups after 90 days ($_{adj}$HR 0.96, 95% CI 0.76, 1.21) from PCI (**Figure 4**).

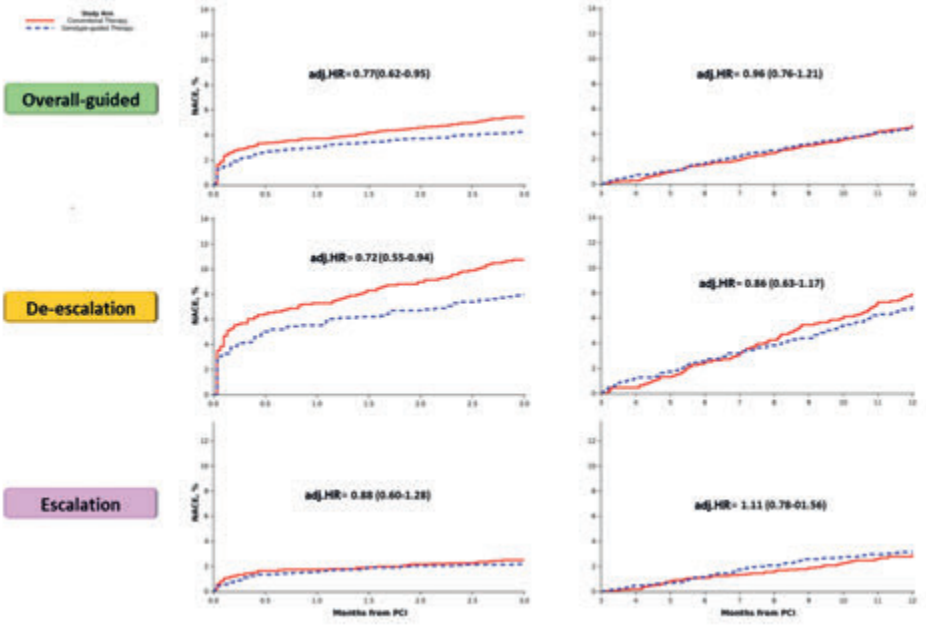

Figure 4. Kaplan-Meier event rates for NACE of overall, de-escalation and escalation genotype-guided therapy vs. conventional therapy before and after 3 months from PCI.

Overall, genotype-guided and genotype-guided de-escalation strategies were effective in reducing NACE within the first 90 days following PCI but not beyond this period. In contrast, genotype-guided escalation did not result in a reduction of NACE either within or beyond the 90-day post-PCI timeframe. Abbreviations: NACE= net adverse cardiovascular events, PCI= percutaneous coronary intervention, HR= Hazard ratio, adj= adjusted.

De-escalation strategy

The primary safety endpoint was lower in the first 90 days in the genotype-guided group ($_{adj}$HR 0.68, 95% CI 0.51, 0.92), while there was no difference between groups after 90 days ($_{adj}$HR 0.93, 95% CI 0.68, 1.29) from PCI (**Table S15** and **S17**). There was no difference in the primary efficacy endpoint between groups prior to 90 days ($_{adj}$HR 0.98, 95% CI 0.59, 1.64) or after 90 days from PCI ($_{adj}$HR 0.67, 95% CI 0.30, 1.51), compared to conventional therapy (**Table S12** and **Figure S11**). Similarly, NACE was lower prior to 90 days in the genotype-guided group ($_{adj}$HR 0.72, 95% CI 0.55, 0.94;), while there was no difference between groups after 90 days ($_{adj}$HR 0.86, 95% CI 0.63, 1.17) from PCI (**Figure 4**).

Escalation strategy

The primary safety endpoint prior ($_{adj}$HR 1.12, 95% CI 0.66, 1.92) or after 90 days ($_{adj}$HR 1.28, 95% CI 0.79, 2.09) from PCI was similar between groups. There was a non-significant trend towards reduced primary efficacy endpoint with genotype-guided escalation prior to 90 days ($_{adj}$HR 0.66, 95% CI 0.39, 1.10) from PCI compared to conventional therapy, while there was no difference between groups after 90 days

$_{adj}$HR 0.93, 95% CI 0.59, 1.48; p=0.77) (**Table S12** and **Figure S12**). There was no difference in NACE between groups prior to 90 days ($_{adj}$HR 0.88, 95% CI 0.60, 1.28) or after 90 days from PCI ($_{adj}$HR 1.11, 95% CI 0.78, 1.56) (**Figure 4**). Interestingly, there was a borderline-significant reduction in MI prior to 90 days ($_{adj}$HR 0.48, 95% CI 0.23, 1.00) from PCI, compared to conventional therapy (**Table S12**).

DISCUSSION

The main findings of this IPD-MA can be summarized as follows. In ACS patients undergoing PCI: (i) in ACS patients, overall genotype-guided selection of oral P2Y12 inhibitors significantly reduces NACE, but not MACE or bleeding, highlighting the importance of evaluating guided de-escalation and escalation strategies as distinct clinical approaches; (ii) a strategy of genotype-guided de-escalation reduced bleeding by 22% and NACE by 23% without any trade-off in MACE at 12 months compared to conventional therapy in ACS patients; (iii) a genotype-guided escalation strategy did not significantly improve safety or efficacy outcomes at 12 months compared to conventional therapy in ACS patients; (iv) the benefits of a genotype-guided selection of oral P2Y12 inhibitors in ACS patients undergoing PCI is mostly confined to the initial three months following ACS. Our IPD-MA findings deriving from RCTs are consistent with the ever- growing evidence from real-world registries supporting the clinical benefits of a genotype-guided selection of oral P2Y12 inhibitors.[23,24] Overall, these consistent observations support recommendations from position papers on the use of genetic testing to guide the selection of oral P2Y12 inhibitors in selected cohorts of patients undergoing PCI.[9,17,25] *CYP2C19* genetic testing may be of particular relevance among ACS patients at both high ischemic and bleeding risk to optimize the safety-efficacy balance of antiplatelet therapy.[9] Clopidogrel is the most commonly utilized P2Y12 inhibitor worldwide.[1] Despite its proven efficacy, a considerable number of patients have inadequate platelet inhibition and persist with HPR, a marker of thrombotic events.[9] *CYP2C19* genetic variants have emerged as a key determinant of clopidogrel response given that clopidogrel is involved in both metabolic steps leading to generation of the active clopidogrel metabolite.[11,12] Carriers of one LoF allele (intermediate metabolizer) are as frequent as 20-45%, depending on ethnicity, and have reduced levels of active clopidogrel metabolite, high rates of on-treatment HPR and increased cardiovascular events.[13-16] Moreover, carriers of two LoF alleles (poor metabolizer) account for the 12-15% of the treated population, depending on ethnicity, and are associated with almost 50% lower active clopidogrel metabolite levels and even higher on-treatment HPR rates and a greater increase in CV events compared to non-carriers.[13-16] These observations prompted the Food and Drug Administration to issue a boxed warning on the product label of clopidogrel to consider the use of alternative agents (i.e., prasugrel or ticagrelor) among poor clopidogrel metabolizers requiring oral P2Y12 inhibitors.[26,27] The European Medicines Agency included a warning in the section on special warning and precautions for use in the clopidogrel's Summary of Product Characteristics (SmPC)27. Similarly, the Clinical Pharmacogenetics Implementation Consortium guideline for *CYP2C19* genotype and clopidogrel therapy recommends the use of alternative P2Y12 inhibitors in patients who are confirmed carriers of *CYP2C19* LoF alleles.[17]

Furthermore, a scientific statement from the American Heart Association and a recent international consensus document also support *CYP2C19* genetic testing before oral P2Y12 inhibitors are prescribed in patients undergoing PCI.[9,25] However, there is weak or no recommendation on the use of genetic testing in practice guidelines which likely stems from some of the limitations of early investigations as well as failure to put the data from more recent RCTs and meta-analyses into the correct context.[2,3]

Thus far, two major RCTs testing a genotype-guided selection of antiplatelet therapy in PCI patients using a comprehensive genotyping panel including both *CYP2C19*2* and **3* LoF alleles are available, and have both been included in this IPD-MA.[18,19] Of these, POPular Genetics selectively included STEMI patients, while TAILOR-PCI also included patients presenting with NSTEMI and CCS.[18,19] Moreover, while the former tested a strategy of genotype-guided de- escalation, the latter tested a strategy of genotype-guided escalation compared to conventional therapy, making it difficult to compare their results, as these strategies have different objectives on outcomes. Furthermore, TAILOR-PCI, was primarily designed to compare genotype-guided vs. conventional therapy selectively among carriers of *CYP2C19* LoF alleles, while the outcomes among the totality of patients undergoing PCI were published as a secondary analysis, which was not powered to draw any definitive conclusions.[19] Statistical power for ischemic endpoints was also limited in the POPular Genetics trial, in which the primary bleeding endpoint was powered for superiority, but the co-primary endpoint included both ischemic and bleeding outcomes using a non-inferiority design.[18]

In an attempt to overcome some of the limitations of individual trials, several study-level meta-analyses have been performed.[28,29] In particular, by increasing statistical power, study-level meta-analysis have shown that strategies of guided escalation and de-escalation of oral P2Y12 inhibiting therapy improve outcomes compared to conventional therapy.[28] Moreover, a network meta-analysis comparing guided vs. standard P2Y12 therapy with prasugrel or ticagrelor among ACS patients undergoing PCI found that guided therapy may be associated with the best clinical performance, reducing MACE without increasing bleeding risk.[29] However, study-level meta- analyses have inherent limitations, most importantly the heterogeneity of the included populations. Moreover, study-level meta-analysis do not allow for adjustments of confounding factors, assessment of endpoints other than those reported, exploring the specific impact of the treatment strategies across subgroups or examining time-varying effects. IPD-MA may overcome these limitations.

This is the first IPD-MA of RCTs selectively conducted in ACS patients undergoing PCI exploring the safety and efficacy of a genotype-guided selection of oral P2Y12 inhibitors according to the strategy used (i.e., de-escalation or escalation), compared with conventional therapy. We observed that the overall genotype-guided strategy did not significantly impact the primary safety or efficacy endpoints individually compared to conventional therapy. However, it was associated with a reduction in NACE. These findings align with international consensus recommendations emphasizing that de-escalation and escalation strategies should be evaluated separately, as their clinical objectives are fundamentally different.[9] Specifically, de-escalation aims to reduce bleeding risk without compromising efficacy, whereas escalation seeks to enhance efficacy without compromising safety.

In our analysis, de-escalation (i.e., switching from ticagrelor, which was the P2Y12 inhibitor used for most patients in the conventional therapy group, to clopidogrel among non-carriers of *CYP2C19* LoF alleles) reduced the primary safety endpoint and NACE without any trade-off in MACE compared with conventional therapy. Although derived from subgroup analyses and thus underpowered and hypothesis-generating, these findings were consistent across various subgroups, including elderly patients, those presenting with STEMI, and individuals undergoing high-risk PCI. Furthermore, time-dependent covariate analysis revealed that the reduction in bleeding with the genotype-guided de-escalation was particularly pronounced early (<3 months) after PCI. These findings hold significant clinical relevance, as they pertain to the critical time frame during which ACS patients undergoing PCI are at the highest risk of bleeding and thrombotic events.[1] This highlights the importance of early implementation of genotype-guided P2Y12 inhibitor therapy in ACS patients undergoing PCI.[1,30] Furthermore, compared to other de-escalation antiplatelet strategies, genotype-guided de-escalation is the only approach that can be implemented immediately at the time of PCI, whereas other strategies are typically initiated 1 to 3 months after standard DAPT.[1,21,31] This early implementation offers a crucial advantage, potentially playing a key role in optimizing outcomes during this critical high-risk period.

Compared to conventional therapy, a genotype-guided escalation strategy was associated with a 17% reduction in MACE, although this did not reach statistical significance, and a significant 32% reduction in MI at 12 months. It is important to note that the findings of this analysis may be influenced by insufficient statistical power to detect differences between groups. In fact, hard ischemic events occur far less frequently than bleeding events in ACS patients undergoing PCI, necessitating a larger sample size to achieve the statistical power to test this hypothesis. On the other hand, it should be acknowledged that guided escalation was associated with a trend toward a 22% increase in bleeding compared with conventional therapy. This potential increase is biologically plausible, as the strategy results in the use of a potent P2Y12 inhibitor in approximately 30% of clopidogrel non-responders. However, a more favorable safety profile is still expected compared to an unguided strategy in which 100% of patients receive a potent P2Y12 inhibitor. Pivotal RCTs that established the higher efficacy but lower safety of potent P2Y12 inhibitors vs. clopidogrel included three to five times the number of patients used in our analysis.[4,5] Nevertheless, it is important to acknowledge that is unlikely that RCTs specifically designed to test the hypothesis that genotype-guided escalation is superior to conventional therapy in the ACS setting will be conducted, given that potent P2Y12 inhibitors remain the standard of care for these patients. Consequently, the findings on genotype-guided de-escalation have more practical implications for daily clinical practice, further underscoring the relevance of our study findings.

Study Limitations

This study has some limitations. First, because POPular Genetics and TAILOR-PCI mainly used a de-escalation and escalation strategy vs. conventional therapy, respectively, it could be argued that performing a pre-specified analysis according to the strategy used (i.e., de-escalation vs. escalation) would reflect the results of the individual studies. However, this potential limitation does not impact the primary analysis, which compares the overall genotype-guided strategy with conventional treatment.

Notably, we found that overall genotype-guided strategy reduced MI and NACE vs. conventional therapy. Additionally, the patients included in this analysis differ slightly from those reported in the original publications of both trials. Specifically, excluded from the POPular Genetics dataset patients with concomitant anticoagulant use (n= 122), but included 179 patients who were enrolled prior to the major protocol revision that shifted the approach from escalation to de-escalation, as well as patients who experienced events within the first 24 hours after PCI. Moreover, we excluded 972 CCS patients and 115 patients with anticoagulation at discharge from the TAILOR-PCI dataset, ensuring that the analysis was conducted on a homogeneous cohort of patients with ACS. Notably, this exclusion did not disrupt the random allocation, as randomization in the TAILOR-PCI trial was stratified based on clinical presentation and only a minority of patients was prescribed anticoagulation at discharge. Finally, the use of MACE and bleeding as co-primary endpoints and the performance of subgroup analysis, analyses with time-dependent treatment effects, and analysis according to multiple events, significantly add to the results of individual studies. Second, although this analysis increased the statistical power for ischemic and bleeding endpoints, it cannot be excluded that some of the results suffer from low statistical power to draw definitive conclusions. Third, although our study did not show that a guided escalation reduced MACE at 12 months, a time-dependent covariate analysis did show a benefit at 90 days, a time frame during which most ischemic events occur. Moreover, it is important to note that our analysis focused on ACS patients undergoing PCI, a population in which the recommended treatment is represented by prasugrel or ticagrelor, except for those deemed at high bleeding risk or for situations in which these two drugs are not available (i.e., low-income countries or budget limitations).[2,3] Therefore, our findings on a strategy of genetic guided de-escalation are clinically more relevant given that escalation may be less likely to occur in ACS patients undergoing PCI and may ultimately help reduce costs and improve adherence to therapy as shown by real-world studies and analytic models.[32,33]

CONCLUSION

Among ACS patients undergoing PCI, a genotype-guided selection of oral P2Y12 inhibitors reduced NACE, but not MACE or bleeding. However, our findings are suggestive that safety and efficacy outcomes may vary according to type strategy implemented (de-escalation vs. escalation) with a strategy of guided de-escalation showing a reduction in bleeding and NACE without trade-off in MACE compared with conventional therapy and hence being more clinically impactful than guided escalation which did not show significant differences in outcomes likely attributed to low statistical power. Our analysis also suggests time-dependent benefits with a genotype-guided approach occurring mostly within the first 90 days after PCI. These findings support the integration of genetic testing to better optimize the balance between ischemic and bleeding risks in ACS patients undergoing PCI.

REFERENCES

1. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneouscoronary intervention. *EuroIntervention*. 2022;17:e1371-e1396. doi: 10.4244/eij-d-21-00904
2. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, Claeys MJ, Dan GA, Dweck MR,Galbraith M, et al. 2023 ESC Guidelines for the management of acute coronary syndromes.*European heart journal*. 2023;44:3720-3826. doi: 10.1093/eurheartj/ehad191
3. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, Bittl JA, Cohen MG,DiMaio JM, Don CW, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Journal of the American College of Cardiology*. 2022;79:e21-e129. doi: 10.1016/j.jacc.2021.09.006
4. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015. doi: 10.1056/NEJMoa0706482
5. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057. doi: 10.1056/NEJMoa0904327
6. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, So D, Geller N, Goodman SG, Hasan A, et al. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y(12) Inhibitor Therapy: A Meta-Analysis. *JACC Cardiovascular interventions* 2021;14:739-750. doi: 10.1016/j.jcin.2021.01.024
7. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, et al. Bleeding and stent thrombosis on P2Y12 inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *European heart journal*. 2015;36:1762-1771. doi: 10.1093/eurheartj/ehv104
8. Claassens DMF, Bergmeijer TO, Vos GJA, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, et al. Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to CYP2C19 Genotype. 2021;14:e009434. doi: doi:10.1161/CIRCINTERVENTIONS.120.009434
9. Angiolillo DJ GM, Alexopoulos D, Aradi D, Bhatt DL, Bonello L, Capodanno D, Cavallari LH, Collet J-P, Cuisset T, Ferreiro JL, Franchi F, Geisler T, Gibson CM, Gorog DA, Gurbel PA, Jeong Y-H, Marcucci R, Siller-Matula JM, Mehran R, Neumann F-J, Pereira NL, Rizas KD, Rollini F, So DYF, Stone GW, Storey RF, Tantry US, Ten Berg J, Trenk D, Valgimigli M, Waksman R, Sibbing D International Consensus Statement on Platelet Function and Genetic Testing for Guiding Oral P2Y12 Inhibitor Treatment inPercutaneous Coronary Intervention: 2024 Update. *JACC Cardiovascular interventions*. 2024.
10. van den Broek WWA, Ingraham BS, Pereira NL, Lee CR, Cavallari LH, Swen JJ, Angiolillo DJ, Ten Berg JM. Genotype-Guided Antiplatelet Therapy: JACC Review Topic of the Week. *Journal of the American College of Cardiology*. 2024;84:1107-1118. doi: 10.1016/j.jacc.2024.06.038
11. Duarte JD, Cavallari LH. Pharmacogenetics to guide cardiovascular drug therapy. *Nature reviews Cardiology*. 2021;18:649-665. doi: 10.1038/s41569-021-00549-w

12. Pereira NL, Rihal CS, So DYF, Rosenberg Y, Lennon RJ, Mathew V, Goodman SG, Weinshilboum RM, Wang L, Baudhuin LM, et al. Clopidogrel Pharmacogenetics. *Circulation Cardiovascular interventions*. 2019;12:e007811. doi: 10.1161/circinterventions.119.007811
13. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias WL, Braunwald E, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119:2553-2560. doi: 10.1161/circulationaha.109.851949
14. Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. 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 (London,England)*. 2010;376:1312-1319. doi: 10.1016/s0140-6736(10)61273-1
15. Paré G, Mehta SR, Yusuf S, Anand SS, Connolly SJ, Hirsh J, Simonsen K, Bhatt DL, Fox KAA, Eikelboom JW. Effects of CYP2C19 Genotype on Outcomes of Clopidogrel Treatment. 2010;363:1704-1714. doi: 10.1056/NEJMoa1008410
16. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Meneveau N, Steg PG, Ferrieres J, Danchin N, Becquemont L, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360:363-375. doi: 10.1056/NEJMoa0808227
17. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, Kisor DF, Limdi NA, Lee YM, Scott SA, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clinical pharmacology and therapeutics*. 2022;112:959-967. doi: 10.1002/cpt.2526
18. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, et al. A Genotype-Guided Strategy for Oral P2Y(12) Inhibitors in Primary PCI. *N Engl J Med*. 2019;381:1621-1631. doi: 10.1056/NEJMoa1907096
19. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae JH, Jeong MH, Chavez I, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. *Jama*. 2020;324:761-771. doi: 10.1001/jama.2020.12443
20. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med*. 2017;36:855-875. doi: 10.1002/sim.7141
21. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, Collet JP, Cuisset T, De Luca G, De Luca L, et al. Defining Strategies of Modulation of Antiplatelet Therapy in Patients With Coronary Artery Disease: A Consensus Document from the Academic Research Consortium. *Circulation*. 2023;147:1933-1944. doi: 10.1161/circulationaha.123.064473
22. Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. *Stat Med*. 2017;36:772-789. doi: 10.1002/sim.7171
23. Azzahhafi J, van den Broek WWA, Chan Pin Yin D, van der Sangen NMR, Sivanesan S, Bofarid S, Peper J, Claassens DMF, Janssen PWA, Harmsze AM, et al. Real-World Implementation of a Genotype-Guided P2Y(12) Inhibitor De-Escalation Strategy in Acute Coronary Syndrome Patients. *JACC Cardiovascular interventions*. 2024. doi: 10.1016/j.jcin.2024.06.020

24. Hulot JS, Chevalier B, Belle L, Cayla G, Khalife K, Funck F, Berthier R, Piot C, Tafflet M, Montalescot G. Routine CYP2C19 Genotyping to Adjust Thienopyridine Treatment After Primary PCI for STEMI: Results of the GIANT Study. *JACC Cardiovascular interventions*. 2020;13:621-630. doi: 10.1016/j.jcin.2020.01.219
25. Pereira NL, Cresci S, Angiolillo DJ, Batchelor W, Capers Qt, Cavallari LH, Leifer D, Luzum JA, Roden DM, Stellos K, et al. CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association. *Circulation*. 2024. doi: 10.1161/cir.0000000000001257
26. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor.
27. https://www.ema.europa.eu/en/documents/product-information/clopidogrel-hcs-epar-product-information_en.pdf.
28. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, Porto I, Angiolillo DJ. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. *Lancet (London, England)*. 2021;397:1470-1483. doi: 10.1016/s0140-6736(21)00533-x
29. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, Vescovo GM, Cavallari LH, Bikdeli B, Ten Berg J, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. *European heart journal*. 2021. doi: 10.1093/eurheartj/ehab836
30. Rodriguez F, Harrington RA. Management of Antithrombotic Therapy after Acute Coronary Syndromes. N Engl J Med. 2021;384:452-460. doi: 10.1056/NEJMra1607714
31. Gorog DA, Ferreiro JL, Ahrens I, Ako J, Geisler T, Halvorsen S, Huber K, Jeong YH, Navarese EP, Rubboli A, et al. De-escalation or abbreviation of dual antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention: a Consensus Statement from an international expert panel on coronary thrombosis. Nature reviews Cardiology. 2023;20:830-844. doi: 10.1038/s41569-023-00901-2
32. van den Broek WWA, Azzahhafi J, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, Dijksman LM, Walhout RJ, Gin MTJ, Breet NJ, Langerveld J, et al. Cost-effectiveness of Implementing a Genotype-Guided De-Escalation Strategy in Patients with Acute Coronary Syndrome. European Heart Journal - Cardiovascular Pharmacotherapy. 2024. doi: 10.1093/ehjcvp/pvae087
33. Kazi DS, Garber AM, Shah RU, Dudley RA, Mell MW, Rhee C, Moshkevich S, Boothroyd DB, Owens DK, Hlatky MA. Cost- effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome. Ann Intern Med. 2014;160:221-232. doi: 10.7326/m13-1999

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

CHAPTER 9

P2Y12 Inhibition in Patients Requiring Oral Anticoagulation After Percutaneous Coronary Intervention The SWAP-AC–2 Study

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ABSTRACT

Background

Among patients treated with a novel oral anticoagulant (NOAC) undergoing percutaneous coronary intervention (PCI), combination therapy with clopidogrel (ie, known as dual antithrombotic therapy [DAT]) is the treatment of choice. However, there are concerns for individuals with impaired response to clopidogrel.

Objectives

The authors sought to assess the pharmacodynamic (PD) effects of clopidogrel vs low-dose ticagrelor in patients with impaired clopidogrel response assessed by the ABCD-GENE score.

Methods

This was a prospective, randomized PD study of NOAC-treated patients undergoing PCI. Patients with an ABCD-GENE score ≥10 (n = 39), defined as having impaired clopidogrel response, were randomized to low-dose ticagrelor (n = 20; 60 mg twice a day) or clopidogrel (n = 19; 75 mg once a day). Patients with an ABCD-GENE score <10 (n = 42) were treated with clopidogrel (75 mg once a day; control cohort). PD assessments at baseline and 30 days post-randomization (trough and peak) were performed to assess P2Y12 signaling (VerifyNow P2Y12 reaction units [PRU], light transmittance aggregometry, and vasodilator-stimulated phosphoprotein); makers of thrombosis not specific to P2Y12 signaling were also assessed. The primary endpoint was PRU (trough levels) at 30 days.

Results

At 30 days, PRU levels were reduced with ticagrelor-based DAT compared with clopidogrel-based DAT at trough (23.0 [Q1-Q3: 3.0-46.0] vs 154.5 [Q1-Q3: 77.5-183.0]; P < 0.001) and peak (6.0 [Q1-Q3: 4.0-14.0] vs 129.0 [Q1-Q3: 66.0-171.0]; P < 0.001). Trough PRU levels in the control arm (104.0 [Q1-Q3: 35.0–167.0]) were higher than ticagrelor-based DAT (P = 0.005) and numerically lower than clopidogrel-based DAT (P = 0.234). Results were consistent by light transmittance aggregometry and vasodilator-stimulated phosphoprotein. Markers measuring other pathways leading to thrombus formation were largely unaffected.

Conclusions

In NOAC-treated patients undergoing PCI with an ABCD-GENE score ≥10, ticagrelor-based DAT using a 60-mg, twice-a-day regimen reduced platelet P2Y12 reactivity compared with clopidogrel-based DAT.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard of care in patients undergoing percutaneous coronary intervention (PCI).[1] However, approximately 10% to 15% of patients undergoing PCI also require treatment with an oral anticoagulant (OAC), raising concerns on the optimal antithrombotic treatment in this setting.[2] Randomized trials, mostly conducted in patients with atrial fibrillation (AF), have consistently shown that, after a brief period of DAPT, dropping aspirin while maintaining a P2Y12 inhibitor in combination with an OAC, known as dual antithrombotic therapy (DAT), is associated with better safety and similar efficacy compared with triple antithrombotic therapy (TAT).[3] Accordingly, in the absence of contraindications, practice guidelines recommend a DAT regimen with a novel oral anticoagulant (NOAC) preferred over a vitamin K antagonist, and clopidogrel as the P2Y12 inhibitor of choice.[4-10] How-ever, it is also important to note that the individual trials were not powered for efficacy, and a meta-analysis composed of larger data sets suggests the potential for an increased risk of thrombotic complications with DAT compared with TAT.[11] Clopidogrel is the most broadly used P2Y12 inhibitor and is associated with synergistic platelet inhibitory effects when combined with aspirin.[12] However, clopidogrel is characterized by broad interindividual response variability, with up to 30% of patients having high platelet reactivity (HPR), a marker of thrombotic risk.[13] Genetic polymorphism of the cytochrome P450 2C19 (CYP2C19) enzyme and clinical factors define clopidogrel response.[14,15] To this extent, the Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping (ABCD-GENE) score is a useful tool to identify patients with HPR on clopidogrel and who are at increased risk for adverse ischemic events.[16] The non-negligible prevalence of HPR among clopidogrel-treated patients raises concerns, particularly if antiplatelet protection is further encumbered by interrupting aspirin therapy, as recommended for NOAC-treated patients undergoing PCI.[17] Alternative P2Y12 inhibitors (ie, prasugrel and ticagrelor) are characterized by more potent and uniform pharmacodynamic (PD) effects compared with clopidogrel, and their use is recommended in patients with impaired clopidogrel response.[13,18]

However, to date, there are limited data on the PD effects of alternative therapies (ie, ticagrelor) in NOAC-treated patients under-going PCI. The aim of this study was to assess the PD effects of clopidogrel vs ticagrelor in patients with impaired clopidogrel response assessed by the ABCD-GENE score in NOAC-treated patients undergoing PCI.

METHODS

Study Design and Participants

The SWAP-AC-2 (Switching Anti-Platelet and Anti-Coagulant Therapy–2) was a prospec-tive, randomized, multicenter, open-label investigation aimed to assess the PD effects of clopidogrel-based DAT vs ticagrelor-based DAT in NOAC-treated patients undergoing PCI (Tailoring P2Y12 Inhibiting Therapy in Patients Requiring Oral Anticoagulation After PCI; NCT04483583). Patients were screened for eligibility

after successful PCI at 2 enrolling centers (University of Florida College of Medicine in Jacksonville, Florida, USA, and St. Antonius Hospital in Nieuwegein, the Netherlands). Details on study in-clusion and exclusion criteria are provided in the Supplemental Appendix. In brief, patients were eligible for the study if they were ≥18 years of age, had undergone successful PCI (ie, PCI completed without complications as defined by site investigators), and were treated with DAPT as per standard of care. All patients needed to be on treatment with a NOAC (ie, apixaban, dabigatran, edoxaban, or rivaroxaban). Patients with any indication to be on a NOAC were eligible, including AF, atrial flutter, venous thromboembolism, and intracardiac thrombus. Key exclusion criteria included any active bleeding, high risk for bleeding, ischemic stroke within 1 month, any history of hemorrhagic stroke or intracranial hemorrhage, end-stage renal disease on hemodialysis, known severe liver dysfunction, treatment with strong inhibitors of both CYP3A4 and P-glycoprotein, hemoglobin ≤9 mg/dL, and platelet count <80 x 10^6/mL. The study complied with the Declaration of Helsinki, was approved by the Western Institutional Review Board, and all patients gave written informed consent.

Clopidogrel response was assessed by the ABCD-GENE score (see the **Supplemental Appendix** for details).[16] Patients with an ABCD-GENE score ≥10 were defined as having impaired clopidogrel response.[16] Randomization occurred post-PCI once results of genetic testing became available, mostly before hospital discharge, but not beyond 3 days post-PCI. Patients with an ABCD-GENE ≥10 score were randomized in a 1:1 ratio to clopidogrel (75 mg once a day; standard of care arm) or ticagrelor (60 mg twice a day; experimental arm). The 60-mg, twice-a-day maintenance dose regimen was chosen in light of data showing that this dose pro-vides platelet inhibitory effects not dissimilar from the 90-mg, twice-a-day dosing regimen but with fewer side effects yet with more potent and consis-tent platelet inhibitory effects than clopidogrel, including after PCI.[19-22] Patients with an ABCD-GENE <10 (control group) were treated with clopidogrel (75 mg once a day). The PCI procedure was performed according to standard of care. Given that the choice of P2Y12 inhibitor during the PCI procedure was at the discretion of the treating physician, the following recommendations were made based on the agent chosen (clopidogrel, prasugrel, or ticagrelor) and the treatment assignment: 1) patients assigned to clopidogrel and treated with clopidogrel during PCI continued with a 75-mg, once-a-day maintenance dose for the duration of the study; 2) patients assigned to clopidogrel but treated with ticagrelor or prasugrel during PCI received a 600-mg loading dose of clopidogrel followed by a 75-mg, once-a-day maintenance dose for the duration of the study; 3) patients assigned to ticagrelor and treated with ticagrelor during PCI continued with ticagrelor 60-mg, twice-a-day maintenance dose for the duration of the study; and 4) patients assigned to ticagrelor but treated with clopidogrel or prasugrel during PCI received a 180-mg loading dose, followed by a 60-mg twice-a-day dose for the duration of the study. These switching strategies are in line with consensus recommendations and practice guide-lines.[23,24] All patients were on aspirin 81 mg once a day during the peri-PCI period and discontinued aspirin at any time between hospital discharge up to 7 days after PCI at the discretion of the treating physician as per guideline recommendations.[3,9] The choice and dose of NOAC was at the discretion of the treating physician and was not changed during the course of the study period.

The assigned treatment was maintained for 30 ± 5 days. PD assessments were conducted at 3 time points: 1) baseline, generally at the time of hospital discharge and before starting randomized treatment; 2) 30 ± 5 days after randomization: before the administration of the morning doses of P2Y12 inhibiting therapy and NOAC (trough levels of platelet reactivity); and 3) 30 ± 5 days after randomization: 2 hours after the administration of the morning doses of P2Y12 inhibiting therapy and NOAC (peak levels of platelet reactivity). Compliance to treatment was assessed by patient interview. **Figure 1** illustrates the overall study design.

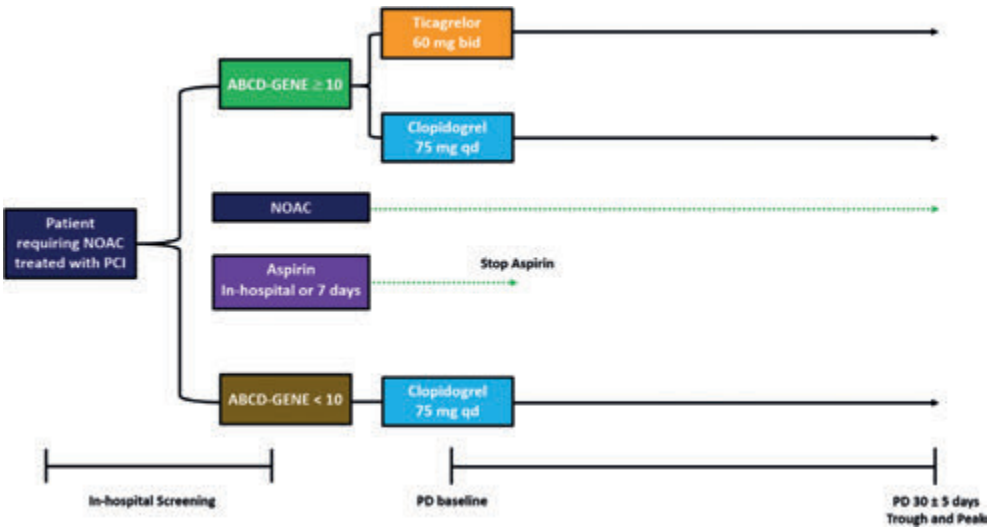

Figure 1. Study design.

Trough and peak denote before drug administration and 2 hours after, respectively. ABCD-GENE score=Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping score; bid=twice a day; DAT=dual antithrombotic therapy; NOAC=novel oral anticoagulant; PCI=Percutaneous coronary intervention; PD=pharmacodynamics; qd=once day.

Blood Sampling and Laboratory Assessments

A detailed description of PD assessments is provided in the **Supplemental Appendix**. In brief, peripheral venous blood samples were drawn through a short venous catheter inserted into a forearm vein and collected in citrate, EDTA, and serum tubes as appropriate for assessments. The first 2 to 4 mL of blood were discarded to avoid spontaneous platelet activation. PD assessments were conducted using a number of different assays, allowing us to assess for markers specific to P2Y12 receptor signaling and other markers of platelet function and thrombus formation. The rationale for the former was that the study was designed to test the effects of ticagrelor specifically on the P2Y12 receptor. However, there are limited data with ticagrelor at a low-dose regimen (ie, 60 mg twice a day) in the post-PCI setting, particularly with early discontinuation of aspirin therapy. The rationale for the latter was to understand

the interplay between P2Y12 inhibitors with varying degrees of platelet inhibitory effects and NOACs on different markers of platelet aggregation and thrombus formation, which has been poorly explored. Markers of P2Y12 receptor signaling were assessed using 3 different assays: 1) VerifyNow PRU system with results reported in P2Y12 reaction units (PRU); 2) light transmission aggregometry (LTA) (Chrono-Log Corp) following adenosine diphosphate (ADP) (20 mmol/L) stimuli with results reported as maximum platelet aggregation (MPA); and 3) whole-blood vasodilator-stimulated phosphoprotein (Biocytex) with results reported as platelet reactivity index (PRI).[25,26] PD assessments to assess other markers of thrombosis included: 1) LTA following stimuli with arachidonic acid (AA) (1 mmol/L), collagen (3 mg/mL), thrombin receptor activating peptide (TRAP) (15 mmol/L), and a combination of agonists (collagen-related peptide 2 mg/mL + ADP 5 mmol/L + TRAP 15 mmol/L; University of Florida only);[27,28] 2) total thrombus-formation analysis system (T-TAS) (Diapharma) using the AA-reacted (AR) and phospholipids-reacted platelets (PL) chips, which evaluates the occlusion time (seconds) and total thrombogenicity (area under the pressure-time curve), respectively;[25,26] and 3) a turbidimetric assay was used to study fibrin clot formation by means of lag time (seconds), maximum absorbance (absorbance units), and clot lysis time (seconds).[29-33] *CYP2C19* genetic polymorphisms (**1*, **2*, **3*, and **17*) allele status were assessed with the Genomadix Cube CYP2C19 system (Genomadix) or TaqMan (Thermo Fisher Scientific).[34,35]

During study treatment, major adverse cardiac events (death, myocardial infarction, stroke, and urgent revascularization procedures), serious adverse events (bleeding and other adverse events), and nonserious adverse events were collected. Bleeding and ischemic events were defined according to the Academic Research Consortium definitions.[36,37] After completing the study, patients resumed an antithrombotic treatment regimen at the discretion of the treating physician.

Sample Size Calculation and Study Endpoints.

The primary endpoint was the comparison of the level of platelet reactivity, measured as trough levels of PRU using the VerifyNow system, between clopidogrel-based and ticagrelor-based DAT at 30 days after randomization in patients with an ABCD-GENE score ≥10. We hypothesized that ticagrelor 60 mg twice a day would lead to lower PRU than clopidogrel 75 mg once a day. Based on previous studies, assuming a SD of 80 and 55 PRU for clopidogrel and ticagrelor, respectively, a total sample size of 34 patients (17 patients per treatment group) with valid primary endpoint data would be required to detect an absolute difference of 90 PRU between clopidogrel-based and ticagrelor-based DAT with a 90% power and a 2-tailed alpha value of 0.05.[19] Assuming a potential 25% in data attrition due to patient drop-out (eg, due to side effects or withdrawal of consent) or invalid PD samples (eg, due to hemolysis or technical reasons), a sample size of up to a total of 42 patients would be required. A control group of up to 42 consecutive patients with an ABCD-GENE score <10 was also enrolled.

Additional exploratory endpoints included the comparisons among the control group (clopidogrel-based DAT in patients with ABCD-GENE score<10) and the other 2 arms and comparisons between groups of rates of HPR. HPR was defined as PRUs >208, PRI >50%, and LTA 20 mmol/L >MPA% 50% and 5 mmol/L >46%, in line with consensus definitions.[13]

Statistical Analysis

Conformity to the normal distribution was evaluated for continuous variables with the Kolmogorov-Smirnov test. For baseline characteristics, categorical variables are expressed as frequencies and percentages; continuous variables were presented as mean ± SD or median (Q1-Q3). Continuous variables were analyzed for normal distribution with the Kolmogorov-Smirnov test. Comparisons for the primary endpoint and other intergroup or intragroup comparisons of continuous variables were performed with the Mann-Whitney U (2-group comparisons) and Kruskal-Wallis tests (3-group comparisons). Comparisons for categorical variables, including rates of HPR, were performed with the chi-square test or Fisher exact test. In line with prior investigations, there was no adjustment for multiple comparisons for the primary endpoint analysis.[30,38,39]

A 2-tailed P value of <0.05 indicated a statistically significant difference for superiority for all the analyses performed. Statistical analysis was performed using SPSS version 29.0 software (IBM). Graphs were plotted with GraphPad Prism version 9.1.0 (Dotmatics).

The safety population included all randomized patients exposed to study medication. The PD population included all patients with valid PD data for the primary endpoint. Laboratory personnel were blinded to treatment assignments. The PD population was used to analyze all primary and exploratory endpoints. Statistical analyses of PD assessments were performed according to the actual treatment received (eg, for patients randomized to one treatment but switched to the other). Secondary analyses were also performed according to the intention-to-treat principle (ie, participants analyzed according to randomized treatment assignment) and excluding participants who crossed over.

RESULTS

Patient population

Between December 8, 2020, and September 6, 2023, a total of 81 participants provided written informed consent to participate in the study. A total of 39 patients had an ABCD-GENE score ≥10 and were randomized; 42 patients had an ABCD-GENE score <10 and were included in the control group. All 81 participants were exposed to assigned treatment, representing the safety population (ticagrelor, n = 20; clopidogrel, n = 19, and control, n = 42). During follow-up, 11 patients withdrew consent, and 4 patients crossed over from the ticagrelor group to clopidogrel. Reasons for crossover were dyspnea (n = 3) and provider decision due to high bleeding risk (n = 1). Ultimately, 69 patients (ticagrelor, n = 14, clopidogrel, n = 20, and control, n = 35) completed the study, representing the PD population (**Figure 2**). Patient characteristics were similar between the randomized groups, except for the ABCD-GENE score, which was higher in the ticagrelor-based DAT group compared with clopidogrel-based DAT (14.7 ± 7.0 vs 11.5 ± 2.2; P = 0.035). The most common indication for NOAC was AF or flutter, and the most used NOAC was apixaban, both without differences among groups (**Table 1**). One patient allocated to clopidogrel-based DAT had Bleeding Academic Research Consortium (BARC) type 3a bleeding (ie, overt bleeding with a decrease in hemoglobin between 3 to < 5g/dL); one patient in the clopidogrel-based DAT and

another in the ticagrelor-based DAT group had BARC type 2 bleeding (hematochezia and hematuria, respectively). A total of 7 patients in the ticagrelor-based DAT group developed dyspnea, causing the switch to clopidogrel in 3 patients (**Supplemental Table 1**).

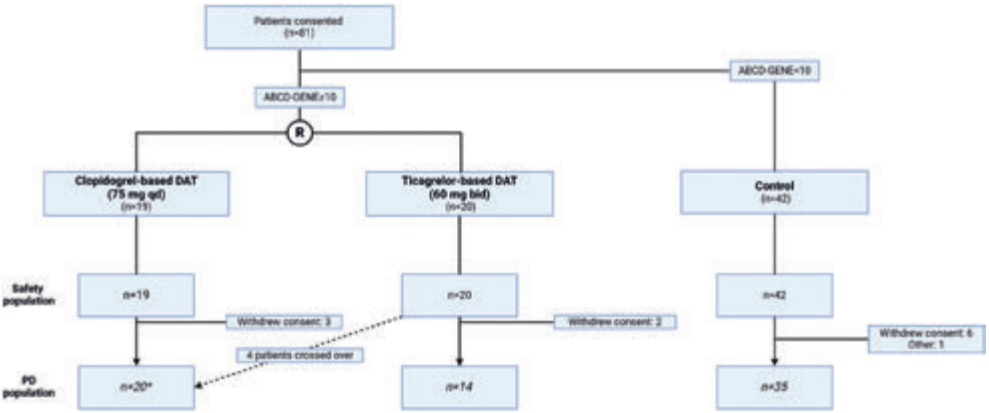

Figure 2. Study consort diagram.

*One patient allocated to ticagrelor was treated with clopidogrel because of the provider's decision due to high bleeding risk, and three patients allocated to ticagrelor were switched to clopidogrel due to dyspnea. ABCD-GENE score=Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping score; PD=pharmacodynamics.

Table 1. Baseline characteristics.

	Ticagrelor-based DAT (n=20)	Clopidogrel-based DAT (n=19)	P-value*	Control (n=42)	P-value**
Age, y	74.1±8.6	74.2±10.2	0.905	70.1±7.7	0.265
Female	8 (40.0)	8 (42.1)	0.774	5 (11.9)	0.018
BMI, kg/m^2	30.6±5.6	31.1±5.5	0.975	28.2±6.1	0.202
Race			0.536		0.156
Black	3 (15.0)	4 (21.1)		3 (7.1)	
Asian	2 (10.0)	1 (5.3)		0	
White	15 (75.0)	14 (73.7)		39 (92.9)	
Current smoker	0	3 (15.8)	0.106	8 (19.0)	0.097
Hypertension	19 (95.0)	17 (89.5)	0.932	34 (81.0)	0.219
Diabetes	11 (55.5)	13 (68.4)	0.389	14 (33.3)	0.027
Hyperlipidemia	20 (100)	17 (89.5)	0.122	38 (90.5)	0.340
Family History of CAD	7 (35.0)	7 (36.8)	0.799	19 (45.2)	0.864
Peripheral artery disease	1 (5.0)	5 (26.3)	0.056	3 (7.1)	0.070
Stroke/TIA	4 (20.0)	6 (31.6)	0.317	8 (19.0)	0.461
Prior MI	9 (45.0)	7 (36.8)	0.968	13 (31.0)	0.553
Prior PCI	12 (60.0)	9 (47.4)	0.515	15 (35.7)	0.240
Prior CABG	9 (45.0)	6 (31.6)	0.454	8 (19.0)	0.088
PCI Indication			0.386		0.795
SIHD	13 (65.0)	9 (47.4)		24 (57.1)	
Unstable Angina	4 (20.0)	3 (15.8)		7 (16.7)	
NSTEMI	3 (15.0)	4 (21.1)		7 (16.7)	
STEMI	0	3 (15.8)		4 (9.5)	
Number of Vessels Treated	1.1±0.3	1.1±0.3	0.625	1.0±0.3	0.486
Number of Stents Placed	1.3±0.6	1.2±0.6	0.674	1.7±0.7	0.068
GPI	1 (5.0)	2 (10.5)	0.932	1 (2.4)	0.344
Heparin	20 (100.0)	19 (100.0)	-	40 (95.2)	0.368
Aspirin	11 (55.0)	15 (78.9)	0.236	25 (59.5)	0.364
Indication for oral anticoagulation			0.164		0.522
Atrial fibrillation/flutter	19 (95.0)	15 (78.9)		34 (81.0)	
Venous thromboembolism	1 (5.0)	4 (21.1)		7(16.6)	
Left ventricle thrombus	0	0		1 (2.4)	
Oral anticoagulation			0.358		0.397
Apixaban	12 (60.0)	16 (84.2)		24 (57.1)	
Dabigatran	1 (5.0)	0		1 (2.4)	
Edoxaban	0	0		2 (4.8)	

Table 1. Continued

Rivaroxaban	7 (35.0)	3 (15.8)		15 (35.7)	
$P2Y_{12}$ receptor antagonist†	15 (75.0)	16 (84.2)	0.326	36 (85.7)	0.288
Clopidogrel	14 (93.3)	13 (81.3)		34 (94.4)	
Ticagrelor	1 (6.7)	3 (18.8)		2 (5.6)	
Beta-blocker	15 (75.0)	15 (78.9)	0.849	35 (83.3)	0.921
ACEi/ARB	14 (70.0)	16 (84.2)	0.536	26 (61.9)	0.201
Statin	17 (85.0)	18 (94.7)	1.000	37 (88.1)	0.609
Nitrates	10 (50.0)	8 (42.1)	0.716	16 (38.1)	0.521
Proton pump inhibitor	15 (75.0)	11 (57.9)	0.180	21 (50.0)	0.173
Ca^{2+} antagonist	12 (60.0)	10 (52.6)	0.533	11 (26.2)	0.009
Oral hypoglycemic	8 (40.0)	9 (47.4)	0.968	5 (11.9)	0.010
Insulin	5 (25.0)	8 (42.1)	0.120	4 (9.5)	0.004
Hemoglobin, g/dL	13.3±1.4	12.1±2.0	0.057	13.6±1.7	0.021
Hematocrit, %	36.0±12.6	37.2±5.7	0.656	39.4±7.6	0.429
Creatinine, mg/dL	1.2±0.4	1.3±0.5	0.798	1.1±0.4	0.329
Platelets, ×1,000/mm^3	214±72	233±69	0.446	222±53	0.658
CYP2C19 genetics			0.080		<0.001
*1/*1	6 (30.0)	7 (36.8)		17 (40.5)	
*1/*17	0	4 (21.1)		18 (42.9)	
*1/*2	9 (45.0)	6 (31.6)		3 (7.1)	
*17/*17	0	0		2 (4.8)	
*2/*17	2 (20.0)	2 (10.5)		2 (4.8)	
*2/*2	3 (15.0)	0		0	
ABCD-GENE score	14.7±7.0	11.5±2.2	0.035	4.1±3.2	<0.001

Values are mean ± SD or n (%). Results were calculated in the safety population. *P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT. **P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT vs. control. †After PCI before randomization. ACEi/ARB=Angiotensin-Converting Enzyme inhibitor/Angiotensin Receptor Blocker; BMI=Body Mass Index; CABG=Coronary Artery Bypass Grafting; CAD=Coronary Artery Disease; GPI=Glycoprotein Inhibitor; MI=Myocardial Infarction; NSTEMI=Non-ST Elevation Myocardial Infarction; PCI=Percutaneous Coronary Intervention; SIHD=Stable Ischemic Heart Disease; STEMI=ST Elevation Myocardial Infarction; TIA=Transient Ischemic Attack

Pharmacodynamic Findings. Markers of P2Y12 signaling

At baseline, median PRU level in the randomized cohort was 161.5 (Q1-Q3: 92.3-194.3); PRU levels were numerically higher in the ticagrelor-based DAT group compared with clopidogrel-based DAT (189.0 [Q1-Q3: 134.0-195.0] vs 135.0 [Q1-Q3: 72.5¬184.0]; P = 0.061). Differences in baseline platelet reactivity could be attributed to the higher ABCD-GENE score of patients randomized to ticagrelor-based DAT and a numerically higher frequency of baseline ticagrelor use in patients randomized to the clopidogrel-

based DAT group compared with ticagrelor-based DAT (**Table 1**). Parallel findings were observed with MPA% and PRI, although they did not yield statistical significance in the latter (**Supplemental Table 2**). Compared with the control group, there were no significant differences in baseline PRU levels in the ticagrelor-based DAT group (P = 0.212) and clopidogrel-based DAT group (P = 0.823) (**Supplemental Table 2**).

At 30 days, PRU levels were significantly lower with ticagrelor-based DAT compared with clopidogrel-based DAT at trough (primary endpoint 23.0 [Q1-Q3: 3.0-46.0] vs 154.5 [Q1-Q3: 77.5-183.5]; P < 0.001) and peak (6.0 [Q1-Q3: 4.0-14.0] vs 129.0 [Q1-Q3: 66.0-171.0]; P < 0.001) (**Figure 3**). Consistent results were observed when participants who crossed over were excluded from the analysis (23.0 [Q1-Q3: 3.0-46.0] vs 162.5 [Q1-Q3: 97.5-189.5]; P < 0.001). Consistent findings were observed with MPA% and PRI, although not reaching statistical significance for trough MPA% (**Table 2**). These findings were consistent among the randomized and control groups (**Table 2**, **Supplemental Table 2**, **Figure 4**). The rates of HPR varied according to the assay used and were overall lower in the ticagrelor-based DAT group (**Table 2**, **Supplemental Table 2**).

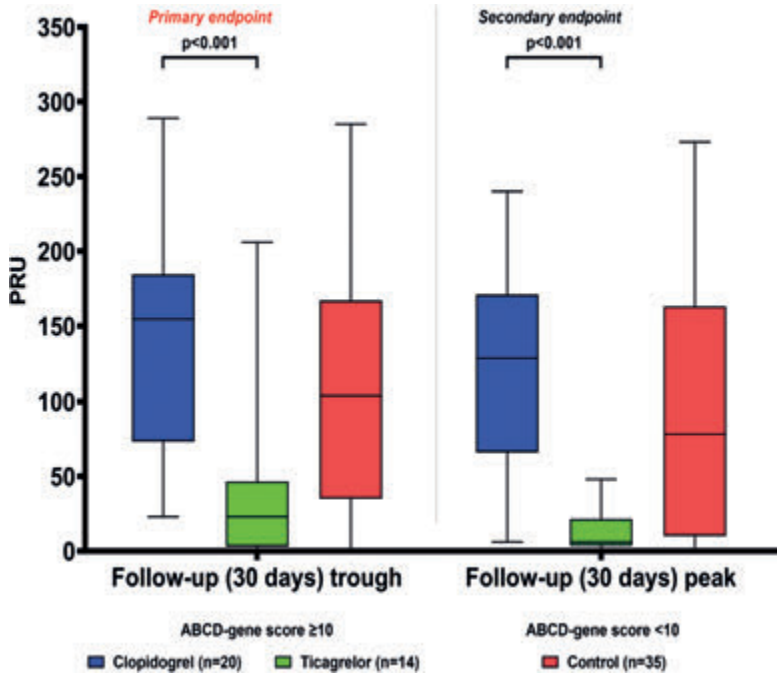

Figure 3. $P2Y_{12}$ reaction units according to allocated group.

Box Whisker plot of the minimum, median, maximum, and interquartile range. ABCD-GENE score=Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping score; IQR=interquartile range; PRU=$P2Y_{12}$ reaction units

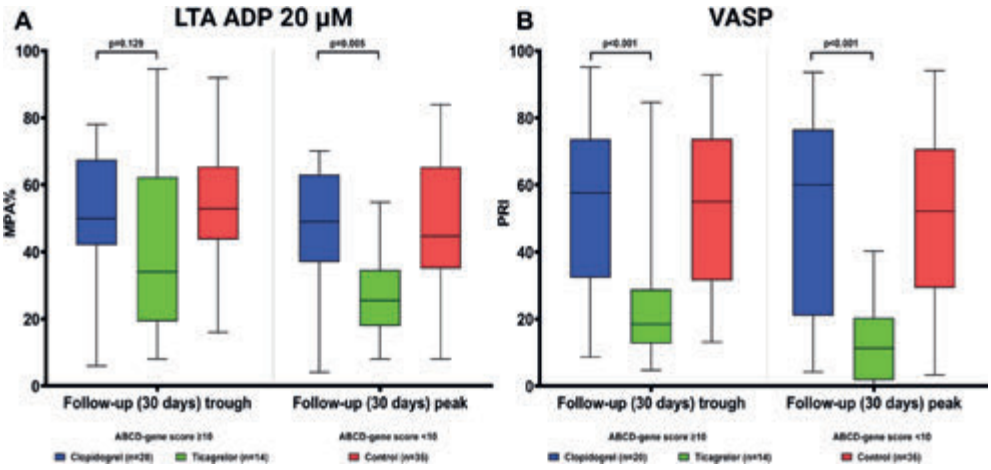

Figure 4. Adenosine phosphate-induced maximal platelet aggregation and platelet reactivity index according to allocated group.

Box Whisker plot of the minimum, median, maximum, and interquartile range. ABCD-GENE score=Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping

At 30 days, compared with the control group, ticagrelor-based DAT led to significantly lower PRU (trough P = 0.005 and peak P = 0.001), ADP-induced MPA% (trough P = 0.071 and peak P = 0.002), and PRI levels (trough P < 0.001 and peak P < 0.001) (**Table 2**). Conversely, levels of platelet reactivity were numerically higher in the clopidogrel-based DAT compared with the control groups, albeit not reaching statistical significance (**Table 2**). Consistent results were observed in the intention-to-treat analyses (**Supplemental Table 3**).

Table 2. Pharmacodynamic findings of markers of $P2Y_{12}$ signaling at 30-day follow-up.

	Ticagrelor-based DAT (n=14)	Clopidogrel-based DAT (n=20)	P-value*	Control (n=35)	P-value**
Trough					
Verify Now, PRU	23.0 (3.0–46.0)	154.5 (77.5–183.0)	<0.001	104.0 (35.0–167.0)	0.002
HPR	0	3 (15.0)	0.251	8 (22.9)	0.141
ADP 20μM, MPA%	34.1 (19.8–61.0)	50.0 (42.2–65.9)	0.129	52.9 (44.5–64.8)	0.154
HPR	4 (28.6)	6 (30.0)	0.928	12 (34.3)	0.782
VASP, PRI	18.4 (12.9–27.3)	57.6 (35.0–73.5)	<0.001	55.0 (32.5–71.6)	<0.001
HPR	1 (7.1)	12 (60.0)	0.003	19 (54.3)	0.003
Peak					
Verify Now, PRU	6.0 (4.0–14.0)	129.0 (66.0–171.0)	<0.001	78.0 (10.0–163.0)	<0.001
HPR	0	1 (5.0)	1.000	7 (20.0)	0.062
ADP 20μM, MPA%	25.5 (19.0–34.5)	49.0 (38.0–62.0)	0.005	44.7 (35.2–65.0)	0.006
HPR	0	6 (30.0)	0.057	9 (25.7)	0.079
VASP, PRI	11.3 (1.9–18.2)	60.1 (21.0–76.5)	<0.001	52.2 (31.4–68.6)	<0.001
HPR	0	10 (50.0)	0.002	15 (42.8)	0.003

Values are median (interquartile range), or n (%). Results were calculated in the pharmacodynamic population*P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT. **P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT vs. control. ADP=adenosine diphosphate; HPR=high platelet reactivity; MPA=maximal platelet aggregation; PRI=platelet reactivity index; PRU=$P2Y_{12}$ reactivity units.

Other markers of platelet aggregation and thrombus formation.

At 30 days, there were no significant differences in AA-induced, collagen-induced, TRAP-induced or combination of agonists– induced MPA% at trough or peak levels between clopidogrel-based DAT and ticagrelor-based DAT (**Table 3**, **Supplemental Figures 1 to 4**). Similarly, there were no significant differences between clopidogrel-based DAT and ticagrelor-based DAT in occlusion time or total thrombogenicity at trough or peak levels as assessed by T-TAS (**Table 3**, **Supplemental Figures 5** and **6**). Assessment of fibrin clot formation at 30 days showed shorter lag time in the clopidogrel-based DAT group compared with ticagrelor-based DAT at trough, but without differences in clot maximum absorbance or lysis. At peak, there were no significant differences between groups in lag time, maximum absorbance, or clot lysis (**Table 3**, **Figure 5**).

Table 3. Pharmacodynamic findings of markers of platelet aggregation and thrombus formation at 30-day follow-up.

	Ticagrelor-based DAT (n=14)	Clopidogrel-based DAT (n=20)	P-value*	Control (n=35)	P-value**
Trough					
AA 1mM†, MPA%	61.2 (44.5–71.0)	70.0 (53.0–79.0)	0.428	63.8 (55.0–79.7)	0.680
TRAP 15µM, MPA%	73.5 (56.0–82.1)	76.1 (61.5–85.0)	0.691	74.2 (65.6–84.1)	0.899
Collagen 3µg/mL†, MPA%	69.0 (64.2–79.5)	81.5 (74.0–86.0)	0.212	79.6 (67.5–88.5)	0.362
CAT‡, MPA%	72.0 (65.0–79.0)	69.5 (61.0–76.0)	0.740	67.0 (64.0–75.0)	0.890
T-TAS AR, occlusion time, seconds	905.0 (799.0–1079.0)	870.5 (704.0–1006.0)	0.332	745.0 (581.0–1085.0)	0.478
T-TAS PL, total thrombogenicity, AUC	277.6 (127.8–365.3)	289.6 (28.5–356.5)	0.682	228.5 (129.5–354.3)	0.882
Lag time, seconds	564.0 (492.0–624.0)	480.0 (444.0–546.0)	0.016	468.0 (420.0–624.0)	0.110
Maximum absorbance, absorbance units	0.355 (0.323–0.362)	0.365 (0.295–0.437)	0.334	0.273 (0.234–0.341)	0.009
Clot lysis, s	1440.0 (1116.0–2160.0)	1284.0 (1122.0–1662.0)	0.413	1212.0 (1044.0–1824.0)	0.523
Peak					
AA 1mM†, MPA%	54.8 (21.0–58.0)	62.0 (51.0–79.7)	0.275	71.0 (48.0–82.0)	0.241
TRAP 15µM, MPA%	72.1 (45.8–77.8)	75.0 (54.1–80.0)	0.509	78.3 (68.0–83.6)	0.189
Collagen 3µg/mL†, MPA%	76.0 (75.0–91.0)	83.0 (72.0–87.0)	0.779	79.9 (65.0–85.0)	0.802
CAT‡, MPA%	72.0 (60.0–73.0)	79.0 (74.0–80.0)	0.224	72.0 (65.0–81.0)	0.500
T-TAS AR, occlusion time, seconds	1248.0 (835.0–1454.0)	926.5 (731.0–1239.0)	0.340	819.0 (693.0–1122.0)	0.188
T-TAS PL, total thrombogenicity, AUC	115.1 (88.9–355.8)	214.4 (79.7–276.1)	0.886	185.8 (94.8–316.2)	0.728
Lag time, seconds	636.0 (528.0–672.0)	540.0 (492.0–660.0)	0.226	600.0 (468.0–s792.0)	0.455
Maximum absorbance, absorbance units	0.329 (0.266–0.379)	0.339 (0.274–0.431)	0.872	0.244 (0.206–0.310)	0.010
Clot lysis, seconds	13440.0 (912.0–1536.0)	1176.0 (864.0–1512.0)	0.679	1260.0 (936.0–1704.0)	0.905

Values are median (interquartile range). Results were calculated in the pharmacodynamic population. *P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT. **P-value of the comparison ticagrelor-based DAT vs. clopidogrel-based DAT vs. control. †Calculated only in patients on concomitant aspirin treatment. ‡CAT cocktail is a combination of collagen-related peptide 2µg/mL + ADP 5 µM + TRAP 15µM. AA=arachidonic acid; ADP=adenosine diphosphate; AUC=area under the pressure-time curve; MPA=maximal platelet aggregation; TRAP=thrombin receptor activator peptide; T-TAS=total thrombus formation analysis system.

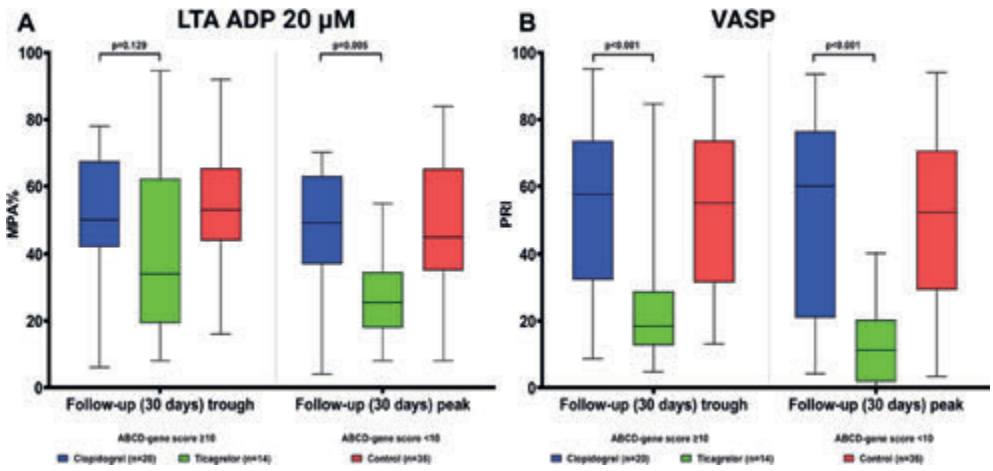

Figure 5. Fibrin Clot Formation Parameters According to Allocated Group.

(A) Lag time reported in seconds. (B) Maximum absorbance reported in absorbance units. (C) Clot lysis reported in seconds. Box Whisker plot of the minimum, median, maximum, and interquartile range. ABCD-GENE score = Age, Body Mass Index, Chronic Kidney Disease, Diabetes Mellitus, and Genotyping score.

DISCUSSION

The present study is the first to prospectively assess the PD effects of clopidogrel vs ticagrelor in NOAC-treated patients undergoing PCI, and who have discontinued aspirin in the peri-PCI period, with impaired clopidogrel response as assessed by the ABCD-GENE score. The key observations from our study can be summarized as follows: 1) in patients with impaired clopidogrel response defined as having an ABCD-GENE score ≥10, ticagrelor at a 60-mg, twice-a-day regimen was associated with enhanced P2Y12 inhibitory effects compared with clopidogrel 75 mg once a day as corroborated by multiple assays of P2Y12-dependent platelet reactivity; 2) ticagrelor at a 60-mg, twice-a-day regimen was associated with reduced rates of HPR, a marker of thrombotic risk; and 3) non-P2Y12 thrombotic pathways showed no difference comparing ticagrelor- and clopidogrel-treated individuals, except for lag time trough levels, which were shorter in the clopidogrel-based DAT group (Central Illustration).

The optimal antithrombotic regimen in patients requiring OAC undergoing PCI has been a topic of extensive investigation over the past decade.[2,17] Studies have consistently shown that maintaining OAC in adjunct to DAPT (ie, aspirin plus a P2Y12 inhibitor), known as TAT, is associated with prohibitively high rates of bleeding complications, underscoring the need for safer antithrombotic regimens yet also efficacious for the prevention of thrombotic complications.[4-8] Trials have shown that dropping aspirin in the peri-PCI period and maintaining single antiplatelet therapy with a P2Y12 inhibitor in adjunct to an OAC is associated with the most favorable safety and efficacy profile.[4-8] In particular, a NOAC should be preferred over a vitamin K antagonist, and clopidogrel is the P2Y12 inhibitor of choice.[3,9,10] However,

cumulative evidence has shown that dropping aspirin in the peri-PCI period and maintaining clopidogrel as the sole antiplatelet agent is associated with a marginal increase in thrombotic complications during the first 30 days post-PCI.[11,17] Indeed, several factors can contribute to these findings. Among these is the nonuniform degree of platelet inhibition induced by clopidogrel, with some patients having impaired P2Y12 inhibitory effects.[13-15] Inadequate antiplatelet protection can be further enhanced by the withdrawal of aspirin therapy. Hence, defining the optimal antiplatelet regimen in patients also requiring treatment with a NOAC undergoing PCI, particularly within the first 30 days, remains an ongoing concern.[17] The SWAP-AC-2 study is a PD investigation to test platelet inhibition with an alternative P2Y12 inhibitor (ie, ticagrelor) in patients with impaired clopidogrel-induced platelet inhibition as identified by the ABCD-GENE score.

Our study is the first to prospectively test different antiplatelet treatment regimens according to ABCD-GENE score. To date, the impact of the ABCD-GENE score on markers of platelet reactivity and clinical outcomes has been derived based on post hoc assessments of registries and randomized trials.[16,40-43] Therefore, the current investigation adds support to using the ABCD-GENE score to guide the selection of P2Y12 inhibitors. Although the use of platelet function testing would have allowed the best identification of patients with HPR, it is well established that there are limitations to this approach.[44] In particular, an accurate assessment of clopidogrel response would need to be performed 1 to 2 weeks after dosing, which limits practicality.[13-15] On the other hand, genetic testing, now available with rapid bedside assays providing results within 60 minutes, integrated with readily available clinical factors can allow for the decision-making of selecting the P2Y12 inhibitor before hospital discharge.[13-15]

Outcomes associated with the use of ticagrelor in NOAC-treated patients are limited as its use was be-tween 4% and 12% of patients in clinical trials.[5-8] Overall, findings were consistent with the main trials results, albeit absolute bleeding rates with ticagrelor were higher compared with clopidogrel.[45] It is important to note that a 90-mg, twice-a-day regimen of ticagrelor was used in these trials. However, our study considered a 60-mg, twice-a-day regimen, given that this provides sustained platelet inhibition, similar to that achieved with a 90-mg, twice-a-day regimen, but with a safer and better tolerability profile.[19-22] A 60-mg, twice-a-day regimen in patients undergoing PCI has been tested in prior PD studies, showing enhanced platelet inhibitory effects compared with clopidogrel.[19,20] Nevertheless, these studies were conducted in patients concomitantly treated with aspirin, and there is limited evidence of a ticagrelor 60-mg, twice-a-day regimen in the absence of aspirin during the peri-PCI period. Thus, another aspect of novelty of our study is the choice of a low-dose ticagrelor regimen (ie, 60 mg), which expands on prior PD investigations using a standard-dose ticagrelor regimen (ie, 90 mg) showing no differences in antithrombotic potency with respect to ex vivo blood thrombogenicity with or without aspirin.[46] The importance of having adequate platelet inhibition in high-risk settings when dropping aspirin is underscored in studies using clopidogrel 75 mg once a day or a very-low dose of prasugrel (3.75 mg once a day), which showed an increase in thrombotic complications.[47,48] The PD observations with ticagrelor 60 mg from this and prior investigations pro-vide reassurance of its efficacy, particularly compared with clopidogrel.

The interplay between antiplatelet and anticoagulant therapy may raise concerns about how this may impact hemostasis and enhance the risk of bleeding.[49] Ex vivo studies in clopidogrel- or ticagrelor-treated patients with established cardio-vascular disease have not shown platelet-mediated global thrombogenicity to be affected by a vascular dose regimen of rivaroxaban (2.5 mg twice a day), which more selectively affected markers of thrombin generation.[49,50] Consistent findings were observed in this study using higher doses of NOACs, showing that other markers of thrombosis not specific to P2Y12 signaling were largely not affected by the agent (ie, clopidogrel or ticagrelor) or response to this agent. We demonstrated no differences in fibrin-related thrombotic markers, using the dynamic clot formation and lysis assay, except for shorter lag time in the clopidogrel-based DAT arm, which may indicate increased thrombosis potential by mechanisms that remain an area for future research. These findings are of potential clinical importance as they suggest that the impact of ticagrelor-based DAT vs clopidogrel-based DAT is mainly driven by their P2Y12 inhibitor effects rather than any differential modulation of other pathways leading to thrombus formation.

Study Limitations

The PD nature of this investigation does not allow for drawing any definitive conclusions on the clinical implications of the observed findings. Due to practical considerations to stratify patients immediately after PCI, our study considered the ABCD-GENE score as a tool to identify patients with impaired clopidogrel-induced platelet inhibition, which, however, is not as accurate as a platelet function test performed while patients have been on steady-state (eg, 1-2 weeks) clopidogrel therapy. Moreover, in our study, patients were stratified based on the ABCD-GENE score, and it cannot be excluded that stratifying patients according to measures of thrombogenicity specific to this population (eg, degree of NOAC-induced thrombin generation) could also help tailor the selection of P2Y12 inhibiting therapy. Despite the reduced rates of dyspnea with a 60-mg compared with a 90-mg regimen of ticagrelor, 35% (7/20) of our patients still experienced this side effect, which remains a major limitation for ticagrelor use in clinical practice. PD investigations using prasugrel, which provides comparable platelet inhibitory effects to ticagrelor but without the dyspnea, represent an area of unmet need. Dyspnea led 3 patients randomized to ticagrelor to switch to clopidogrel, which reduced the sample size of ticagrelor-treated patients for our primary endpoint analysis. However, laboratory personnel were blinded to treatment assignment to maintain the scientific rigor of the study, which was completed according to the pre-specified plan of having 34 patients with valid PD samples for the primary endpoint at 30 days. Nevertheless, our study still met the predefined primary endpoint, which was corroborated by multiple assays specific to P2Y12 signaling, supporting the superior PD efficacy of ticagrelor-based DAT compared with clopidogrel-based DAT in NOAC-treated patients undergoing PCI with an ABCD-GENE score ≥10. Moreover, consistent findings were observed when data were analyzed following the intention-to-treat principle and excluding participants who crossed over. Although our study showed HPR rates to be lower with ticagrelor-based DAT, these differences were not always statistically significant. However, our study was not powered for a reduction in HPR, which would have required a larger sample size, and rates of HPR after ticagrelor dosing (ie, peak) were consistently null across assays. Ultimately, a ticagrelor

90-mg, twice-a-day group was not included as a comparator for the ticagrelor 60-mg group. How-ever, from a PD perspective, both doses provide similar levels of platelet inhibition.[19-22]

CONCLUSION

In NOAC-treated patients undergoing PCI with an ABCD-GENE score ≥10, ticagrelor-based DAT using a 60-mg, twice-daily regimen significantly reduced P2Y12-mediated platelet reactivity compared with clopidogrel-based DAT. Markers measuring other pathways leading to thrombus formation were largely unaffected by these treatments. The safety and efficacy of a tailored section of P2Y12 inhibiting therapy in NOAC-treated patients undergoing PCI warrants further research in adequately powered randomized controlled trials.

REFERENCES

1. Angiolillo DJ, Galli M, Collet JP, Kastrati A, O'Donoghue ML. Antiplatelet therapy after percutaneous coronary intervention. *Euro-Intervention*. 2022;17:e1371–e1396.
2. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74:83– 99.
3. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation*. 2021;143:583–596.
4. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–1115.
5. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation un-dergoing PCI. *N Engl J Med*. 2016;375:2423–2434.
6. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCIin atrial fibrillation. *N Engl J Med*. 2017;377:1513– 1524.
7. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380: 1509–1524.
8. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335–1343.
9. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guide-lines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74:104–132.
10. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2021;42:373–498.
11. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double vs triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials. *Eur Heart J*. 2019;40: 3757–3767.
12. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. *Circulation*. 2000;101:2823–2828.
13. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y(12) receptor inhibitor treatment in percutaneous cor-onary intervention. *J Am Coll Cardiol Intv*. 2019;12: 1521–1537.

14. Galli M, Ortega-Paz L, Franchi F, Rollini F, Angiolillo DJ. Precision medicine in interventional cardiology: implications for antiplatelet therapy in patients undergoing percutaneous coronary intervention. *Pharmacogenomics*. 2022;23:723– 737.
15. Capodanno D, Angiolillo DJ. Personalised antiplatelet therapies for coronary artery disease: what the future holds. *Eur Heart J*. 2023;44:3059– 3072.
16. Angiolillo DJ, Capodanno D, Danchin N, et al. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *J Am Coll Cardiol Intv*. 2020;13: 606–617.
17. De Caterina R, Agewall S, Andreotti F, et al. Great debate: triple antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting should be limited to1 week. *Eur Heart J*. 2022;43:3512–3527.
18. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. *Clin Pharmacol Ther*. 2022;112:959–967.
19. Orme RC, Parker WAE, Thomas MR, et al. Study of two dose regimens of ticagrelor compared with clopidogrel in patients undergoing percutaneous coronary intervention for stable coronary artery disease. *Circulation*. 2018;138: 1290–1300.
20. Franchi F, Rollini F, Been L, et al. Pharmacodynamic and pharmacokinetic effects of a low maintenance dose ticagrelor regimen versus standard dose clopidogrel in diabetes mellitus patients without previous major cardiovascular events undergoing elective percutaneous coronary intervention: the OPTIMUS-6 study. *Circulation*. 2020;142:1500–1502.
21. Storey RF, Angiolillo DJ, Bonaca MP, et al. Platelet inhibition with ticagrelor 60 mg versus 90 mg twice daily in the PEGASUS-TIMI 54 trial. *J Am Coll Cardiol*. 2016;67:1145–1154.
22. Bonaca MP, Bhatt DL, Cohen M, et al. Longterm use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372: 1791–1800.
23. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y(12) receptor-inhibiting therapies. *Circulation*. 2017;136:1955–1975.
24. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. *J Am Coll Cardiol*. 2018;72: 2915–2931.
25. Franchi F, Ortega-Paz L, Rollini F, et al. Cangrelor in patients with coronary artery disease pretreated with ticagrelor: The Switching Anti-platelet (SWAP)-5 study. *J Am Coll Cardiol Intv*. 2023;16:36–46.
26. Franchi F, Rollini F, Ortega-Paz L, et al. Switching from cangrelor to prasugrel in patients undergoing percutaneous coronary intervention: the Switching Antiplatelet-6 (SWAP-6) study. *J Am Coll Cardiol Intv*. 2023;16:2528–2539.
27. Franchi F, Rollini F, Kairouz V, et al. Pharmacodynamic effects of vorapaxar in patients with and without diabetes mellitus: results of the OPTIMUS-5 study. *J Am Coll Cardiol Basic Trans Science*. 2019;4:763–775.
28. Franchi F, Rollini F, Faz G, et al. Pharmacodynamic effects of vorapaxar in prior myocardial infarction patients treated with potent oral P2Y(12) receptor inhibitors with and without aspirin: results of the VORA-PRATIC study. *J Am Heart Assoc*. 2020;9:e015865.
29. Franchi F, Rollini F, Rivas Rios J, et al. Pharmacodynamic effects of switching from ticagrelor to clopidogrel in patients with coronary artery disease: results of the SWAP-4 study. *Circulation*. 2018;137:2450–2462.

30. Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation*. 2019;139:1661– 1670.
31. Franchi F, Rollini F, Aggarwal N, et al. Phar-macodynamic comparison of prasugrel versus ticagrelor in patients with type 2 diabetes mellitus and coronary artery disease: the OPTIMUS (Optimizing Antiplatelet Therapy in Diabetes Mellitus)-4 study. *Circulation*. 2016;134:780–792.
32. Carter AM, Cymbalista CM, Spector TD, Grant PJ, EuroCLOT Investigators. Heritability of clot formation, morphology, and lysis: the Euro-CLOT study. *Arterioscler Thromb Vasc Biol*. 2007;27:2783–2789.
33. Scott DJ, Prasad P, Philippou H, et al. Clot architecture is altered in abdominal aortic aneurysms and correlates with aneurysm size. *Arterioscler Thromb Vasc Biol*. 2011;31:3004–3010.
34. Franchi F, Rollini F, Rivas J, et al. Prasugrel versus ticagrelor in patients with CYP2C19 loss-of-function genotypes: results of a randomized pharmacodynamic study in a feasibility investigation of rapid genetic testing. *J Am Coll Cardiol Basic Trans Science*. 2020;5:419–428.
35. Cavallari LH, Weitzel KW, Elsey AR, et al. Institutional profile: University of Florida Health Personalized Medicine Program. *Pharmacogenomics*. 2017;18:421–426.
36. Mehran R, Rao SV, Bhatt DL, et al. Standard-ized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Aca-demic Research Consortium. *Circulation*. 2011;123: 2736–2747.
37. Garcia-Garcia HM, McFadden EP, Farb A, et al. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. *Circulation*. 2018;137:2635–2650.
38. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004;10:307– 312.
39. Rollini F, Franchi F, Hu J, et al. Crushed prasugrel tablets in patients with STEMI undergoing primary percutaneous coronary intervention: the CRUSH study. *J Am Coll Cardiol*. 2016;67:1994– 2004.
40. Capodanno D, Angiolillo DJ, Lennon RJ, et al. ABCD-GENE score and clinical outcomes following percutaneous coronary intervention: insights from the TAILOR-PCI trial. *J Am Heart Assoc*. 2022;11: e024156.
41. Dai L, Xu J, Yan H, et al. Application of age, body mass index, chronic kidney disease, diabetes, and genotyping score for efficacy of clopidogrel: secondary analysis of the CHANCE trial. *Stroke*. 2022;53:465–472.
42. Jin Y, Ma J, Wang Z, et al. Performance of the ABCD-GENE score for predicting clinical outcomes in clopidogrel-treated patients with ACS. *J Cardiovasc Transl Res*. 2022;15:1385–1392.
43. Thomas CD, Franchi F, Keeley EC, et al. Impact of the ABCD-GENE score on clopidogrel clinical effectiveness after PCI: a multi-site, real-world investigation. *Clin Pharmacol Ther*. 2022;112:146– 155.
44. Angiolillo DJ. Dual antiplatelet therapy guided by platelet function testing. *Lancet*. 2017;390: 1718–1720.
45. Oldgren J, Steg PG, Hohnloser SH, et al. Dabi-gatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. *Eur Heart J*. 2019;40:1553–1562.
46. Baber U, Zafar MU, Dangas G, et al. Ticagrelor with or without aspirin after PCI: the TWILIGHT platelet substudy. *J Am Coll Cardiol*. 2020;75:578– 586.

47. Watanabe H, Morimoto T, Natsuaki M, et al. Comparison of clopidogrel monotherapy after 1 to 2 months of dual antiplatelet therapy with 12 months of dual antiplatelet therapy in patients with acute coronary syndrome: the STOPDAPT-2 ACS randomized clinical trial. *JAMA Cardiol*. 2022;7:407–417.
48. Natsuaki M, Watanabe H, Morimoto T, et al. An aspirin-free versus dual antiplatelet strategy for coronary stenting: STOPDAPT-3 randomized trial. *Circulation*. 2024;149:585–600.
49. Galli M, Franchi F, Rollini F, et al. Dual pathway inhibition in patients with atherosclerotic disease: pharmacodynamic considerations and clinical implications. *Expert Rev Clin Pharmacol*. 2023;16:27–38.
50. Galli M, Franchi F, Rollini F, et al. Pharmacodynamic profiles of dual-pathway inhibition with or without clopidogrel versus dual antiplatelet therapy in patients with atherosclerotic disease. *Thromb Haemost*. 2022;122:1341–1351.

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

PART III

Clinical Implementation of a Genotype Guided Antiplatelet Therapy

CHAPTER 10

The Clinical Implementation of CYP2C19 Genotyping in Patients with an Acute Coronary Syndrome: Insights From the FORCE-ACS Registry

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ABSTRACT

Background

Guidelines recommend prasugrel or ticagrelor for acute coronary syndrome (ACS) patients. However, these P2Y12 inhibitors increase bleeding risk compared to clopidogrel. Although genotype-guided P2Y12 inhibitor selection has been shown to reduce bleeding risk, data on its clinical implementation is lacking.

Methods

The study included ACS patients receiving genotype-guided antiplatelet therapy, utilising either a point-of-care (POC) device or laboratory-based testing. We aimed to collect qualitative and quantitative data on genotyping, eligibility for de-escalation, physician adherence to genotype results, time to de-escalation and cost reduction.

Results

Of the 1,530 patients included in the ACS registry from 2021 to 2023, 738 ACS patients treated with ticagrelor received a *CYP2C19* genotype test. The median turnover time of genotyping was 6.3 hours (interquartile range [IQR], 3.216.7), with 82.3% of the genotyping results known within 24 hours after admission. POC genotyping exhibited significantly shorter turnaround times compared to laboratory-based testing (with respective medians of 5.7 vs 47.8 hours; $P < .001$). Of the genotyped patients, 81.7% were eligible for de-escalation which was carried out within 24 hours in 70.9% and within 48 h in 93.0%. The time to de-escalation was significantly shorter using POC (25.4 hours) compared to laboratory-based testing (58.9 hours; $P < .001$). Implementing this strategy led to a reduction of €211,150.50 in medication costs.

Conclusions

CYP2C19 genotype-guided-de-escalation in an all-comers ACS population is feasible. POC genotyping leads to shorter turnaround times and quicker de-escalation. Time to de-escalation from ticagrelor to clopidogrel in noncarriers was short, with high physician adherence to genotype results.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the cornerstone of treatment for patients with acute coronary syndrome (ACS).[1,2] Guidelines recommend the use of ticagrelor or prasugrel, given their more consistent anti-platelet response, over clopidogrel for patients with ACS. This recommendation is based on the pivotal trials TRITON-TIMI 38 and PLATO demonstrating superiority over clopidogrel in reducing cardiovascular events.[3–6] However, ticagrelor and prasugrel are associated with a higher bleeding risk than clopidogrel.[1,4,6,7]

Clopidogrel is a pro-drug and needs to be oxidised by the CYP2C19 enzyme to become effective. However, around 30% of Europeans and 60% of Asians carry at least one loss-of-function (LoF) allele for the *CYP2C19* genotype (**2* or **3*), leading to reduced metabolisation.[8] As a result, the United States Food and Drug Administration (FDA) warns against the use of clopidogrel in these patients and recommends the use of an alternative P2Y12 inhibitor. In line with the FDA's recommendation, the European Medicines Agency (EMA) has also acknowledged the impact of *CYP2C19* LoF alleles on clopidogrel efficacy, emphasising the use of alternative antiplatelet therapies in poor metabolizers.9 This reflects a global awareness of the clinical implications associated with *CYP2C19* genetic variation in the context of antiplatelet therapy. This is based on data demonstrating that, compared to noncarriers, carriers of one (intermediate metabolizer) or two (poor metabolizer) CYP2C19 LoF alleles have a higher risk for major adverse cardiovascular events (MACE) when treated with clopidogrel.[10–12]

The randomised clinical trial POPular Genetics showed that applying a genotype-guided de-escalation strategy in ST-elevation myocardial infarction (STEMI) patients led to a reduction in bleeding without an increase in ischaemic events.[13] However, to date the implementation of this strategy in an all-comers ACS population has not been reported.

The objective of this study was to provide objective insights on the feasibility of implementing an early routine *CYP2C19* genotype-guided de-escalation strategy in patients with ASC, using both point-of-care (POC) genotyping and laboratory-based testing (**Table 1**).

Table 1. The different *CYP2C19* phenotypes and genotype, with their associated expected response to clopidogrel and treatment recommendation. This table is part of the local protocol.

Metabolizer phenotype	Genotype	Response to clopidogrel	Recommendation to switch from ticagrelor to clopidogrel	Start of loading dose Clopidogrel (according to the ESC Guideline)
Ultra-rapid (UM)	CYP*17/*17	Normal or increased antiplatelet response to clopidogrel	Yes	24h after last Ticagrelor dose
Rapid (RM)	CYP *1/*17	Normal or increased antiplatelet response to clopidogrel	Yes	24h after last Ticagrelor dose
Normal (NM)	CYP *1/*1	Normal antiplatelet response to clopidogrel	Yes	24h after last Ticagrelor dose
Intermediate (IM)	1 LOF allele (*1/*2, *1/*3, *2/*17, *3/*17)	Reduced antiplatelet response to clopidogrel	No	-
Poor (PM)	2 LOF alleles (*2/*2, *2/*3, *3/*3)	Significantly reduced antiplatelet response to clopidogrel	No	-

METHODS

Study Design and Population

The rationale and design of the FORCE-ACS registry have been described previously.[14] In brief, the FORCE-ACS registry is an ongoing prospective registry in which nine Dutch hospitals participate. All hospitals are capable of performing coronary angiography and six hospitals have on-site percutaneous coronary intervention (PCI) facilities. One hospital has on-site genotyping facilities and performs routine genotyping. On August 2021, the genotype-guided strategy was implemented. From then on, all consecutive patients who were diagnosed with an ACS and had an indication for dual antiplatelet therapy (DAPT), were eligible for a genotype-guided antiplatelet therapy. The diagnosis of ACS included STEMI, non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UAP). Patients were followed up by questionnaires at 1, 12, 24 and 36 month(s) after initial admission. Clinical data abstraction from the electronic health record (EHR) was per-formed manually. Only patients who had complete data regarding their P2Y12 inhibitor therapy were included for this analysis. Written informed consent was obtained from each patient. The institutional review boards of all approved the protocol of the FORCE-ACS registry. The current study complies with the principles of the Declaration of Helsinki (**Table 2**).

Table 2. Baseline characteristics

Characteristic	N = 855
Age	65 (± 11)
Female	237 (27.7%)
BMI	28 (± 5)
Previous MI	150 (17.5%)
Previous PCI with stent	152 (17.8%)
Previous CABG	24 (2.8%)
Previous CVA or TIA	18 (2.1%)
Peripheral arterial disease	14 (1.6%)
Hypertension	444 (51.9%)
Diabetes mellitus	170 (19.9%)
Hypercholesterolemia	648 (75.8%)
Positive family history for CAD	368 (43%)
History of smoking	489 (57.2%)

Abbreviations: BMI: body mass index; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CVA: cerebrovascular accident; MI: myocardial infarction; PCI: percutaneous coronary intervention; TIA: transient ischemic attack.

Genotyping

Initially, genotyping was performed using the POC device of Genomadix, which requires a buccal sample to operate. This device has Conformité Européenne (CE) marking and is therefore compliant with European Union legislation for safety, health, and environmental requirements. As of March 2022, the implementation protocol was updated to also include *CYP2C19* genotyping using genomic DNA isolated from venous EDTA-anticoagulated blood. These samples were analysed in the laboratory of the clinical pharmacy. The LoF alleles *CYP2C19*2* (*G681A*, *rs4244285*) and *CYP2C19*3* (*G636A*, *rs4986893*) were determined by real-time polymerase chain reaction using the StepOnePlusTM Real-Time PCR system (Applied Biosystems), pre-validated Drug Metabolism TaqMan Genotyping Assays (for *CYP2C19*2* Assay ID C__25986767_70 and for *CYP2C19*3* Assay ID C__27861809_10) and TaqMan GTXpress Master Mix (Thermo Fisher Scientific, USA), according to the manufacturer's instructions. The laboratory-based test results were entered into the EHR system by qualified laboratory personnel. The POC genotyping results were processed on a separate computer, printed, and scanned into the EHR by the nurses. Nurses also reported the *CYP2C19* genotype into the EHR, which was automatically linked to the overall lab results of patients.

The *CYP2C19* genotyping results were classified according to the guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC): Normal metabolizer (NM): **1/*1*; Intermediate metabolizer (IM): **1/*2*, **1/*3*, **2/*17* or **3/ *17*; Poor metabolizer (PM): **2/*2, *3/*3* or **2/*3*; rapid metabolizer (RM): **1/*17*; Ultra-rapid metabolizer (UM): **17/*17*.[8]

The POC device utilised comprehensive analysis of the *CYP2C19* gene, including relevant LoF-alleles such as **2*, **3*, and the hyperactivity encoding allele **17*. The laboratory-based testing only assessed the presence of the LoF **2* and **3* alleles. Previous studies have indicated that the **17* allele is not associated with clinically significant variations in clopidogrel metabolism, leading to its exclusion in the testing protocol of laboratory-based testing for clopidogrel users.[15] All RM and UM identified by the POC device were considered normal metabolizers.[16]

Antiplatelet Therapy

All patients admitted with an ACS were initially treated with ticagrelor unless they had an indication for oral anticoagulation (mostly atrial fibrillation) or had a high bleeding risk (PRECISE-DAPT score ≥25 or at least 1 major or 2 minor criteria according to the ARC-HBR criteria) in which case clopidogrel was prescribed (**Figure 1**).[1]

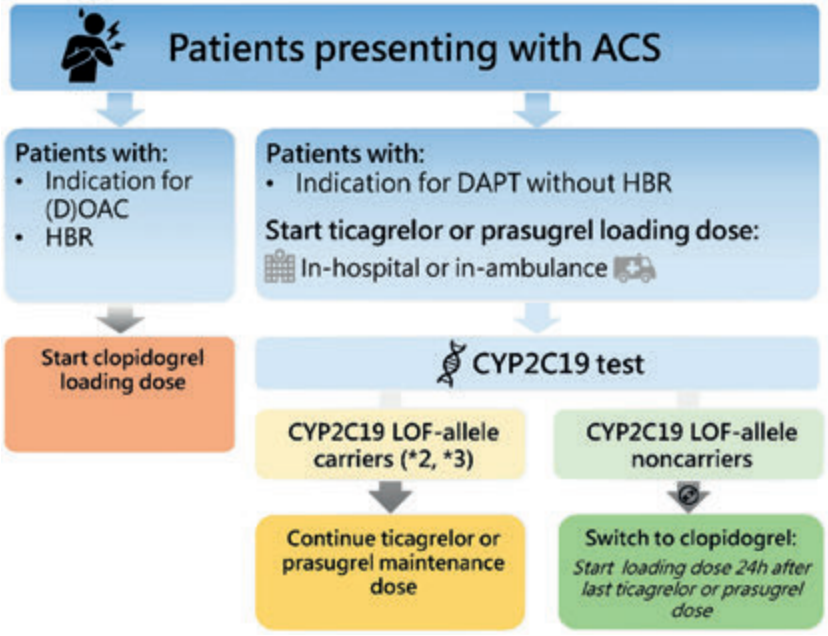

Figure 1.

Flowchart depicting the clinical decision-making process for the genotype-guided de-escalation strategy. This flowchart provided guidance to treating physicians, who retained full discretion in clinical management. They were free to deviate from the flowchart as needed.

In the genotyped patients, antiplatelet therapy was adjusted based on the *CYP2C19* genotyping results. Attending physicians would receive an automatic notification from the EHR to change the antiplatelet therapy from ticagrelor to clopidogrel in patients who appeared to be normal or (ultra-) rapid

metabolizers, starting with a 600 mg loading dose followed by 75 mg clopidogrel once daily (**Figure 2**). No notification was shown in intermediate and poor metabolizers, who continued to use ticagrelor 90 mg twice daily. All clinical management was left at the discretion of the attending physician. Patients were at least followed until their first follow-up visit in order to gain information regarding the use of antiplatelet therapy.

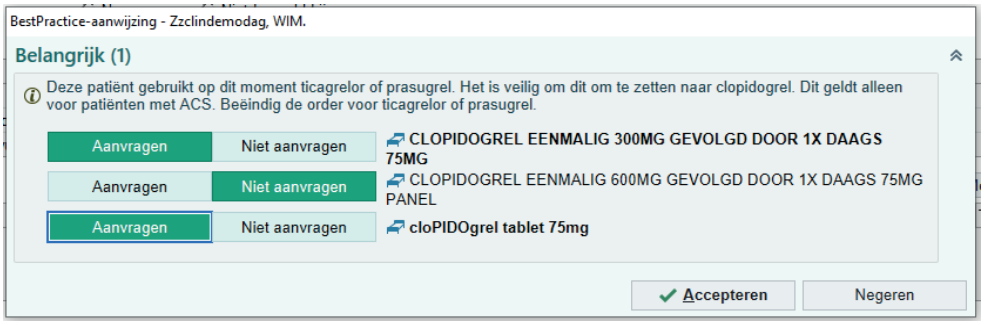

Figure 2. Example of the pop-up used in the medical record to propose a therapy switch to clopidogrel when an ACS patient is currently treated with ticagrelor, but is an normal metabolizer for clopidogrel.

The pop-up states the following: "Important (1) This patient is currently taking ticagrelor or prasugrel. It is safe to convert this to clopidogrel. This only applies to patients with ACS. Terminate the order for ticagrelor or prasugrel" followed by a proposal for new orders for a clopidogrel loading dose and maintenance treatment, which the physician can accept or decline.

Clinical Endpoints

This registry was used to provide qualitative and quantitative data such as number of patients being genotyped, the genotyping method used, turnover times of genotyping, number of patients undergoing genotype-guided de-escalation, number of cases where physicians disregarded the genotype results and cost reduction. We separately evaluated the following time intervals: the time from admission to genetic test result, the time from test result to de-escalation and the time from admission to de-escalation.

We assessed the association between changing antiplatelet therapy and the type of genotyping method (laboratory-based testing vs POC genotyping).

Statistical Analysis Methods

Continuous variables are presented as median and 25th-75th interquartile range (IQR) or mean and standard deviation (SD). Discrete variables are presented as frequencies and percentages (%). The Mann–Whitney and Chi-square test or Fisher's exact test were used to compare quantitative and discrete variables, respectively. Differences in successful P2Y12-therapy de-escalation among the different

genotyping methods were assessed using the Chi-square and Mann–Whitney U test. Significance was set at a P-value of <.05. Statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL).

RESULTS

A total of 1,530 patients were included in the ACS registry from June 2021 to January 2023. In 855 patients, a *CYP2C19* genotype test was performed (mean age 65 years, 28% female). From these, 269 (31.5%) patients were carriers of a *CYP2C19* LoF-allele, with 28.2% of patients being intermediate and 3.3% poor metabolizers. Most patients were genotyped using the POC device (n = 752, 88.0%). The remaining 12.0% (n= 103) were genotyped using laboratory-based testing.

De-escalation Rates

Of the 855 patients who were genotyped, 85 patients (14.5%) were already treated at admission with clopidogrel (thus not with ticagrelor or prasugrel). These patients had a prior indication for clopidogrel such as a previous cerebrovascular accident (CVA), had a high bleeding risk or were treated with an oral anticoagulant (OAC). In addition, in 22 (3.8%) patients, initial suspicion of ACS was ruled out by coronary angiography and, as such, the need for a P2Y12 inhibitor was waived. Despite being an intermediate metabolizer, nine patients (3.3%) were switched to clopidogrel for a variety of reasons, as depicted in **Figure 3** (eg, new indication for OAC during admission, increased bleeding risk after coronary artery bypass grafting [CABG]). In one patient (0.1%) the test result remained inconclusive, and no additional genotype testing was performed. In total, 478 noncarriers treated with ticagrelor (64.8%) were eligible for de-escalation. Successful de-escalation from ticagrelor to clopidogrel occurred in 433 of 478 (90.4%) patients. Of the other 45 patients, 32 (71.1%) were not switched to clopidogrel due to non-compliance by the treating physician and 4 (8.9%) because of an early transfer to a referral centre before switching could take place. In three patients (6.7%) medication was not switched at the discretion of the physician based on the high thrombotic risk of the patient and three patients (6.7%) died before therapy could be switched (**Figure 3**).

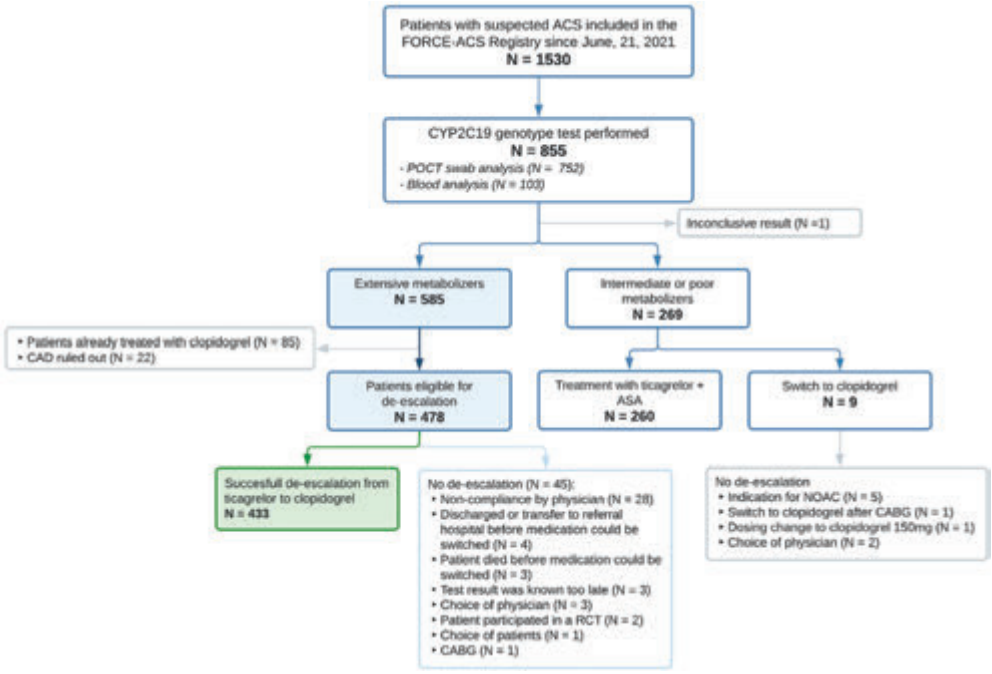

Figure 3. Flowchart of patients included in the FORCE-ACS registry undergoing *CYP2C19* genotyping.

Turnover Time Genotyping

The median turnover time of genotyping was 6.3 h (IQR 3.2-16.7), with 82.3% of test results known within 24 h of admittance, and 91.7% within 48 h. When using POC genotyping, median turnover time was 5.7 h (IQR 3.0-12.6), with 90.5% of test results known within 24 h and 96.9% within 48 h. In patients genotyped using laboratory-based testing the median turnover time was significantly longer with 47.8 h (IQR 29.0-69.2, P < .001), with 17.0% of test results known within 24 h and 50.0% within 48 h.

Time From Test-Results to De-escalation

After the test results were available, de-escalation to clopidogrel was carried out within 24 h in 70.9% of patients and within 48 h in 93.0%, with a median time of 20.3 h (15.3-24.9). There was no significant difference regarding time from test result to first dose of clopidogrel between POC genotyping and laboratory-based testing (20.3 vs 19.0h).

Time From Hospital Admission to De-Escalation

The median time from hospital admission to de-escalation was significantly lower in patients analysed using POC genotyping compared to patients analysed using the laboratory-based testing (25.4 vs 58.9 h, P < .001). In patients analysed with POC genotyping significantly more patients were de-escalated within 24 h compared to the laboratory-based testing (41.4% vs 14.3%, P = .005), and 48 h (88.9% vs

32.1%, P < .001). Due to the overall longer turnover time of laboratory-based testing, de-escalation occurred less frequently compared to POC genotyping (93.0% vs 72.7%, P < .001).

Cost Reduction

A total of 855 patients underwent genotyping, of whom 752 were tested using POC genotyping and 103 using laboratory-based testing. The cost per POC genotyping analysis (sum of disposable and employee costs) was €150, while the cost per laboratory-based test was €75 (sum of machine and employee costs), resulting in a total cost of €120,525.

By implementing the genotype-guided de-escalation strategy, 433 were de-escalated from ticagrelor to clopidogrel. The daily costs of ticagrelor (still under patent protection) in the Netherlands were €2.16 per patient, resulting in an annual expenditure of €341,377.20 for the entire population. In contrast, the cost of the generic clopidogrel was €0.06 per day per patient, totalling €9482.70 annually for the overall pop-ulation.[17,18] This led to a net reduction of €211,369.50 (**Table 3**). However, no data on cost reductions related to clinical endpoints were reported in this study.

DISCUSSION

In our study, we evaluated (a) the feasibility of routine early *CYP2C19* genotyping in clinical practice utilising both POC genotyping and laboratory-based testing in an all-comers ACS population and (b) the turnover times of the two genotyping strategies (POC genotyping and laboratory-based testing) as well as the rate of de-escalation to clopidogrel in ticagrelor-treated patients.

Table 3. Cost reduction by implementing a de-escalation strategy whereby genotyped patients are switched from ticagrelor to clopidogrel

Strategy	Number of patients	Costs	Total cost
De-escalation strategy 855 genotyped patients	752 103	€150,- (POC) €75,- (lab-based)	€120,525
Standard care ticagrelor therapy	433 patients	€2.16 per day	€341,377.20 per year
De-escalation Clopidogrel therapy	433 patients	€0.06 per day	€9,701.70 per year
Reduction in costs by using de-escalation			€341,377.20 - €9,701.70 - €120,525 = + €211.150.50

*POC = point-of-care

Feasibility

Our data shows that the clinical implementation and usage of *CYP2C19* genotyping via POC and laboratory-based testing is feasible. In almost 90% of genotyped patients eligible for guided de-escalation, physicians prescribed clopidogrel. The median turnaround time for POC genotyping was little over 6 h, and over 90% of test results were known within 24 h. Even for laboratory-based tests,

turnaround times were fair with a median of 47.8 h and over 50% of results known within 48 h. Higher turnover time of this laboratory-based test was associated with lower de-escalation rates. These findings support earlier studies showing that *CYP2C19* genotyping is feasible in acute and non-acute settings.[19,20]

We think that several prerequisites need to be present for a successful implementation of a genotype-guided de-escalation strategy. First, staff and nurses have to be well-trained and informed about the background and clinical benefits of the treatment strategy. Second, automatic integration and interpretation of the *CYP2C19* results into the EHR to guide and advise the physician to implement de-escalating from ticagrelor to clopidogrel, needs to be present. Third, the presence of genotyping facilities such as the POC device (with a turnover time less than an hour) for acute settings and laboratory-based testing facilities for non-acute settings makes it possible to get quick results and de-escalate during admission. A potential disadvantage of POC genotyping is that it is occupied for 60 min when analysing one patient. If more patients are expected to be analysed simultaneously, it is advisable to have multiple POC devices.

Routine Genotyping. Current guidelines do not encourage routine genotyping for DAPT patients, but emerging research suggests a more tailored approach is appropriate. A meta-analysis by Galli et al found that guided antiplatelet treatment selection reduced MACE and haemorrhage.[21] ACS patients undergoing PCI often receive ticagrelor or prasugrel due to their superior efficacy. Genotype-guided clopidogrel may be equally effective and even safer.[22] In a meta-analysis, Pereira et al reported that LoF carriers taking ticagrelor or prasugrel had lower MACE rates than those taking clopidogrel.[23] However, in noncarriers the efficacy of clopidogrel was comparable to that of prasugrel and ticagrelor. The test of interaction showed that *CYP2C19* genotype status was a key modifier to the overall beneficial effect of ticagrelor and prasugrel com-pared to clopidogrel.[24] Genotype-driven treatment strategies are increasingly supported by the literature, however, our study is unique as it entails a large-scale application of a de-escalation strategy in an all-comers population. In contrast, in US and Asian centres clopidogrel remains a primary therapeutic agent and implementing a genotype-guided strategy typically results in an escalation strategy.25,26

The GIANT trial, conducted at 57 French hospitals, revealed important *CYP2C19* genotyping insights in STEMI patients.[27] In this study poor metabolizers were mostly treated with prasugrel and not ticagrelor. In contrast to their findings, our research demonstrated a noteworthy improvement of the laboratory-based turnover time within 48 h (50.0% vs 18.4%), and that this can be significantly be further improved to 91.7% by using a POC device as well. These faster turnover times allow for rapid de-escalation of P2Y12 inhibition prior to patient discharge, which improves successful de-escalation and implementation.

Cost-Effectiveness

By applying a genotype-guided strategy in ACS patients treated with ticagrelor or prasugrel, 60-70% of patients can be de-escalated to clopidogrel, which results in reduced side effects and lower costs.[28–30] Our findings match the POPular Genetics trial cost-effectiveness analyses.[29] This study showed that a de-escalation strategy has the potential to yield cost savings of more than €300 per patient in the first

year after ACS. In a scenario analysis where there were no differences in health states at the start of the Markov model, expenditures can be reduced by €277 per patient. This cost reduction was driven by a decrease in bleeding events and medication usage. Our study showed a €247 cost savings per patient, excluding the possible cost reduction by lesser bleeding events. Our real-world data reveals that while some genetic test results were not succeeded by de-escalation, the rate of successful de-escalation was high enough to be cost saving.

Genotype-guided strategies are still uncommon in clinical practice. The cost of genetic testing appears to be a barrier to routine implementation of genotype-guided treatment. This may seem contradictory, as genotype-guided treatment has been proved to be cost-effective. Until recently, hospitals incurred the costs associated with genetic tests for genotype-guided de-escalation, while health insurers benefited from the resulting reduction in drug costs and associated healthcare savings. However, one of the Netherlands' largest health insurers fully reimbursed our local initiative. Current evidence has however not let yet to reimbursement of this strategy on a national scale. A more widespread pre-emptive genotyping method may be reimbursed after the PREPARE (Preemptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions) trial showed a 30% reduction in adverse drug reactions, in which clopidogrel was the second most common index drug.[31]

POC Genotyping or Laboratory-Based Testing. The American College of Cardiology and the European Society of Cardiology recommend POC genotyping in some clinical settings for ACS management.[1,32] Our data shows that ad-hoc POC genotyping has the shortest turnover times, which speeds up de-escalation and enhances the likelihood of successful de-escalation in a real-world setting. POC devices are easier to implement in hospitals without a pharmacogenetics laboratory. On the other hand, laboratory-based genotyping is cheaper than POC genotyping and has relatively fast turnaround times when a dedicated lab is available. While we showed the feasibility of ad-hoc genotyping, the most optimal scenario could involve pre-emptive testing, wherein genetic testing occurs before the initiation of actual drug therapy. This approach facilitates the immediate start of treatment with the appropriate medication. Nevertheless, implementing this approach in patients presenting with ACS is yet impractical, as it would require genetic testing in a broad population that is at-risk for ACS.

Limitations

This study has several important limitations. First, we genotyped all ACS patients, however, some were not analysed due to lack of informed consent to participate in the FORCE-ACS registry. This could have resulted in selection bias, however, only a small proportion of patients refused to participate. Second, clinical outcome data was not available for the current analysis, limiting our ability to fully interpret the feasibility of this treatment strategy. Despite this limitation, we believe our study offers valuable preliminary insights into the practical implementation of genotype-guided therapy. Third, as a single-centre Dutch registry, local practice and geographical variances in treatment may influence study outcomes and implementation. Only 855 of the 1530 patients enrolled from June 2021 to January 2023 were genotyped. Other participating hospitals participating in the FORCE-ACS registry lacked on-site genotyping capabilities at the time of data collection. Therefore, extrapolating results to other clinical

settings should be done cautiously. At last, it is important to acknowledge that the present study did not record patient ethnicity, and thus, formal information on racial demographics is lacking in the FORCE-ACS registry. This limitation is particularly relevant considering the disparities highlighted in recent literature, emphasising the lack of diversity in major antiplatelet pharmacogenomic studies.[33] These studies have demonstrated that racial and ethnic diversity remains limited within the scope of investigations surrounding genotype-guided antiplatelet therapy, potentially leading to gaps in understanding the effectiveness and applicability of precision medicine strategies across underrepresented patient populations.[33] Therefore, while our study contributes valuable insights, it is essential to recognise that the broader impact of genotype-guided interventions across diverse ethnic groups warrants further investigation and consideration.

CONCLUSION

Early *CYP2C19* genotyping as a routine procedure to guide P2Y12-inhibition in an all-comers ACS population is feasible. Time to de-escalation from ticagrelor to clopidogrel in noncarriers of *CYP2C19* LoF alleles was within 24 h in the majority of patients. The shorter time to genotype-guided de-escalation with the use of POC genotyping as compared to laboratory-based testing, holds promise for implementation in sites without genotyping facilities.

REFERENCES

1. Collet J-P, Thiele H, Barbato E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020; 2020:1-79. doi:10.1093/eurheartj/ehaa575
2. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardio-Thoracic Surg*. 2018;53(1):34-78. doi:10.1093/ejcts/ezx334
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopi-dogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/nejmoa0904327
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015. doi:10.1056/NEJMoa0706482
5. Montalescot G, Bolognese L, Dudek D, et al. Pretreatment with prasu-grel in non–ST-segment elevation acute coronary syndromes. *N Engl J Med*. 2013;369(11):999-1010. doi:10.1056/NEJMOA1308075/ SUPPL_FILE/NEJMOA1308075_DISCLOSURES.PDF
6. James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. Clopidogrel in patients with acute coronary syndromes and diabetes: A substudy from the PLATelet inhibition and patient out-comes (PLATO) trial. *Eur Heart J*. 2010;31(24):3006-3016. doi: 10.1093/EURHEARTJ/EHQ325
7. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidog-rel in patients with acute coronary syndromes intended for non-invasive management: Substudy from prospective randomised PLATelet inhibition and patient outcomes (PLATO) trial. *BMJ*. 2011;342(7812):1-11. doi:10.1136/bmj.d3527
8. Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for *CYP2C19* genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013;94(3):317-323. doi:10.1038/CLPT.2013.105
9. Medicines Agency E. Committee for medicinal products for human use (CHMP) guideline on key aspects for the use of phar-macogenomics in the pharmacovigilance of medicinal products Draft Agreed by Pharmacogenomics Working Party. 2015. Accessed August 25, 2023. www.ema.europa.eu/contact
10. Wallentin L, James S, Storey RF, et al. Effect of *CYP2C19* and ABCB1 single nucleotide polymorphisms on outcomes of treat-ment with ticagrelor versus clopidogrel for acute coronary syn-dromes: A genetic substudy of the PLATO trial. *Lancet*. 2010; 376(9749):1320-1328. doi:10.1016/S0140-6736(10)61274-3
11. Marian AJ. Cytochrome p-450 polymorphisms and response to clopidogrel. *Curr Atheroscler Rep*. 2009;11(3):157-160. doi:10. 1007/s11883-009-0025-7
12. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: Relationship to phar-macokinetic, pharmacodynamic, and clinical outcomes. *Circulation*. 2009;119(19):2553-2560. doi:10.1161/CIRCULATIONAHA.109. 851949
13. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med*. 2019;381(17):1621-1631. doi:10.1056/NEJMoa 1907096
14. Chan Pin Yin DRPP, Vos G-JA, van der Sangen NMR, et al. Rationale and design of the future optimal research and care eval-uation in patients with acute coronary syndrome (FORCE-ACS) registry: Towards "personalized medicine" in daily clinical prac-tice. *J Clin Med*. 2020;9(10):3173. doi:10.3390/jcm9103173

15. Lee CR, Thomas CD, Beitelshees AL, et al. Impact of the *CYP2C19**17 allele on outcomes in patients receiving genotype-guided antiplatelet therapy after percutaneous coronary interven-tion. *Clin Pharmacol Ther*. 2021;109(3):705-715. doi:10.1002/ CPT.2039
16. Li-Wan-Po A, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of *CYP2C19*: Functional and clinical implications of a new variant *CYP2C19**17. *Br J Clin Pharmacol*. 2010;69(3): 222-230. doi:10.1111/j.1365-2125.2009.03578.x
17. ticagrelor. Accessed May 2, 2023. https:/www.farmacotherap eutischkompas.nl/bladeren/preparaatteksten/t/ticagrelor
18. clopidogrel. Accessed May 2, 2023. https:/www.farmacotherap eutischkompas.nl/bladeren/preparaatteksten/c/clopidogrel
19. Lee CR, Sriramoju VB, Cervantes A, et al. Clinical outcomes and sustainability of using *CYP2C19* genotype-guided antiplatelet therapy after percutaneous coronary intervention. *Circ Genomic Precis Med*. 2018;11(4):e002069. doi:10.1161/CIRCGEN.117. 002069
20. Bergmeijer TO, Vos GJ, Claassens DM, et al. Feasibility and implementation of *CYP2C19* genotyping in patients using anti-platelet therapy. *Pharmacogenomics*. 2018;19(7):621-628. doi: 10.2217/PGS-2018-0013
21. Galli M, Benenati S, Capodanno D, et al. Articles 1470. 2021;397. Accessed February 7, 2023. www.thelancet.com
22. 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(17):1621-1631. doi:10.1056/NEJMOA 1907096
23. Pereira NL, Rihal C, Lennon R, et al. Effect of *CYP2C19* genotype on ischemic outcomes during oral P2Y12 inhibitor therapy A meta-analysis. *JACC Cardiovasc Interv*. 2021;14(7):739-750. doi:10.1016/j.jcin.2021.01.024
24. Pereira NL, Rihal C, Lennon R, et al. Effect of *CYP2C19* genotype on ischemic outcomes during oral P2Y12 inhibitor therapy: A meta-analysis. *JACC Cardiovasc Interv*. 2021;14(7):739-750. doi:10.1016/j.jcin.2021.01.024
25. Xi Z, Wang Y, Lu Q, et al. Implementation of *CYP2C19* genotyp-ing and clinical outcomes following percutaneous coronary inter-vention in east Asian patients treated with oral P2Y12 inhibitors. *Thromb Res*. 2023;228:85-93. doi:10.1016/J.THROMRES.2023. 05.023
26. Beitelshees AL, Thomas CD, Empey PE, et al. *CYP2C19* genotype-guided antiplatelet therapy after percutaneous coronary intervention in diverse clinical settings. *J Am Heart Assoc*. 2022;11(4). doi:10.1161/JAHA.121.024159
27. Hulot JS, Chevalier B, Belle L, et al. Routine *CYP2C19* genotyp-ing to adjust thienopyridine treatment after primary PCI for STEMI: Results of the GIANT study. *JACC Cardiovasc Interv*. 2020;13(5):621-630. doi:10.1016/J.JCIN.2020.01.219
28. Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syn-drome undergoing percutaneous coronary intervention: A cost-effectiveness analysis. *J Thromb Haemost*. 2013;11(1):81-91. doi:10.1111/jth.12059
29. Claassens DMF, van Dorst PWM, Vos GJA, et al. Cost effective-ness of a *CYP2C19* genotype-guided strategy in patients with acute myocardial infarction: Results from the POPular genetics trial. *Am J Cardiovasc Drugs*. 2021;22(2):195-206. doi:10.1007/ s40256-021-00496-4
30. Limdi NA, Cavallari LH, Lee CR, et al. Cost-effectiveness of *CYP2C19*-guided antiplatelet therapy in patients with acute coro-nary syndrome and percutaneous coronary intervention informed by real-world data. *Pharmacogenomics J*. 2020;20(5):724-735. doi:10.1038/s41397-020-0162-5

31. Swen JJ, van der Wouden CH, Manson LE, et al. A 12-gene phar-macogenetic panel to prevent adverse drug reactions: An open-label, multicentre, controlled, cluster-randomised crossover imple-mentation study. *Lancet*. 2023;401(10374):347-356. doi:10.1016/ S0140-6736(22)01841-4
32. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/ CHEST/SAEM/SCCT/ SCMR guideline for the evaluation and diagnosis of chest pain: A report of the American college of car-diology/American heart association joint committee on clinical practice guidelines. *Circulation*. 2021; 144(22):E368-E454. doi: 10.116 1/CIR.000000000000 1029
33. Nguyen AB, Cavallari LH, Rossi JS, Stouffer GA, Lee CR. Evaluation of race and ethnicity disparities in outcome studies of *CYP2C19* genotype-guided antiplatelet therapy. *Front Cardiovasc Med*. 2022;9:991646. doi:10.3389/ FCVM.2022. 991646/BIBTEX

CHAPTER 11

Real-world implementation of a genotype-guided P2Y12 inhibitor de-escalation strategy in acute coronary syndrome patients

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ABSTRACT

Background

CYP2C19 genotype–guided de-escalation from ticagrelor or prasugrel to clopidogrel may optimize the balance between ischemic and bleeding risk in patients with acute coronary syndrome (ACS).

Objectives

This study sought to compare bleeding and ischemic event rates in genotyped patients vs standard care.

Methods

Since 2015, ACS patients in the multicenter FORCE-ACS (Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome) registry received standard dual antiplatelet therapy (DAPT). Since 2021, genotype-guided P2Y12 inhibitor de-escalation was recommended at a single center, switching noncarriers of the loss-of-function allele *CYP2C19*3* or *CYP2C19*2* from ticagrelor or prasugrel to clopidogrel, whereas loss-of-function carriers remained on ticagrelor or prasugrel. The primary ischemic endpoint, a composite of cardiovascular mortality, myocardial infarction, or stroke, and the primary bleeding endpoint, Bleeding Academic Research Consortium 2, 3, or 5 bleeding, were compared between a genotyped cohort and a cohort treated with standard DAPT after 1 year.

Results

Among 5,321 enrolled ACS patients, 406 underwent genotyping compared with 4,915 nongenotyped ACS patients on standard DAPT. In the genotyped cohort, 65.3% (n = 265) were noncarriers, 88.7% (n = 235) of whom were switched to clopidogrel. The primary ischemic endpoint occurred in 5.2% (n = 21) of patients in the genotyped cohort compared to 7.0% (n = 344) in the standard care cohort (adjusted HR: 0.86; 95% CI: 0.55-1.35). The primary bleeding rate was significantly lower in the genotyped cohort compared to the standard care cohort (11.1% vs 15.3%; adjusted HR: 0.72; 95% CI: 0.53-0.98).

Conclusions

The implementation of a *CYP2C19* genotype–guided P2Y12 inhibitor de-escalation strategy in a real-world ACS population resulted in lower bleeding rates without an increase in ischemic events compared to a standard DAPT regimen.

INTRODUCTION

Dual antiplatelet therapy (DAPT), including aspirin and a P2Y12 inhibitor, is the default strategy to prevent ischemic events after percutaneous coronary intervention (PCI) and acute coronary syndrome (ACS).[1,2] Over time, improvements in stent technologies and management strategies (eg, more potent P2Y12 inhibitors) have led to a decrease in ischemic events.[3-6] Although DAPT with more potent P2Y12 inhibitors has reduced the risk for ischemic events, the associated increased bleeding risk remains challenging.[3,4,7,8] The adverse implications of bleeding, including an increased mortality risk, have paved the way for strategies that address this safety concern without compromising efficacy.[8-11] These strategies include shortening DAPT duration or de-escalation of DAPT intensity (ie, switching from more potent P2Y12 inhibitors such as ticagrelor and prasugrel to a less potent inhibitor such as clopidogrel).[9,12-15] Although traditional risk stratification has encompassed clinical, demographic, angiographic, and laboratory factors, the advent of rapid genotyping assays enables a more personalized selection of P2Y12 inhibitor therapy. This method is based on genotyping *CYP2C19*, the enzyme pivotal in clopidogrel activation.[16-19] The POPular Genetics (Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment) trial showed that in patients with ST-segment elevation myocardial infarction (STEMI), a genotype-guided de-escalation strategy led to fewer bleeding events without increasing thrombotic events compared to the standard of care including ticagrelor.[20] These results are backed by a meta-analysis of 15,949 coronary artery disease patients indicating that individuals carrying a CYP2C219 loss-of-function allele had less thrombotic events when treated with ticagrelor or prasugrel compared to those treated with clopidogrel; yet, when compared solely in wild-type patients (normal metabolizers), clopidogrel demonstrated comparable efficacy in preventing thrombotic events.[21]

Despite the evidence of previous studies, on which the rationale for our implementation was based, results are limited by the controlled settings in which these studies were performed and may not reflect real-world outcomes. Thus, the question remains whether a genotype-guided de-escalation of P2Y12 inhibitors is safe and effective in a real-world all-comers ACS population. Our study aimed to compare the bleeding and ischemic event rates of ACS patients undergoing routine *CYP2C19* genotype–guided de-escalation from ticagrelor to clopidogrel vs patient undergoing standard care.

MATERIALS AND METHODS

Study Design

The FORCE-ACS registry (NCT03823547), as previously described, is a prospective, ongoing initiative involving 9 Dutch hospitals.[22] Participating medical centers possess the capacity to conduct coronary angiography, with 6 of them equipped for on-site PCI. Commencing in 2015, the registry has enrolled consecutive adult patients (18 years and older) presenting with (suspected) ACS. Follow-up has been instituted through questionnaires administered at the following predefined intervals: 1, 12, 24, and 36 months after admission. The primary objective of the FORCE-ACS registry is to facilitate a comprehensive

understanding of diverse facets concerning the diagnosis, management, and longitudinal clinical and patient-reported outcomes of patients with ACS.

From 2021 onward, 1 of the hospitals implemented a *CYP2C19* genotype–guided P2Y12 inhibitor de-escalation strategy from ticagrelor or prasugrel to clopidogrel. Information regarding the genotyping process has been described previously.[23] In brief, patients with ACS and an indication for DAPT were genotyped on the day of admittance if performed by the buccal swab or within 2 working days if performed by a laboratory blood test. Loss-of-function carriers (intermediate or poor metabolizers, carrying at least 1 loss-of-function *CYP2C19*2* or *CYP2C19*3* allele) remained on ticagrelor. In noncarriers ([ultra]rapid or normal metabolizers), a switch to clopidogrel was recommended. In alignment with the 2017 European Society of Cardiology guidelines on DAPT, patients transitioning from ticagrelor to clopidogrel received a 600-mg loading dose of clopidogrel 24 hours after the last ticagrelor intake followed by a maintenance dose of 75 mg daily. For those switching from prasugrel to clopidogrel, a 75-mg daily maintenance dose of clopidogrel was initiated 24 hours after the last dose of prasugrel without an additional loading dose.[1] Writ-ten informed consent was obtained from each patient.

The research protocol of the FORCE-ACS registry was approved by the Institutional Review Boards of all participating medical centers. This study adheres to the principles of the Declaration of Helsinki. Results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[24]

Study Population

The total population was divided into 2 cohorts: a standard care cohort in which patients were treated with a P2Y12 inhibitor (ticagrelor, prasugrel, or clopidogrel) at the discretion of the treating physician and a genotyped cohort in which all patients received a *CYP2C19* genotype test with a treatment recommendation based on the *CYP2C19* test result.

Sensitivity analyses were conducted in a more selected subgroup of patients to provide a more targeted assessment of the treatment effect of the genotype-guided strategy. In the first sensitivity analysis, patients who were not treated according to their *CYP2C19* genotype were excluded from the genotyped cohort, meaning that noncarriers treated with ticagrelor or prasugrel and loss-of-function carriers treated with clopidogrel were excluded. This genotype-guided group was compared to the standard care cohort. In a second sensitivity analysis, all patients treated with clopidogrel and prasugrel were excluded from the standard care group. This ticagrelor-only standard care group was compared to the genotype-guided group.

The implementation was part of a pilot program in which health insurers reimbursed a part of the costs for genetic testing. This analysis was part of an initial review to assess the effectiveness and safety of the

implementation, evaluating whether further expansion of the implementation of genetic testing was appropriate and advisable. Therefore, this analysis was not based on a predetermined sample size.

Clinical Endpoints

The primary ischemic endpoint was a composite of cardiovascular mortality, myocardial infarction (MI), and stroke. The primary bleeding endpoint was a composite of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding. The secondary endpoints consisted of all individual endpoints of the primary endpoints and of net adverse clinical events (NACEs) defined as a composite of all-cause mortality, MI, stent thrombosis, stroke, and BARC 3 or 5 bleeding. All patients were monitored for a 1-year follow-up period.

DAPT adherence was analyzed during the follow-up period. This involved categorizing changes in medication adherence into alterations (any change in P2Y12 inhibitor) and disruptions (discontinuation of a P2Y12 inhibitor therapy longer than 14 days). Data collection focused on the genotyped cohort and a subset of the standard care group for whom complete DAPT adherence data were available.

Statistical Methods

Continuous variables were reported as median values with IQRs or mean ± SD, whereas categoric variables were described in frequencies and percentages. Comparisons between cohorts (standard care vs genotyped) were made using Mann-Whitney or *t*-tests for continuous variables and chi-square or Fisher exact tests for categoric variables. The primary analyses were performed using the Cox proportional hazards model to calculate the HR and its 95% CI. Possible confounders were included in the multivariable model and were selected based on clinical relevance. Violation of the proportional hazards assumption was evaluated by calculating Schoenfeld residuals. Both primary out-comes were also assessed in 6 subgroups based on sex, age, kidney function, discharge diagnosis, bleeding risk, and diabetes. Kaplan-Meier curves were used for a time-to-event analysis. For sensitivity analysis, we conducted propensity score matching using covariates selected for their clinical relevance and differences at baseline. Matching followed a 1-to-3 protocol without replacement (nearest neighbor method) with a caliper of 0.2 SDs of the logit of the propensity score.

We refrained from testing for statistical significance to mitigate the risk of alpha spending, particularly considering our intention to perform additional analyses based on a predetermined sample in subsequent phases of the study. Consequently, we focused solely on assessing outcome rates and constructing CIs, aimed at determining any potential patterns in outcomes.

All statistical analyses were conducted using SPSS version 26 (IBM Corp) and R studio version 3.6.1 (The R Foundation).

RESULTS

Patient Characteristics

Among the 6,847 patients enrolled in the registry study between February 2015 and December 2020, 4,915 patients had ACS, were treated with DAPT, did not undergo *CYP2C19* genotyping, and had a complete follow-up. These patients were selected for the standard care cohort. Of the 579 patients enrolled in the study between June 2021 and September 2022, 406 were genotyped, had ACS, were treated with DAPT, and had a complete follow-up. These patients were selected for the genotyped cohort (**Figure 1**).

The baseline characteristics of the study population are presented in **Table 1**. The median age in the genotyped cohort was 64 years (Q1-Q3: 55-73 years), whereas in the standard care cohort, it was 66 years (Q1-Q3: 56-74 years). Overall, 27.8% of the patients were women. Patients in the genotyped cohort more often had previous spontaneous bleeding at baseline (10.8% [n = 44/406] vs 4.3% [n = 208/4,915]) and an initial presentation with STEMI (57.6% [n = 234/406] vs 42.4% [n = 2,086/4,915]) compared to patients in the standard care cohort. On the other hand, patients receiving standard care more often had a previous MI (19.9% [n = 57/406] vs 14.0% [n = 975/4,915]), previous PCI (20.5% [n = 1,006/4,915] vs 14.0% [n = 57/406]), atrial fibrillation (3.2% [n = 158/4,915] vs 0.5% [n = 2/406]), peripheral artery disease (6.8% [n = 336/4,915] vs 3.2% [n = 13/406]), and a presentation with either unstable angina pectoris (7.5% [n = 368/4,915] vs 3.0% [n = 12/406]) or non–ST-segment elevation myocardial infarction (47.0% [n = 2,309/4,915] vs 36.2% [n = 147/406]). All other baseline characteristics were similar across the 2 cohorts.

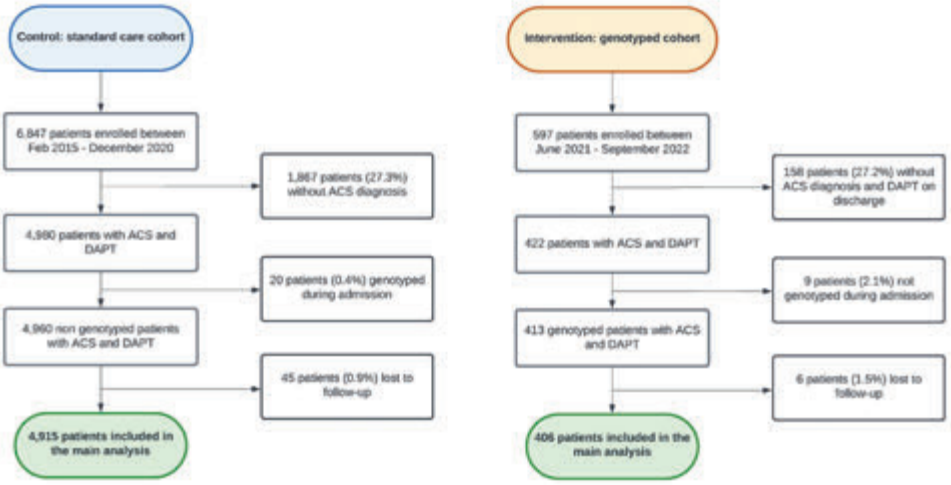


Figure 1. Flowchart of the study.

The standard care cohort consisted of patients enrolled between 2015 and 2020. The genotyped cohort consisted of patients enrolled between 2021 and 2022. For both cohorts, only patients diagnosed with ACS, treated with DAPT and not lost to follow-up were selected for the main analysis. ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy

Treatment And Management

The median duration of hospital admission was 3 days (Q1-Q3: 2-5 days) for the standard care cohort vs 3 days (Q1-Q3: 2-4 days) for the genotyped cohort. During the index hospital admission, coronary angiography was performed in 96.6% (n = 392/406) of all genotyped patients and in 96.1% (n = 4,725/4,915) of all standard care patients. Radial access was used in 82.3% (n = 320/389) of the genotyped and 83.8% (n = 2,849/ 3,401) of the standard care patients. In addition, the genotyped cohort more often underwent PCI (82.0% [n = 333/406]) compared to the standard care cohort (75.5% [n = 3,710/4,915]).

Antithrombotic Therapy

At discharge, clopidogrel was prescribed to 59.4% (n = 241/406) of genotyped patients compared to only 24.6% (n = 1,207/4,915) in the standard care cohort, whereas ticagrelor was prescribed in 40.4% (n = 164/406) of the genotyped cohort and 74.8% (n = 3,67 4/4,915) of the standard care cohort.

In the genotyped cohort, 265 (6 5.3%) patients were identified as noncarriers (ultrarapid, rapid, or normal metabolizer), with 88.7% (n = 235) of these patients being successfully treated with clopidogrel (**Supplemental Figure 1**). The remaining 141 (34.7%) patients of the genotyped patients were classified as loss-of-function allele carriers (intermediate or poor metabolizers), and 95.0% (n = 134/141) of them were discharged with ticagrelor and 0.7% with prasugrel (n =1/141) (**Supplemental Table 1**).

In contrast, in the standard care cohort, a majority of patients (74.8% [n = 3,674/ 4,915]) were treated with ticagrelor, 24.6% (n = 1,207/4,915) were treated with clopidogrel, and only 0.7% with prasugrel (n = 34/4,9 15). Furthermore, optimal medical therapy consisting of DAPT, an angiotensin-converting enzyme inhibitor or an angiotensin II antagonist, beta blocker, and a lipid-lowering drug was prescribed to 54.2% (n = 220/406) of genotyped and 58.3% (n = 2,864/4,915) of standard care patients. Notably, the use of triple therapy was less common in the genotyped cohort (0.5% [n = 2/406]) compared to the standard care cohort (5.4% [n = 267/4,915]; **Table 2**).

Table 1. Baseline table for the genotyped cohort compared to the standard care cohort.

Patients characteristics		Genotyped cohort n=406	Standard care cohort N = 4,915	P-value
Age in years, median (IQR)		64.00 [55.25, 73.00]	66.00 [56.00, 74.00]	0.077
Female sex, n (%)		115 (28.3)	1369 (27.9)	0.884
BMI, mean (SD)*		27.83 (5.00)	27.50 (4.41)	0.153
Current smoking, n (%)		144 (30.3)	1488 (35.5)	0.034
Hypertension, n (%)		202 (49.8)	2649 (53.9)	0.047
Hypercholesterolemia, n (%)		341 (84.0)	2698 (57.5)	<0.001
Diabetes mellitus, n (%)		80 (19.7)	959 (19.5)	1.000
Medical history, n (%)	Previous MI	57 (14.0)	975 (19.9)	0.005
	Previous PCI	57 (14.0)	1006 (20.5)	0.002
	Previous CABG	21 (5.2)	347 (7.1)	0.181
	Previous stroke	21 (5.2)	377 (7.7)	0.082
	Atrial fibrillation	2 (0.5)	158 (3.2)	0.003
	Heart failure	4 (1.0)	73 (1.5)	0.552
	Renal failure[a]	13 (3.2)	131 (2.7)	0.630
	Peripheral artery disease	13 (3.2)	336 (6.8)	0.006
	Active malignancy	12 (3.0)	111 (2.3)	0.467
	Relevant spontaneous bleeding[b]	44 (10.8)	208 (4.3)	<0.001
Index event diagnosis, n (%)	UA	12 (3.0)	368 (7.5)	<0.001
	NSTEMI	147 (36.2)	2309 (47.0)	<0.001
	STEMI	234 (57.6)	2086 (42.4)	<0.001
	Semi-recent MI[c]	13 (3.2)	152 (3.1)	0.88
OHCA, n (%)		13 (3.2)	174 (3.5)	0.847
GRACE risk score >140, n (%)		54 (13.3)	635 (12.9)	0.886
High-bleeding risk (PRECISE-DAPT ≥25)*		75 (20.8)	1030 (22.4)	0.525

Values are median (Q1-Q3), n (%), or mean ± SD. [a]BMI was missing in 5.2% of patients (n = 275), and the PRECISE-DAPT score was missing in 6.9% of all patients. [b]Renal failure was estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m2 for a duration of 3 months or longer. [c]Relevant spontaneous bleeding was non–intervention-related or nontraumatic bleeding events significant enough to require medical assessment (≥ Bleeding Academic Research Consortium 2). [d]Semirecent MI was MI occurring more than 12 hours before presentation but still influencing the current clinical management of the patient. BMI = body mass index; CABG = coronary artery bypass grafting; GRACE = Global Registry of Acute Coronary Events; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; OHCA = out-of-hospital cardiac arrest; PCI = percutaneous coronary intervention; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

Table 2. Procedural and treatment characteristics

	Genotyped cohort (N=406)	Standard care cohort (N = 4,915)	P-value
Procedural characteristics			
CAG, n (%)	392 (96.6%)	4725 (96.1%)	0.77
Radial access site, n (%)*	320 (82.3%)	2849 (83.8%)	0.49
Femoral access site, n (%)*	69 (17.7%)	505 (14.8%)	0.15
1-vessel disease, n (%)	181 (44.6%)	1448 (29.5%)	<0.001
2- vessel disease, n (%)	115 (28.3%)	867 (17.6%)	<0.001
3- vessel disease, n (%)	79 (19.5%)	751 (15.3%)	0.03
PCI, n (%)	333 (82.0%)	3710 (75.5%)	<0.001
DES, n (%)	311 (93.4%)	3395 (91.5%)	0.23
Other/Unknown, n (%)	22 (6.6%)	315 (8.5%)	
CABG, n (%)	29 (7.1%)	442 (9.0%)	0.29
Antithrombotic or anticoagulant therapy			
Acetylsalicylic acid, n (%)	406 (100%)	4915 (100%)	-
P2Y12 inhibitor, n (%)			
Clopidogrel, n (%)	241 (59.4%)	1207 (24.6%)	<0.001
Ticagrelor, n (%)	164 (40.4%)	3674 (74.8%)	<0.001
Prasugrel, n (%)	1 (0.2%)	34 (0.7%)	0.46
Oral anticoagulation, n (%)			
Vitamin K antagonist, n (%)	1 (0.2%)	124 (2.5%)	0.006
DOAC, n (%)	1 (0.2%)	144 (2.9%)	0.002
DAPT, n (%)	406 (100%)	4915 (100%)	-
Dual therapy, n (%)[a]	2 (0.5%)	267 (5.4%)	<0.001
Triple therapy, n (%)[b]	2 (0.5%)	267 (5.4%)	<0.001
Other relevant drugs			
ACE-inhibitors or AT-II antagonists, n(%)	296 (72.9%)	3760 (76.5%)	0.12
Betablockers, n(%)	298 (73.4%)	3696 (75.2%)	0.46
Lipid lowering drugs, n(%)	385 (94.8%)	4652 (94.6%)	0.97
Diuretics, n(%)	73 (18.0%)	1076 (21.9%)	0.08
PPI, n(%)	390 (96.1%)	4167 (84.8%)	<0.001
Optimal medical therapy, n (%)	220 (54.2 %)	2864 (58.3%)	0.12

Values are n (%). [a]Data on access site was missing in 28.8% of patients (n ¼ 1,531), 4.1% (n ¼ 17) in the genotyped cohort, and 30.8% (n ¼ 1,514) in the standard of care cohort. [b]Dual therapy was the combination of a single antiplatelet agent (a P2Y12 inhibitor) and an anticoagulant. [c]Triple therapy was the concurrent use of aspirin (acetylsalicylic acid), a P2Y12 inhibitor, and an anticoagulant.

ACE = angiotensin-converting enzyme; AT-II = angiotensin II; CABG = coronary artery bypass grafting; CAG = coronary angiography; DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor.

In the genotyped cohort, a switch from one P2Y12 inhibitor to another occurred in 7.1% of patients (n = 29/406), whereas this was 16.5% in the standard care cohort (n = 810/4,915; **Table 3**). Disruption of P2Y12 inhibitor treatment because of side effects or nonadherence occurred in 2.0% (n = 8/406) of the patients in the genotyped cohort and 1.6% (n = 79/4,915) in the standard care cohort. Dyspnea was a common reason for P2Y12 alteration or disruption and occurred in 3.4% (n =14/406) of the genotype patients and 6.6% (n = 323/4,915) in the standard care cohort.

Table 3. Distribution of P2Y12 switches during follow-up

	Genotyped cohort (N=406)	**Standard care cohort (N=4,915)**
Alteration, n (%)	29 (7.1%)	810 (16.5%)
Disruption, n (%)	8 (2.0%)	79 (1.6%)
Dyspnea, n (%)	14 (3.4%)	323 (6.6%)

Values are n (%).

Outcomes

Primary out comes. At the 1-year follow-up, the primary ischemic endpoint occurred In 365 (6.9%) patients in the total population (**Table 4**). The primary bleeding endpoint, consisting of BARC 2, 3, or 5 bleeding at 1 year, occurred in 795 patients (14.9%). NACEs occurred in 10.3% of patients (n = 546/5,321). The primary ischemic endpoint rate was comparable between the genotyped cohort and standard care cohort, even after adjusting for the potential confounders of age, discharge diagnosis, and PCI during index admission (5.2% [n = 21/406] vs 7.0% [n = 344/4,915]; adjusted HR: 0.86; 95% CI: 0.551.35). The rate of the primary bleeding endpoint was significantly lower in the genotyped cohort (11.1% [n = 45/406] vs 15.3% [n = 750/4, 915]; adjusted HR: 0.72; 95% CI: 0.53-0.98) compared to the standard care cohort. Kaplan-Meier curve analysis showed congruent results with comparable survival curves for the primary ischemic outcome, whereas the lines for the primary bleeding outcome consistently diverged over time (**Figures 2A** and **2B**).

Secondary Outcomes

At the 1-year follow-up, there were no clear differences with regard to the rate of all-cause mortality, cardiovascular mortality, MI, stroke, or s tent thrombosis (**Table 4**). However, the rates for BARC 3 bleeding (0.7% [n = 3/406] vs 3.0% [n = 149/4,915]; adjusted HR: 0.26; 95% CI: 0.08-0.84) and BARC 2 bleeding (10.6% [n = 43/406] vs 12.8% [n = 630/4,915]; adjusted HR: 0.79; 95% CI: 0.58-1.0 9) were lower in the genotyped cohort compared to the standard care cohort (**Table 4**). The rate of NACEs was 6.9% (n = 28/406) in the genotyped cohort and 10.5% (n = 518/4,915) in the standard care cohort (adjusted HR: 0.70; 95% CI: 0.47-1.03). BARC 3 or 5 bleeding occurred in 0.7% (n = 3/406) of the genotyped patients and in 3.1% (n = 154/4,915) of patients treated with standard DAPT (adjusted HR: 0.26; 95% CI: 0.08-0.83) as outlined in **Table 4** and **Supplemental Figure 2** (Central Illustration).

Table 4. Event Rates of the Primary Endpoints and Individual Components of the Primary Outcomes

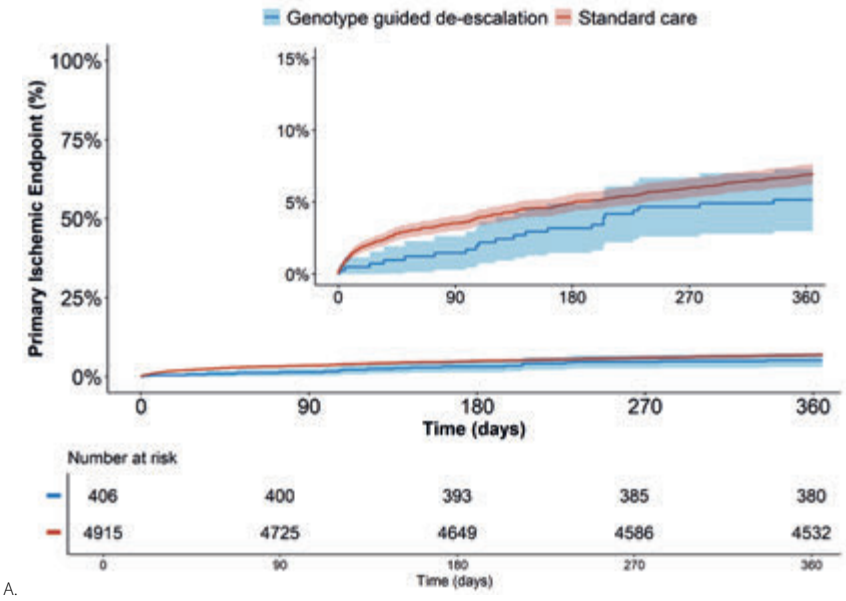
	Total (*N=5,321*)	**Genotyped cohort (*N=406*)**	**Standard care cohort (*N=4,915*)**	**Adjusted Hazards Ratios* HR (95% CI)**
Primary ischemic endpoint	365 (6.9%)	21 (5.2%)	344 (7.0%)	0.86 (0.55-1.35)
NACE	546 (10.3%)	28 (6.9%)	518 (10.5%)	0.70 (0.47-1.03)
Primary bleeding outcome	795 (14.9%)	45 (11.1%)	750 (15.3%)	0.72 (0.53-0.98)
All-cause mortality	138 (2.6%)	9 (2.2%)	129 (2.6%)	0.91 (0.46-1.81)
Cardiovascular mortality	82 (1.5%)	5 (1.2%)	77 (1.6%)	0.88 (0.35-2.18)
Myocardial infarction	227 (4.3%)	12 (3.0%)	215 (4.4%)	0.81 (0.44-1.46)
Stroke	83 (1.6%)	6 (1.5%)	77 (1.6%)	1.11 (0.47-2.59)
Stent thrombosis	52 (1.0%)	1 (0.2%)	51 (1.0%)	0.18 (0.03-1.32)
BARC 3 or 5 bleeding	157 (3.0%)	3 (0.7%)	154 (3.1%)	0.26 (0.08-0.83)
BARC 5 bleeding	5 (0.1%)	0 (0.0%)	5 (0.1%)	-
BARC 3 bleeding	152 (2.9%)	3 (0.7%)	149 (3.0%)	0.26 (0.08-0.84)
BARC 2 bleeding	673 (12.6%)	43 (10.6%)	630 (12.8%)	0.79 (0.58-1.09)

Values are n (%) unless otherwise indicated. [a]HRs are adjusted for age, discharge diagnosis, and percutaneous coronary intervention during index admission. BARC = Bleeding Academic Research Consortium; NACE = net adverse clinical event(s).

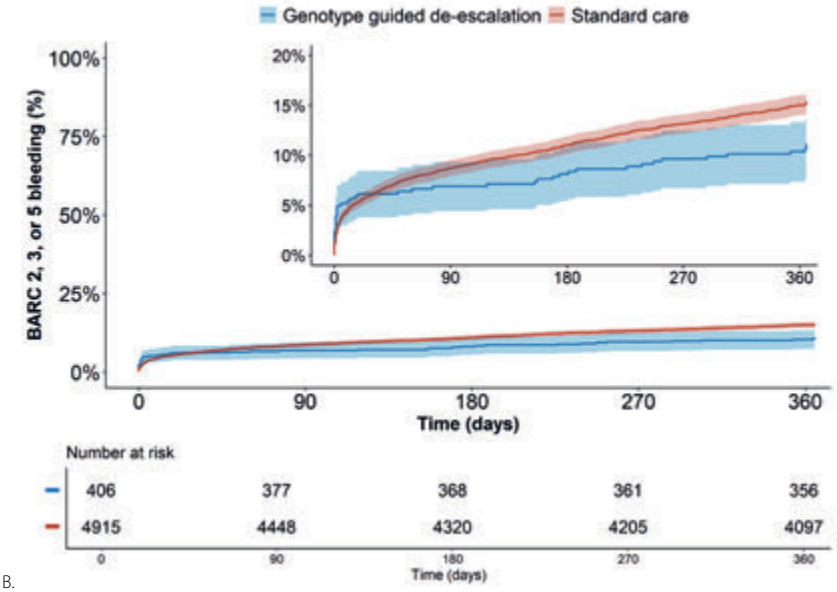
Sensitivity Analysis

After propensity score matching, all 406 patients in the genotyped cohort were matched to 1,203 patients in the standard care cohort, which resulted in a more balanced population based on baseline characteristics (**Supplemental Tables 2** and **3**). Analysis of the primary outcome rates showed robust results with the primary analysis in the unmatched cohorts, showing similar rates for the primary ischemic endpoint (5.2% [n = 21/406] vs 5.8% [n = 70/1,203]; HR: 0.85; 95% CI: 0. 52-1.39; **Supplemental Table 4**) and lower rates for the primary bleeding outcome (11.1% [n = 45/406] vs 19.6% [n = 236/1,203]; HR: 0.53; 95% CI: 0.39-0.74).

In the sensitivity analysis focusing on 370 patients adequately treated according to their *CYP2C19* genotype and compared with 4,915 patients in the standard care cohort, we observed consistent results with the primary analysis for the primary ischemic outcome (4.9% [n = 18/370] vs 7.0% [n = 344/4,915]; adjusted HR: 0.82; 95% CI: 0.51-1.33). A similar reduction was noted for the primary bleeding outcome with rates of 11.9% (n = 44/406) in the genotype-guided group compared to 15.3% (n = 750/ 4,915) in the standard care cohort (adjusted HR: 0.78; 95% CI: 0.57-1.06; **Supplemental Table 5**). Addition-ally, a sensitivity analysis was performed comparing 370 genotype-guided patients with 3,674 ticagrelor-only treated patients in the standard care cohort. Baseline characteristics were now more comparable between both groups (**Supplemental Tables 6** and **7**).



A.



B.

Figure 2. Kaplan Meier curves for the primary ischemic and bleeding endpoint.

Kaplan-Meier curves for the cumulative incidence of (A) the primary ischemic endpoint (composite of cardiovascular mortality, myocardial infarction, or stroke) showing a comparable event rate between the genotyped cohort (blue) and the standard care cohort (red), and (B) the primary bleeding endpoint (BARC 2, 3, or 5 bleeding) demonstrating lower bleeding rates in the genotyped cohort (blue) with diverging curves over time compared to the standard care cohort (red). BARC = Bleeding Academic Research Consortium

Clinical outcomes still indicated a similar rate of the primary ischemic endpoint in the genotype-guided group compared to the ticagrelor-only treated group (4.9% [n = 18/370] vs 5.9% [n = 217/3,674]; adjusted HR: 0.86; 95% CI: 0.53-1.42; **Supplemental Table 8**), whereas the primary bleeding outcome rate was again lower (11.9% [n = 44/370] vs 14.4% [n = 530/3,674]; adjusted HR: 0.81; 95% CI: 0.59-1.11) with a similar observation for NACEs (6.5% [n = 24/370] vs 9.1% [n = 333/3,674]; adjusted HR: 0.70; 95% CI: 0.46-1.07).

Analyses of the primary outcomes were performed in 6 subgroups (**Supplemental Figures 3** and **4**). The results were generally consistent with those in the whole cohort.

DISCUSSION

In this large prospective observational registry, we assessed the impact of a *CYP2C19* genotype–guided de-escalation strategy on the rate of bleeding and ischemic events in patients with ACS treated with DAPT. The main findings suggest that genotype-guided de-escalation is associated with a lower bleeding rate, whereas it did not seem to result in an opposing increased rate of ischemic events. These findings support the potential safety and efficacy of a genotype-guided approach to DAPT de-escalation in an all-comers ACS population.

Our study shows a near 30% lower rate of BARC 2, 3, or 5 bleeding in the genotyped cohort compared to the standard care cohort, with consistent results after propensity score matching and several other sensitivity analyses. Additionally, we did not observe an increase in ischemic event rates despite the more frequent use of the less potent clopidogrel, which aligns with a meta-analysis showing comparable efficacy with clopidogrel compared to ticagrelor/prasugrel in patients without a *CYP2C19* loss-of-function allele.[21] Our findings are consistent with the results of the POPular Genetics trial and provide additional real-world evidence for the beneficial impact on bleeding risk because of a *CYP2C19* genotype–guided antiplatelet therapy.[20] The POPular Genetics trial enrolled 2,488 STEMI patients and found a 22% decrease in major or minor bleeding events in the genotype-guided group (9.8% vs 12.5%; HR: 0.78; 95% CI: 0.61-0.98) and a lower numerical rate for the combined ischemic outcome of cardiovascular death, MI, definite stent thrombosis, or stroke (2.7% vs 3.3%; HR: 0.83; 95% CI: 0.53-1.31). Compared to the patients enrolled in the POPular Genetics trial, the patients in the current analysis were older, more often presented with non–ST-segment elevation myocardial infarction, and had more comorbidities and more complex medical backgrounds, which can explain the higher ischemic event rates in the current analysis. Of interest is that, similar to the POPular Genetics trial, the reduction in bleeding was mainly driven by minor bleeding (defined as BARC 2). Previous studies have underlined the clinical relevance for these bleeding events, showing that even minor bleeding events are linked to an increased risk of mortality.[8,25,26] In addition, bleeding continues to represent the most common noncardiac adverse event after PCI and is also associated with morbidity, prolonged hospitalization, and incremental costs.[26]

Furthermore, it is important to consider the temporal distribution of our patient cohorts. Although there is no immediate rationale to suggest significant differences between patients treated before and after 2021, this time frame could be a contributing factor to the observed variances. The post-2021 cohort, potentially more aligned with updated guideline-based treatment and risk score–driven management, might have undergone a more individualized assessment of bleeding risks, thereby influencing the choice of P2Y12 therapy. However, this aspect was not directly examined in our study.

The TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention) also evaluated ticagrelor vs clopidogrel in patients with ACS or chronic coronary syndrome requiring PCI. This study compared the efficacy and safety of an escalation strategy in the subset of patients with at least 1 loss-of-function allele. The authors reported no significant difference in major or minor bleeding be-tween the genotype-guided group and conventional therapy after 12 months (HR: 1.22; 95% CI: 0.60-2.51; P $^{1}/_{4}$ 0.58).[27] In contrast to our de-escalation approach, Beitelshees et al[28] conducted a study across 9 medical centers investigating an escalation strategy in a real-world setting. This retrospective analysis found no significant difference in bleeding events between loss-of-function allele carriers who were escalated from clopidogrel to prasugrel or ticagrelor. Further-more, at the University of North Carolina at Chapel Hill, where a genotype-guided therapy was implemented, a subgroup of 316 patients initiated treatment with ticagrelor or prasugrel.[29] Among these, 69 patients (21.8%) were de-escalated to clopidogrel. Nonetheless, the analysis showed no significant difference in major adverse cardiovascular or cerebrovascular events or clinically significant bleeding between standard care and de-escalation groups, although the small number of events limited the study's power to detect such differences.

Building on these observed advantages regarding safety and efficacy, it is pertinent to also highlight the broader implications of our findings. First, the ability to de-escalate the P2Y12 inhibitor in 60% to 70% of patients from a strong and more expensive P2Y12 inhibitor to the cheap and safer clopidogrel (in loss-of-function allele noncarriers) is an important finding. Our findings, supplemented by previous feasibility analysis, demonstrate that the majority of noncarriers were effectively transitioned to clopidogrel within 24 hours, affirming the practical implementation of genotype-guided therapy in a real-world clinical setting.[23] Second, this switch has been shown to also decrease health care costs as shown in the POPular Genetics cost-effectiveness analysis.[30,31] Third, rapid (median turnaround time of 6.3 hours) and reliable (point-of-care) genetic tests facilitate the implementation of personalized antiplatelet therapy without delaying treatment commencement.[23]

Study Limitations

First, there is a potential for temporal bias because the genotyped cohort represents a more recent cohort (2021-2022) compared to the standard care cohort, which spans from 2015 to 2020. This difference in time frames could have influenced the outcomes because of evolving clinical practices and advancements in treatment. We sought to mitigate this through adjustments for confounders regarding treatment in the Cox proportional hazards model. Continuing using genotype de-escalation in our registry will make it possible to substantiate or refute our findings in the future. Second, the patients in

the genotyped cohort who were not de-escalated were included in the primary analysis to represent the real-world situation. This inclusion might have introduced variability in our findings. However, we performed sensitivity analyses, confirming the robustness of our primary findings. Third, the primary endpoint consisting of BARC 2, 3, or 5 bleeding events and the ischemic endpoints of cardiovascular mortality, MI, or stroke may seem disproportionate because BARC 2 bleedings are not clinically equivalent to the other severe ischemic events. However, this comparison is standard in larger randomized controlled trials, offering a context for interpretation, and earlier studies showed that BARC 2 bleeding is associated with higher morbidity, mortality, and incremental costs.[8,26,32] Fourth, it is important to highlight that in the Netherlands the predominant use of ticagrelor or prasugrel as a P2Y12 inhibitor necessitates a focus on de-escalation strategies. Consequently, our findings centered on this approach may not be directly applicable to settings in which clopidogrel is the mainstay of treatment and escalation strategies are more common. This regional practice pattern must be considered when extrapolating our results to different international contexts in which treatment protocols may vary significantly. Importantly, our study was not powered to definitively demonstrate noninferiority for ischemic events or superiority for bleeding events, necessitating further research with a larger sample size for conclusive results.

CONCLUSIONS

In an all-comers ACS population, a *CYP2C19* genotype–guided de-escalation strategy showed no increase in ischemic events and a lower rate of bleeding compared to a standard DAPT regimen. These findings underline the improved safety of implementing a genotype-guided de-escalation strategy in clinical practice without affecting efficacy and support a more extensive clinical adoption.

REFERENCES

1. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardio-thoracic Surg. 2017;53:34–78.
2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023. Published onlineAugust 2023. https://doi.org/10.1093/eurheartj/ehad191.
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2009;361:1045–1057.
4. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2007;357:2001–2015.
5. Wijns W, Investigators for the PSC and, Steg PG, et al. Endeavour zotarolimus-eluting stent reduces stent thrombosis and improves clinical outcomes compared with cypher sirolimus-eluting stent: 4-year results of the PROTECT randomized trial. Eur Heart J. 2014;35:2812–2820.
6. Yoshikawa Y, Shiomi H, Morimoto T, et al. Stent-Related Adverse Events as Related to Dual Antiplatelet Therapy in First- vs Second-Generation Drug-Eluting Stents. JACC Asia. 2021;1:345–356.
7. Urban P, Gregson J, Owen R, et al. Assessing the Risks of Bleeding vs Thrombotic Events in Patients at High Bleeding Risk After Coronary Stent Implantation: The ARC–High Bleeding Risk Trade-off Model. JAMA Cardiol. 2021;6:410–419.
8. Valgimigli M, Costa F, Lokhnygina Y, et al. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J. 2016;38:804–810.
9. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med. 2019;381:2032–2042.
10. Costa F, Van Klaveren D, Feres F, et al. Dual Antiplatelet Therapy Duration Based on Ischemic and Bleeding Risks After Coronary Stenting. J Am Coll Cardiol. 2019;73:741–754.
11. Vranckx P, White HD, Huang Z, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. J Am Coll Cardiol. 2016;67:2135–2144.
12. Valgimigli M, Frigoli E, Heg D, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med. 2021;385:1643–1655.
13. Hahn JY, Song Y Bin, Oh JH, et al. Effect of P2Y12 Inhibitor Monotherapy vs Dual Antiplatelet Therapy on Cardiovascular Events in Patients Undergoing Percutaneous Coronary Intervention: The SMART-CHOICE Randomized Clinical Trial. JAMA- J Am Med Assoc. 2019;321:2428–2437.
14. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA- J Am Med Assoc. 2019;321:2414–2427.
15. Kim CJ, Park MW, Kim MC, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. Lancet. 2021;398:1305–1316.

16. Kheiri B, Abdalla A, Osman M, et al. Personalized antiplatelet therapy in patients with coronary artery disease undergoing percutaneous coronary intervention: A network meta-analysis of randomized clinical trials. Catheter Cardiovasc Interv. 2019;94:181–186.
17. Cavallari LH. Genetic Determinants of P2Y 12 Inhibitors and Clinical Implications. Interv Cardiol Clin. 2020;6:141–149.
18. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: A genetic substudy of the PLATO trial. Lancet. 2010;376:1320–1328.
19. 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 - J Am Med Assoc. 2010;304:1821–1830.
20. 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;381:1621–1631.
21. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 Genotype on Ischemic Outcomes During Oral P2Y12 Inhibitor Therapy: A Meta-Analysis. JACC Cardiovasc Interv. 2021;14:739–750.
22. Chan Pin Yin DRPPPP, Vos G-JAJA, van der Sangen NMRR, et al. Rationale and Design of the Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) Registry: Towards "Personalized Medicine" in Daily Clinical Practice. J Clin Med. 2020;9:3173.
23. Azzahhafi J, Broek WWA va. den, Chan Pin Yin DRPP, Harmsze AM, van Schaik RHN, Ten Berg JM. The Clinical Implementation of CYP2C19 Genotyping in Patients with an Acute Coronary Syndrome: Insights From the FORCE-ACS Registry. J Cardiovasc Pharmacol Ther. 2023;28.
24. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495–1499.
25. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention: Results from a patient-level pooled analysis of the REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events), ACUITY (Acute Catheterization and Urgent In. JACC Cardiovasc Interv. 2011;4:654–664.
26. Piccolo R, Oliva A, Avvedimento M, et al. Mortality after bleeding versus myocardial infarction in coronary artery disease: A systematic review and meta-analysis. EuroIntervention. 2021;17:550–560.
27. Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes after Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA- J Am Med Assoc. 2020;324:761–771.
28. Beitelshees AL, Thomas CD, Empey PE, et al. CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention in Diverse Clinical Settings. J Am Heart Assoc. 2022;11:e024159.
29. Martin J, Williams AK, Klein MD, et al. Frequency and clinical outcomes of CYP2C19 genotype-guided escalation and de-escalation of antiplatelet therapy in a real-world clinical setting. Genet Med. 2020;22:160–169.

30. 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;20:724–735.
31. Claassens DMF, van Dorst PWM, Vos GJA, et al. Cost Effectiveness of a CYP2C19 Genotype-Guided Strategy in Patients with Acute Myocardial Infarction: Results from the POPular Genetics Trial. Am J Cardiovasc Drugs. 2021. Published online2021. https://doi.org/10.1007/s40256-021-00496-4.
32. Giustino G, Mehran R, Dangas GD, et al. Characterization of the Average Daily Ischemic and Bleeding Risk After Primary PCI for STEMI. J Am Coll Cardiol. 2017;70:1846–1857.

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data

CHAPTER 12

Cost-effectiveness of implementing a genotype-guided de-escalation strategy in patients with acute coronary syndrome

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ABSTRACT

Aims

A genotype-guided P2Y12 inhibitor de-escalation strategy, switching acute coronary syndrome (ACS) patients without a *CYP2C19* loss-of-function allele from ticagrelor or prasugrel to clopidogrel, has shown to reduce bleeding risk without affecting the effectivity of therapy by increasing ischaemic risk. We estimated the cost-effectiveness of this personalized approach compared to standard dual antiplatelet therapy (DAPT; aspirin plus ticagrelor/prasugrel) in the Netherlands.

Methods and Results

We developed a 1-year decision tree based on results of the FORCE-ACS registry, comparing a cohort of ACS patients who underwent genotyping with a cohort of ACS patients treated with standard DAPT. This was followed by a lifelong Markov model to compare lifetime costs and quality-adjusted life years (QALYs) for a fictional cohort of 1000 patients. The cost-effectiveness analysis was performed from the perspective of the Dutch healthcare system. A genotype-guided de-escalation strategy led to an increase of 57.73 QALYs and saved €808788 compared to standard DAPT based on a lifetime horizon. Probabilistic sensitivity analysis showed that the genotype-guided strategy was cost-saving in 96% and increased QALYs in 87% of simulations. The intervention remained cost-effective in the scenario where prices for all P2Y12 inhibitors were equalized. The genotype-guided strategy remained dominant in various other scenarios and sensitivity analyses.

Conclusion

A genotype -guided de-escalation strategy in patients with ACS was both cost-saving and yielded higher QALYs compared to standard DAPT, highlighting its potential for implementation in clinical practice.

INTRODUCTION

The default antiplatelet treatment in patients with acute coronary syndrome (ACS) is dual antiplatelet therapy (DAPT), comprising aspirin and a potent P2Y12 inhibitor (ticagrelor or prasugrel) for 12 months.[1] Its goal is to mitigate ischaemic risk, albeit with an associated increase in bleeding risk.[2] With advancements in secondary prevention and stent technology, ischaemic risk has decreased, opening the door for new strategies that minimize bleeding risk without compromising the reduction of ischaemic risk.[2,3] The POPular Genetics trial showed in a randomized setting that a *CYP2C19* genotype-guided de-escalation strategy reduced the risk of bleeding without affecting ischaemic risk, compared to standard DAPT in patients with ST-elevation myocardial infarction.[4] This de-escalation strategy involves switching from the more potent drugs ticagrelor or prasugrel to the less potent clopidogrel in patients without a *CYP2C19* loss-of-function allele. By implementing this strategy, theoretically, 70% of patients who would otherwise receive ticagrelor can instead be treated with clopidogrel, a drug significantly more affordable than ticagrelor and prasugrel.[5, 6] Accordingly, the cost-effectiveness analysis (CEA) of the POPular Genetics demonstrated that a genotype-guided de-escalation strategy is both cost-saving and increases quality of life (QoL).[7] While randomized clinical trials (RCTs) are crucial for establishing evidence-based foundations for new interventions, the question remains whether results mirror real-world outcomes, where populations are often at higher risk and adoption rates may be lower. Whether the implementation of routine genetic *CYP2C19* testing of ACS patients to guide the selection of the P2Y12 inhibitor is cost-effective compared to standard DAPT remains uncertain. In this analysis, we aimed to assess the cost- efficacy of a genotype-guided de-escalation strategy directly after hospital admission, compared to standard DAPT based on real-world data.

METHODS

Study Design

For this analysis we used data from the FORCE-ACS registry (NCT03823547), of which the rationale and design have been described previously.[8] In brief, the FORCE-ACS registry is an ongoing, prospective, multicentre registry involving nine Dutch hospitals , consecutively enrolling adult patients with (suspected) ACS since 2015. It's primary objective is to gain insight into the various aspects of care for ACS patients. Before 2021, all local protocols recommended the use of DAPT with a more potent P2Y12 inhibitor (ticagrelor or prasugrel) as the default strategy in ACS patients without an indication for anticoagulation. Since 2021, one hospital (St. Antonius Hospital, Nieuwegein, The Netherlands) has implemented a genotype-guided P2Y12 inhibitor de-escalation strategy in its ACS protocol. At admission, all ACS patients underwent *CYP2C19* genotype testing, either through point- of- care testing (POC T) using the Cube CYP2C19 System (Genomadix) or through lab-based testing with the StepOnePlus™ Real-Time PCR system (Applied Biosystems, Thermofisher Scientific). In non-carriers of a *CYP2C19* loss-of-function allele (normal metabolizers), the recommendation was to switch from

ticagrelor/prasugrel to clopidogrel. Patients who carried a *CYP2C19* loss-of-function, remained on their current treatment with ticagrelor/prasugrel. Approval was obtained from institutional review boards, adhering to the Declaration of Helsinki and reporting results per STROBE guidelines.

Population

Patients enrolled in the FORCE-ACS registry were divided into two cohorts: a standard care cohort, in which patients were treated with a P2Y12 inhibitor (ticagrelor, prasugrel, or clopidogrel) at the discretion of the treating physician, and a genotyped cohort, in which patients received a *CYP2C19* genotype test with a treatment recommendation based on the result. For the current model, we used the propensity score-matched population from the FORCE-ACS registry, which has been published previously (**Supplementary material online, Table S1**).[9] This allowed for adjustment of multiple baseline characteristics, yielding two cohorts that were comparable regarding age, medical history, and comorbidities. The median age of the trial population was 64 years old, 28% female and 14% had a prior history of myocardial infarction (MI).

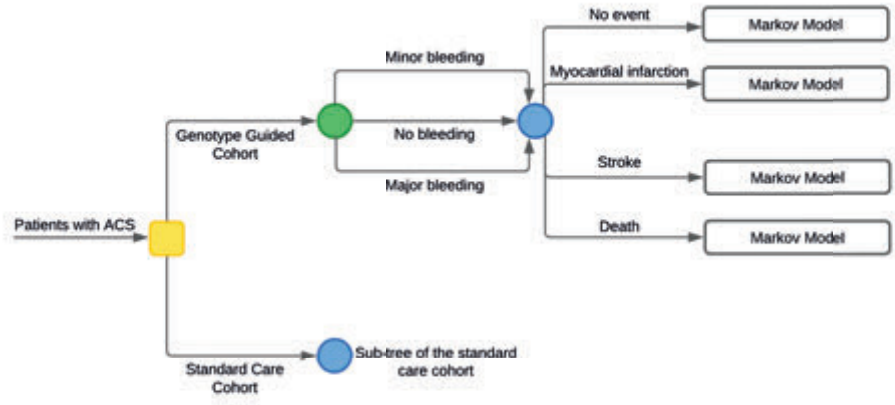
Model Overview

We developed a two-part decision-analytic model: a 1-year decision tree to allocate patients across Markov states (**Figure 1A**), followed by a Markov model to simulate lifelong costs and effects (**Figure 1B**). All individuals in the hypothetical cohort were at the age of 64 at the start of the model. In the decision tree, all patients had the possibility of experiencing minor or major bleeding, irrespective of other events. Throughout the initial year, patients who experienced a MI or stroke transitioned into corresponding health states , while patients who passed away entered the all-cause death state; all remaining patients entered the no-event state. Following the 1-year decision tree period, patients transitioned between different Markov states based on different transition probabilities. These health states comprised the no event, non-fatal stroke, non-fatal MI, post-stroke, post-MI, and all-cause death states, reflecting the lifetime progression of patients after ACS. The non-fatal MI and non-fatal stroke states were termed 'tunnel states', indicating that patients could only remain in each state for one cycle. The structure of the Markov model was aligned with previously published and clinically validated models.[10,11] A hypothetical cohort of 1000 patients was used to simulate progression and transitions across various health states. In the base case analysis, the lifetime horizon was set at the age of 100 years.

Model Assumptions

We made the assumption that bleeding risk after the 1-year follow-up was comparable in both groups, as patients in both groups were assumed to be treated with aspirin, in line with current ESC guidelines and local protocols.[12] Because use of oral anticoagulants was rare and comparable between groups, we did not expect this to impact the bleeding rates in the Markov model after the first year. In line with previously published literature, bleeding was not included as a separate health state in the Markov model and decreased QoL for only a short period.[10] Patients could not develop multiple events during one cycle and could only experience a recurrent stroke or MI with a minimum interval of 1 year.

A.



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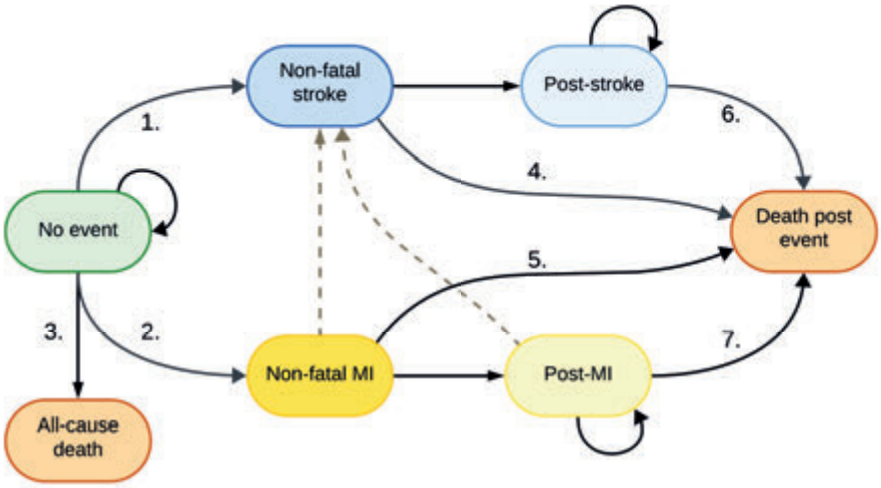

Figure 1. Cost-effectiveness model.

(A) One-year decision tree. ACS; acute coronary syndrome. (B) Long-term Markov model. Markov model transitions in figure: (1) risk of non-fatal stroke based on literature. (2) Risk of non-fatal MI based on literature. (3) Mortality risk for patients with no event based on Dutch population data. (4) Mortality risk after a non-fatal stroke. (5) Mortality risk after a non-fatal MI. (6) Mortality risk at second and subsequent years after a non-fatal stroke. (7) Mortality risk at second and subsequent years after a non-fatal MI. MI; myocardial infarction. The dotted lines indicate the transition of patients in the non-fatal MI or post-MI state to the non-fatal stroke state.

Model Input Parameters

Transition probabilities

Probabilities for the distributions in the 1-year decision tree were derived from the propensity score-matched results of the clinical implementation of the genotype-guided strategy.[9] After constructing the decision tree, patients were assigned to their respective health state in the long-term Markov model. The Markov model, with yearly cycles, simulated disease progression over their lifetime. Patients in each health state faced the possibility of experiencing a stroke, MI, or death in each cycle. As the subsequent event risk and costs were higher in the stroke and post-stroke states , patients could not transition from the non-fatal stroke or post-stroke states to the non-fatal MI or post-MI states . Transition probabilities were based on a previous CEA with similar populations.[10] Transition probabilities for subsequent events were derived by multiplying baseline probabilities by relative risk factors. Patients in ' Post- MI' and ' Post-stroke' states had a higher risk of subsequent events than those in the ' No- event' state. Mortality rates , based on age-specific data from Dutch population life tables , increased with age. All model inputs are detailed in **Table 1**.

Table 1. Model Input Parameters

Parameters	Base -case value	Range	Distribution	Source
Probabilities (decision tree)				
Standard care				
Minor bleeding	0.166	0.125–0.208	Beta	Azzahhafi *et al.*[9]
Major bleeding	0.042	0.001–0.052	Beta	Azzahhafi *et al.*[9]
MI	0.032	0.024–0.041	Beta	Azzahhafi *et al.*[9]
Stroke	0.017	0.013–0.022	Beta	Azzahhafi *et al.*[9]
All-cause death	0.026	0.019–0.028	Beta	Azzahhafi *et al.*[9]
Genotype-guided treatment				
Minor bleeding	0.106	0.079–0.132	Beta	Azzahhafi *et al.*[9]
Major bleeding	0.0070	0.0055–0.0092	Beta	Azzahhafi *et al.*[9]
MI	0.030	0.022–0.037	Beta	Azzahhafi *et al* .9
Stroke	0.015	0.011–0.018	Beta	Azzahhafi *et al.*[9]
All-cause death	0.022	0.017–0.028	Beta	Azzahhafi *et al.*[9]
Probabilities (Markov model)[a]				
Annual risk from ' No- event' to 'MI'	0.019	0.01–0.05	Beta	Nikolic *et al.*[10]
Annual risk from ' No- event' to 'Stroke'	0.003	0.001–0.002	Beta	Nikolic *et al.*[10]
Annual risk from ' No- event' to ' Non-C V death'	Age specific mortality rate		Beta	CBS[37]
Increased risk of a subsequent event after having an event	2.0	1.0–4.0	LOGNORMAL	Lala *et al.*[38]
Increased risk of death in ' No- event'	2.0	1.5–2.5	LOGNORMAL	Nikolic *et al.*[10]

Table 1. Continued

Increased risk of death in 'Non-fatal MI'	6.0	4.5–7.5	LOGNORMAL	Nikolic *et al.*[10]
Increased risk of death in 'post MI'	3.0	2.25–3.75	LOGNORMAL	Nikolic *et al.*[10]
Increased risk of death in 'Non-fatal stroke'	7.43	5.57–9.29	LOGNORMAL	Nikolic *et al.*[10]
Increased risk of death in 'post stroke'	3.0	2.25–3.75	LOGNORMAL	Nikolic *et al.*[10]
Costs (in euro's)[b]				
Costs CYP2C19 lab test	75	56.25–93.75	Gamma	Azzahhafi *et al.*[14]
Costs CYP2C19 POCT test	150	112.50–187.50	Gamma	Azzahhafi *et al.*[14]
1 year clopidogrel treatment	51.10	38.33–63.88	Gamma	ZIN[39]
1 year ticagrelor treatment	876.00	657–1095	Gamma	ZIN[40]
1 year prasugrel treatment	478.10	358.61–597.69	Gamma	ZIN[41]
Minor bleeding	321.03	221.68–508.5	Gamma	Jacbos *et al.*[42]
Major bleeding	5601.92	3243.55–9476.25	Gamma	Ten Cate-Hoek *et al.*[43]
MI	5734.33	3320.21–9700.3	Gamma	Soekhlal *et al.*[44]
Post-MI	2620.61	2776.3–3128.85	Gamma	De Jong *et al.*[45]
Stroke	29166.05	21 554.88–45512.13	Gamma	De Jong *et al.*[45]
Post-stroke	11932.74	9059.22–17118.81	Gamma	De Jong *et al.*[45]
All-cause death	3558.19	3495.21–3769.77	Gamma	Greving *et al.*[46]
Utilities[c]				
No event	0.838	0.7179–0.927	Beta	FORCE-ACS
Myocardial infarction	0.744	0.66–0.87	Beta	FORCE-ACS
Post-MI	0.744	0.66–0.87	Beta	FORCE-ACS
Stroke	0.620	0.6–0.64	Beta	Nikolic *et al.*[10]
Post-stroke	0.620	0.6–0.64	Beta	Nikolic *et al.*[10]
Death	0	NA	NA	
Minor bleeding (disutility 2 days)	0.073	0.054–0.091	Beta	FORCE-ACS
Major bleeding (disutility 14 days)	0.140	0.07–0.21	Beta	Stevanovic *et al.*[47]

CI, confidence interval; CBS, Central Bureau of Statistics; CV, cardiovascular; NA, not applicable; MI, myocardial infarction; ZIN , Zorginstituut Nederland [National Health Care Institute Netherlands]. [a] Range indicating min/max as provided by paper. If min/max was unavailable, ranges were 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.

Costs

The CEA was performed from the healthcare perspective, and all costs were based on the Dutch healthcare system. Costs were inflated to 2023 using a calculator based on the consumer price index inflation from the Dutch Central Bureau of Statistics (**Supplementary material online, Table S1**).[13] They consisted of treatment costs of the different antiplatelet drugs, genetic tests, and costs associated with cardiovascular events (minor bleeding, major bleeding, non-fatal MI, non-fatal stroke, post-MI, post-stroke, and death). Based on a previous analysis , de-escalation occurred within 48h in the majority of patients.[14] Therefore, the use of ticagrelor, prasugrel, and clopidogrel during the first year was based on the prescribed P2Y12 inhibitor at discharge in both cohorts and the treatment adherence during that year. Unplanned switching between P2Y12 inhibitors occurred frequently, especially from ticagrelor to clopidogrel, and predominantly early, with a median time to switch from ticagrelor to clopidogrel of 65 days and clopidogrel to ticagrelor of 19 days (**Supplementary material online, Table S1**). Therefore, regarding drug costs , we assumed that patients who switched to another P2Y12 inhibitor were treated with the latter P2Y12 inhibitor for the entire year. Both the costs and allocation between the use of a *CYP2C19* POC test (in 88% of patients) and lab test (in 12% of patients) were determined from a prior feasibility analysis of the clinical implementation of a genotype-guided de-escalation strategy.[14] All costs were discounted using an annual rate of 3% in line with existing Dutch guidelines for health-economic evaluations.[15]

Health Utilities

Health utilities were quantified in quality-adjusted life years (QALYs) and derived from the FORCE-ACS registry population for minor bleeding, no-event state, MI state, and post-MI state. At 12 months after initial hospital admission, QoL was measured using the 12-item Short Form Survey version 2. EQ-5D results were based on complete SF-12 questionnaire responses, and estimated using the method outlined by Gray *et al.*[16] Because of the limited number of patients who experienced major bleeding and/or stroke and completed an SF-12 questionnaire at 1 year, we derived the utilities for these events in similar populations from literature.[10,17]

Based on prior literature, bleeding resulted in temporary disutility throughout the first year of the model.[17] We assumed that adverse events from antiplatelet therapy, like dyspnoea or bruises, did not have long-term prognostic effects on QoL and, therefore, were not accounted for the calculation of utilities for the base-case values.[10]

Outcomes

The outcome measures were costs , QALYs , increment al cost-effectiveness ratios (ICERs) expressed in euros per QALY gained, and net monetary benefit (NMB), calculated as (incremental benefit × threshold)— incremental cost. If both incremental costs and QALYs were positive, the ICER was calculated. If both incremental costs and QALYs were negative, NMB was calculated, as the resulting ICER would not be informative.[18] A positive NMB would indicate that the genotype-guided strategy is cost-

effective compared with standard DAPT at the given willingness-to-pay threshold. Since antiplatelet therapy is used for tertiary prevention, we used a reference value of €20 000 per QALY.[19]

Sensitivity Analysis and Scenario Analysis

The base-case analysis was based on model inputs shown in **Table 1**. To address model uncertainties , we conducted both univariate deterministic (DSA) and probabilistic sensitivity analyses (PSA). Parameter ranges were based on 95% confidence intervals (CI) or a standard error of 25%. In the univariate DSA, each parameter was varied individually over its 95% CI or fixed range. The PSA employed a Monte Carlo simulation with 10 000 iterations, randomly and simultaneously varying all parameters within their 95% CIs or fixed ranges. The distributions used for each parameter are detailed in **Table 1**.

To evaluate the robustness of the results, scenario analyses were con-ducted with different time horizons (scenario 1) and by equalizing all prices to mimic the availability of generic versions of ticagrelor and prasugrel (scenario 2). We performed additional analyses to illustrate the impact of decreasing drug prices on cost-efficacy. In the base case model, we used the event rates from the FORCE-ACS registry. Since the confidence intervals showed no difference in ischaemic event rates between the two groups, we conducted a third scenario where ischaemic event rates were identical (scenario 3). Finally, as both minor and major bleeding have been associated with increased morbidity and lower QoL for a prolonged time, a fourth scenario analysis accounted for a prolonged duration of disutility of bleeding (scenario 4).[20–22]

RESULTS

Base-case and Alternative Case Analyses

Based on a hypothetical cohort of 1000 patients admitted for ACS, a genotype -guided de -escalation strategy resulted in a lifetime increase of 57.30 QALYs, while saving €808 788, compared to standard prescription of DAPT. This equated to an average gain of 0.058 QALYs and €809 saved per patient. The incremental NMB of the genotyped guided strategy was €1962 per patient. The univariate DSA, represented in a tornado plot (**Figure 2**), revealed that the distribution of patients across the different health states by the decision tree (all-cause mortality, MI, and stroke) exerted the most significant impact on the model outcomes. Furthermore, the findings from probabilistic sensitivity analysis (PSA), depicted in a cost-effectiveness plane (**Figure 3**), indicated that treatment with clopidogrel was cost saving in 96% of the 10 000 Monte Carlo simulation iterations, whereas it increased QALYs in 87% of the iterations. In 95% of the iterations, the NMB was higher in the genotype-guided group compared to the standard DAPT group, indicating cost-efficacy.

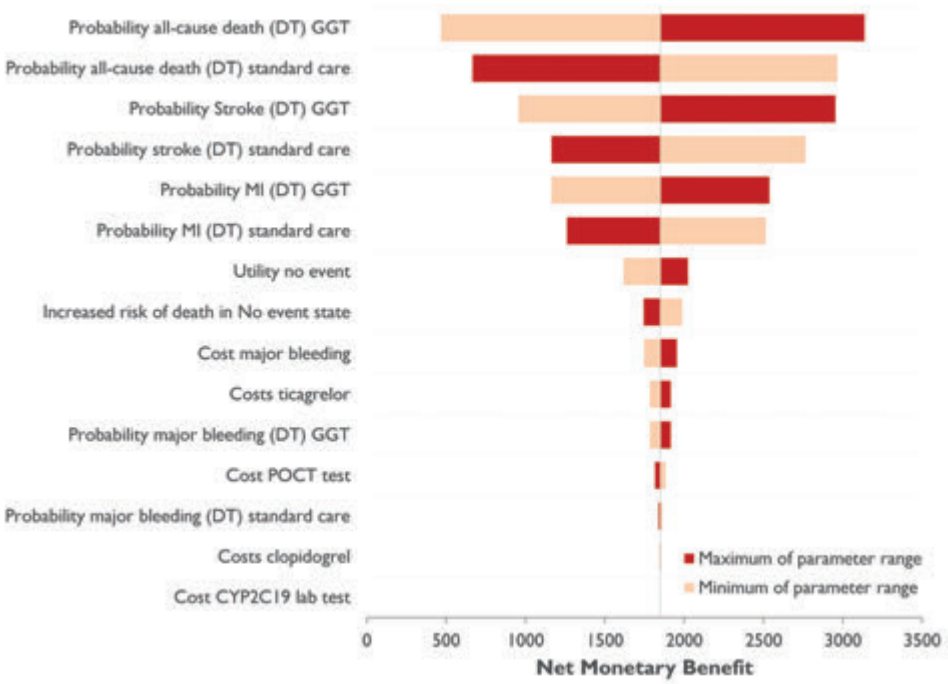

Figure 2. Deterministic sensitivity analysis.

Tornado plot showing the net monetary benefit (NMB). In the deterministic sensitivity analysis (DSA), the minimum and maximum value of the parameter range of every individual parameter is alternately put into the model. The results of the DSA depict the influence on the NMB when the minimum or maximum value of the individual parameter is used, while all other parameters stay the same. The base case value of the NBM was 1850.7 DT: decision tree, MI, myocardial infarction.

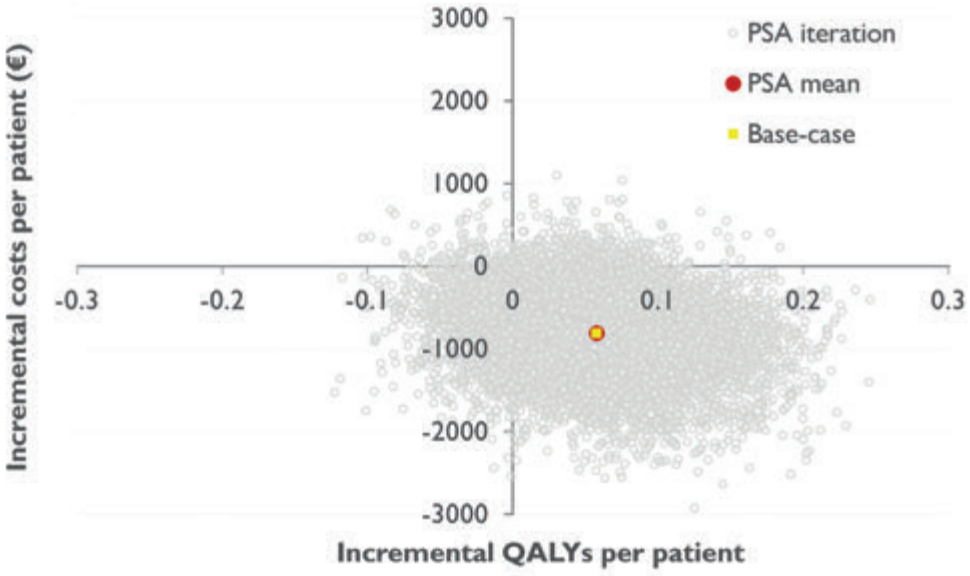

Figure 3. Probabilistic sensitivity analysis.

Cost-effectiveness plane showing the results of the probabilistic sensitivity analysis (PSA) demonstrating the varying outcomes of the Monte Carlo analysis, with 10 000 iterations per patient, where all model inputs are randomly adjusted based on their respective uncertainty distributions. Both the average PSA value and the outcome of the base-case scenario are displayed in the figure. QALY, quality-adjusted life year.

Scenario Analyses

Table 2 shows the results of the different scenario analyses. In scenario 1, adjusting the time horizon did not alter the conclusions regarding the cost-effectiveness of the intervention. After 1 year, implementing a de-escalation strategy led to a net cost reduction of –€460 924. This reduction was primarily driven by decreased medication expenses (–€261 723) compared to standard care, despite the costs associated with performing the genetic tests (+ €140 965) in the genotype-guided cohort. The intervention remained cost-saving in scenario 2, where prices for all P2Y12 inhibitors were equalized, primarily due to the increased costs associated with higher bleeding rates in the standard care cohort. In addition, when applying this scenario over a 1-year time horizon, the genotype-guided strategy was cost-saving (–€199 202). In **Figure 4**, we illustrated the potential impact of de-creasing prices for ticagrelor on cost-savings. Under varying scenarios and time horizons, the genotype-guided strategy was cost-saving compared to standard care with ticagrelor prices ranging from €0 to €3/day. In scenario 3, where ischaemic events rates were identical, costs remained lower in the genotype-guided group. In this scenario, the increase in QALYs (0.20) is attributable to the decrease of bleeding in the intervention group. In the fourth scenario, the period of the disutility of bleeding was extended. This increased QALYs associated with the guided strategy from 57.53 (base case) to 61.76 (182 days) and 66.22 (365 days).

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

	Costs genotype-guided strategy (€)	Costs Standard Care (€)	ΔCosts (€)	QALYs genotype-guided strategy	QALYs Standard Care	ΔQALY	ICER[a] (€/QALY)
Base case	€ 14,486,401	€ 15,295,189	-€ 808,788	10555.88	10498.35	57.53	Dominating
Scenario analyses							
Scenario 1							
Different time horizons							
1 year	€ 1,245,054	€ 1,705,979	-€ 460,924	813.35	809.28	4.07	Dominating
5 years	€ 4,462,851	€ 5,094,354	-€ 631,503	4424.88	4402.64	22.23	Dominating
10 years	€ 8,239,353	€ 8,975,510	-€ 736,157	7222.22	7185.16	37.06	Dominating
20 years	€ 13,582,781	€ 14,390,327	-€ 807,546	10167.31	10112.71	54.59	Dominating
Scenario 2							
Identical prices for $P2Y_{12}$ inhibitors	€ 14,198,874	€ 14,745,940	-€ 547,065	10555.88	10498.35	57.53	Dominating
Scenario 3							
Equal distribution over health states for all-cause death, MI and stroke	€ 14,713,834	€ 15,068,187	-€ 354,353	10527.22	10527.02	0.20	Dominating
Scenario 4							
Prolonged duration of bleeding disutility							
182 days[b]	€ 14,486,401	€ 15,295,189	-€ 808,788	10551.71	10489.95	61.76	Dominating
365 days[b]	€ 14,486,401	€ 15,295,189	-€ 808,788	10547.44	10481.22	62.91	Dominating

ICER: incremental cost-effectiveness ratio, NA: not applicable, QALY: quality-adjusted life year. [a]When both the incremental costs and QALYs were negative, the ICER could not be calculated. [b]Disutility for both BARC 2 (minor bleeding) and BARC 3 bleeding (major bleeding).

DISCUSSION

This is the first CEA evaluating the economic benefits of a genotype-guided de-escalation strategy using data from its implementation in clinical care. These cost-efficacy data suggest that implementing a genotype -guided de -escalation strategy in clinical practice is associated with an increase in QALYs and a reduction in costs compared to standard DAPT in patients with ACS. Multiple sensitivity and scenario analyses consistently replicated the findings of the base-case analysis, confirming that a genotype-guided strategy dominated standard care, as it was both cost-saving and yielded higher QALYs.

In recent years, numerous strategies have been explored to reduce bleeding risk without compromising ischaemic outcomes in patients undergoing DAPT. Considering the growing body of evidence, the preference may shift toward ticagrelor monotherapy after a brief period of DAPT in the coming years.[23] However, with the ever-rising costs of healthcare, one should not neglect the impact of longer or more frequent prescription of costly drugs like ticagrelor or prasugrel.[24]

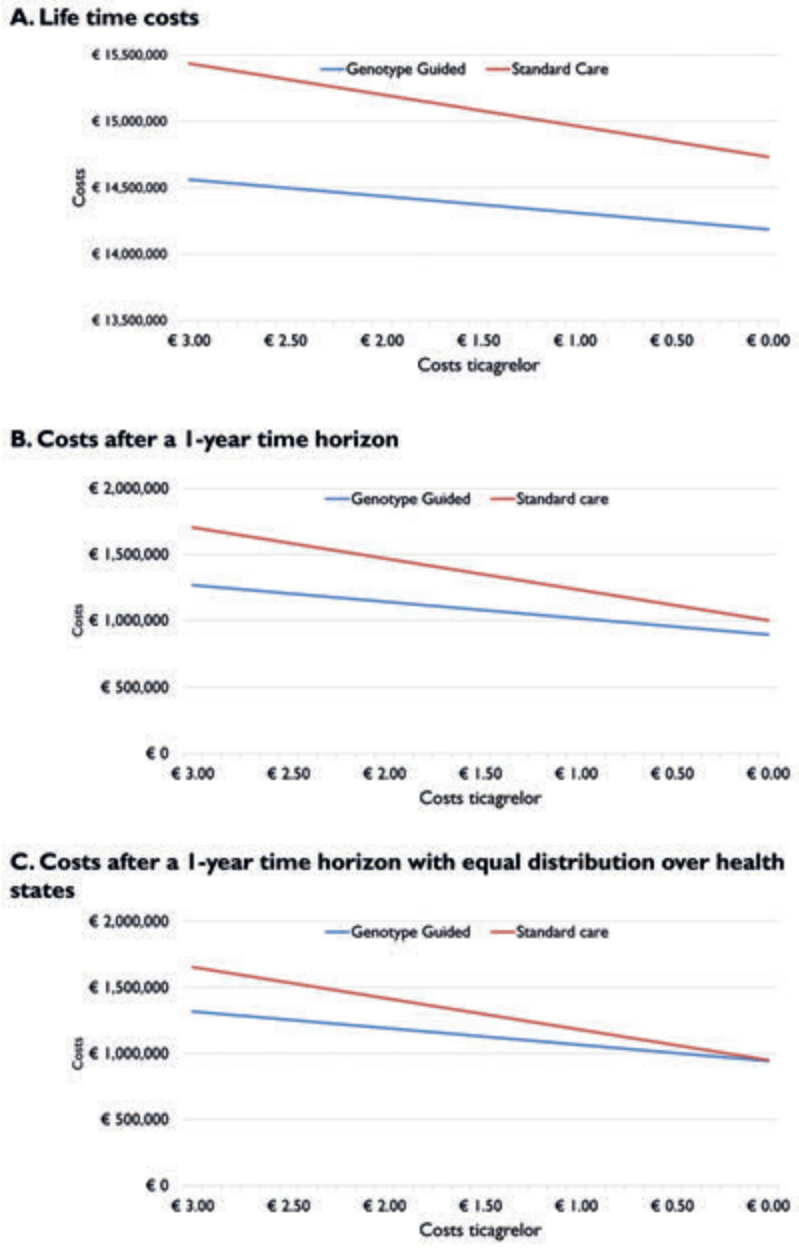

Figure 4. Figure 4 Impact of reducing ticagrelor prices on costs in different scenarios.

Results of a scenario analysis demonstrating the impact of reducing ticagrelor prices on total costs in the genotype-guided and standard care cohorts. (A) Total costs based on the base-case analysis and a lifetime horizon. (B) Total costs based on the base-case analysis and a 1-year horizon. (C) Costs based on the scenario with equal distribution over health states and a 1-year horizon.

While ticagrelor and prasugrel are the most effective at reducing platelet reactivity in patients with a *CYP2C19* loss-of-function allele compared to standard dose clopidogrel, high-dose clopidogrel also lowers platelet reactivity in these patients and may serve as a low-cost option in clinical settings where ticagrelor or prasugrel are unavailable.[25] However, this approach is not recommended by clinical guidelines, such as those from CPIC, as clopidogrel doses as high as 300 mg may not fully overcome genotype effects in certain intermediate metabolizers (e.g. those with diabetes) or poor metabolizers.[5]

The POPular Genetics trial was the first large RCT to demonstrate that a genotype-guided de-escalation strategy can reduce bleeding events.[4] Although there were no significant differences in the combined thrombotic outcome between the two groups, a limitation of this study is that it was not powered to detect non-inferiority for ischaemic events. Nevertheless, similar findings have been reported in other observational studies and a meta-analysis, suggesting that clopidogrel has comparable efficacy to ticagrelor or prasugrel in patients without a loss-of-function allele, but reduced efficacy in intermediate or poor metabolizers and those with a high ABCD-GENE (age, body mass index, chronic kidney disease, diabetes, and *CYP2C19* genetic variants) score.26 , 27 These results are reinforced by a network meta-analysis indicating that guided selection of P2Y12 inhibitor therapy in ACS patients offers a better balance of safety and efficacy than routine potent P2Y12 inhibitor therapy.[28]

Our results are in line with the CEA of the POPular Genetics, which demonstrated the cost-efficacy of a *CYP2C19* genotype-guided strategy based on data from a randomized trial.[29] Despite higher overall costs in both groups, which can be attributed to inflation and increased rates of ischaemic events, the incremental cost-savings from both base-case analyses were comparable (FORCE-ACS: –€698,286 vs. POPular Genetics: –€725 551). The increase in incremental QALYs was more pronounced in our analysis (FORCE-ACS: 57.73 vs. POPular Genetics: 8.98), which may be due to the larger disparity in event rates used in the base case. In the PSA cost-effectiveness plane, the POPular Genetics study shows more iterations skewed toward the southeast quadrant, indicating greater cost-effectiveness. Unlike our study, their CEA lacked specified probability ranges for decision tree variables, which may explain the differences. Since our study was not powered to detect event differences, we took a more conservative approach by incorporating uncertainty around the event rates in our model. The tornado plot in *Figure 2* shows that changes in the probabilities used in the decision tree during the initial cycle exert the largest impact on the lifetime outcome of the model.

Despite this conservative approach, the genotype-guided strategy saved costs and was associated with more QALYs gained in 84% of the iterations.

Several studies have explored the cost-effectiveness of *CYP2C19* genotype -guided strategies . However, none have used data from a study where a de-escalation strategy was implemented.[30-32] In a secondary analysis, Limdi *et al.* assessed the cost-efficacy of a genotype -guided de -escalation applied 30 days post-PCI. They found it was not cost-effective (ICER of $188 680/QALY), but resulted in a higher NMB than universal use of ticagrelor. An important constraint is that this analysis relied on data from an escalation strategy, rather than a de-escalation strategy, making it challenging to assess cost-effectiveness for a de-escalation approach. A CEA based on the Veterans Health Administration

showed that a combined approach of genotype-guided escalation and de-escalation strategies can improve cardiovascular outcomes and reduce costs within 12 months.[33] How-ever, the analysis relied on RCT data for treatment effects rather than real-world data, which may limit the generalizability of the findings. Notably, the study emphasized that health systems should prioritize high adherence to the de-escalation strategy, as it was the primary driver of cost-effectiveness.

Our analysis benefits from using prospectively registered real-world data, allowing us to account for adherence to the de-escalation protocol and P2Y12 inhibitor therapy in the first year after ACS. Instead of assuming universal de-escalation to clopidogrel, we considered that only 89% did so, aligning with prior data.[14] We also adjusted the standard care cohort to reflect that only 64% received ticagrelor. These considerations lead to more conservative results, but ones that are closer to clinical practice.

With the anticipated expiration of the patent for ticagrelor, prices are expected to gradually decrease in the coming years. We demonstrated that even with decreasing ticagrelor prices, a genotype-guided de-escalation strategy remains cost-effective, as the beneficial effect on bleeding can offset these lower prices.

Our findings, alongside results from RCTs and consensus recommendations, should prompt guideline committees to provide stronger recommendations on the use of genetic testing in clinical practice, as current guidelines either omit this strategy or offer only weak guidance.[34–36]

Limitations

Our analysis is subject to several limitations . First, as the FORCE-ACS registry could only provide data regarding treatment and outcomes during the first year, we had to make assumptions based on other data to estimate long-term cost-effectiveness. However, the majority of these assumptions are based on data from comparable populations and similar clinical settings. Second, the probabilities in the decision tree were derived from observational data comparing two cohorts enrolled during different time periods. Since this analysis was not powered to detect differences in ischaemic and bleeding rates, further research with a larger sample size is required for more conclusive results. Third, as less than 1% of patients were treated with prasugrel, our findings are mainly relevant to treatment with clopidogrel and ticagrelor. Fourth, while converting SF-12 data to EQ-5D responses is pragmatic given the data constraints, it introduces some uncertainty in the precision of QALY calculations. Fifth, our analysis used a healthcare perspective, though a societal perspective is preferable. This would include non-healthcare costs and productivity loss, which we could not account for, as we did not register this data. Finally, while our results advocate for the cost-effectiveness of genotype -guided de -escalation, the routine implementation of *CYP2C19* genotyping may vary based on local infrastructure and associated costs, which can differ across healthcare settings in different countries.

CONCLUSION

A genotype -guided de -escalation strategy in patients with ACS dominated standard DAPT consisting of aspirin plus ticagrelor/prasugrel by being cost-saving and yielding higher QALYs. These findings underscore the cost-effectiveness of implementing a genotype-guided de-escalation strategy into clinical practice.

REFERENCES

1. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023.
2. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, et al. Defining strategies of modulation of antiplatelet therapy in patients with coronary artery disease: a consensus document from the Academic Research Consortium. Circulation 2023;147:1933–1944.
3. Gorog DA, Ferreiro JL, Ahrens I, Ako J, Geisler T, Halvorsen S, et al. De-escalation or abbreviation of dual antiplatelet therapy in acute coronary syndromes and percutaneous coronary intervention. Nat Rev Cardiol 2023;20:830–844.
4. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Van 't Hof AWJ, Van der Harst P, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med 2019;381:1621–1631.
5. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM, et al. CPIC guideline for CYP2C19 genotype and clopidogrel therapy: 2022 update. Clin Pharmacol Ther 2022;112:959–967.
6. van den Broek WWA, van Paassen JG, Gimbel ME, Deneer VHM, ten Berg JM, Vreman RA. Cost-effectiveness of clopidogrel versus ticagrelor in patients ≥70 years with NSTE-ACS. Eur Heart J Cardiovasc Pharmacother 2022;9:76–84.
7. Claassens DMF, van Dorst PWM, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, et al. Cost effectiveness of a CYP2C19 genotype-guided strategy in AMI: POPular Genetics. Am J Cardiovasc Drugs 2021;22:195–206.
8. Chan Pin Yin DRPP, Vos GJA, Van der Sangen NMR, Walhout R, Tjon Joe Gin RM, Nicastia DM, et al. FORCE-ACS registry design. J Clin Med 2020;9:3173.
9. Azzahhafi J, Van den Broek WWA, Chan Pin Yin DRPP, Van der Sangen NMR, Sivanesan S, Bofarid S, et al. Real-world genotype-guided P2Y12 de-escalation. JACC Cardiovasc Interv 2024;17:1996–2007.
10. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M. Cost-effectiveness of ticagrelor: PLATO. Eur Heart J 2013;34:220–228.
11. Wang Y, Yan BP, Liew D, Lee VWY. Cost-effectiveness of CYP2C19*2 guided therapy in Chinese ACS. Pharmacogenomics J 2018;18:113–120.
12. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for chronic coronary syndromes. Eur Heart J 2020;41:407–477.
13. Statistiek CB. Prijzen toen en nu. 2024.
14. Azzahhafi J, Broek WWA, Chan Pin Yin D, Harmsze AM, van Schaik RHN, Ten Berg JM. Clinical implementation of CYP2C19 genotyping: FORCE-ACS. J Cardiovasc Pharmacol Ther 2023;28.
15. Oostenbrink JB, Koopmanschap MA, Rutten FFH. Standardisation of costs. Pharmacoeconomics 2002;20:443–454.
16. Gray AM, Rivero-Arias O, Clarke PM. Mapping SF-12 to EQ-5D. Med Decis Mak 2006;26:18–29.
17. Stevanovic J, Pompen M, Le HH, Rozenbaum MH, Tieleman RG, Postma MJ. Apixaban in NVAF Netherlands. PLoS One 2014;9:e103974.
18. Paulden M. ICERs and net benefit. Pharmacoeconomics 2020;38:785–807.
19. Zorginstituut Nederland. Budget impact rivaroxaban. 2019.

20. Ismail N, Jordan KP, Rao S, Kinnaird T, Potts J, Kadam UT, et al. Post-discharge bleeding after ACS. BMJ Open 2019;9:e023337.
21. Amin AP, Wang TY, McCoy L, Bach RG, Effron MB, Peterson ED, et al. Bleeding and QoL on DAPT. J Am Coll Cardiol 2016;67:59–65.
22. Amin AP, Bachuwar A, Reid KJ, Chhatriwalla AK, Salisbury AC, Yeh RW, et al. Nuisance bleeding after MI. J Am Coll Cardiol 2013;61:2130–2138.
23. Valgimigli M, Gragnano F, Branca M, Franzone A, Da Costa BR, Baber U, et al. Ticagrelor or clopidogrel monotherapy vs DAPT. JAMA Cardiol 2024;9:437–448.
24. Luengo-Fernandez R, Walli-Attaei M, Gray A, Torbica A, Maggioni AP, Huculeci R, et al. Economic burden of CVD in EU. Eur Heart J 2023;44:4752–4767.
25. Galli M, Occhipinti G, Benenati S, Laborante R, Ortega-Paz L, Franchi F, et al. CYP2C19 LoF network meta-analysis. Eur Heart J Cardiovasc Pharmacother 2024;10:526–536.
26. Thomas CD, Franchi F, Rossi JS, Keeley EC, Anderson RD, Beitelshees AL, et al. ABCD-GENE score. J Am Coll Cardiol 2024;83:1370–1381.
27. Pereira NL, Rihal C, Lennon R, Marcus G, Shrivastava S, Bell MR, et al. CYP2C19 genotype meta-analysis. JACC Cardiovasc Interv 2021;14:739–750.
28. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Guided vs potent P2Y12 therapy. Eur Heart J 2022;43:959–967.
29. Claassens DMF, Van Dorst PWM, Vos GJA, Bergmeijer TO, Hermanides RS, Van 't Hof AWJ, et al. POPular Genetics cost-effectiveness. Am J Cardiovasc Drugs 2021;22:195–206.
30. Limdi NA, Cavallari LH, Lee CR, Hillegass WB, Holmes AM, Skaar TC, et al. CYP2C19-guided therapy cost-effectiveness. Pharmacogenomics J 2020;20:724–735.
31. Lala A, Berger JS, Sharma G, Hochman JS, Braithwaite RS, Ladapo JA. Genetic testing after PCI. J Thromb Haemost 2013;11:81–91.
32. Borse MS, Dong OM, Polasek MJ, Farley JF, Stouffer GA, Lee CR. CYP2C19-guided PCI. Pharmacogenomics 2017;18:1155–1166.
33. Dong OM, Friede KA, Chanfreau-Coffinier C, Voora D. Veterans PCI cost-effectiveness. Eur Heart J Qual Care Clin Outcomes 2023;9:249–257.
34. Pereira NL, Cresci S, Angiolillo DJ, Batchelor W, Capers Q, Cavallari LH, et al. AHA scientific statement. Circulation 2024;150:e129–e150.
35. Angiolillo DJ, Galli M, Alexopoulos D, Aradi D, Bhatt DL, Bonello L, et al. Platelet function/genetic testing consensus. JACC Cardiovasc Interv 2024;17:2639–2663.
36. Van den Broek WWA, Ingraham BS, Pereira NL, Lee CR, Cavallari LH, Swen JJ, et al. Genotype-guided antiplatelet therapy. J Am Coll Cardiol 2024;84:1107–1118.
37. Central Bureau for Statistics. Lifetables 2024.
38. Lala A, Berger JS, Sharma G, Hochman JS, Braithwaite RS, Ladapo JA. Genetic testing after PCI. J Thromb Haemost 2013;11:81–91.
39. Zorginstituut Nederland. Clopidogrel kosten 2024.
40. Zorginstituut Nederland. Ticagrelor kosten 2024.

41. Zorginstituut Nederland. Prasugrel kosten 2024.
42. Jacobs MS, de Jong LA, Postma MJ, Tieleman RG, van Hulst M. Rivaroxaban cardioversion. Eur J Health Econ 2018;19:957–965.
43. Ten Cate-Hoek AJ, Toll DB, Büller HR, Hoes AW, Moons KGM, Oudega R, et al. DVT rule-out cost-effectiveness. J Thromb Haemost 2009;7:2042–2049.
44. Soekhlal RR, Burgers LT, Redekop WK, Tan SS. AMI costs Netherlands. Netherlands Heart J 2013;21:230–235.
45. de Jong LA, Groeneveld J, Stevanovic J, Rila H, Tieleman RG, Huisman MV, et al. Apixaban real-world cost-effectiveness. PLoS One 2019;14:e0222658.
46. Greving JP, Visseren FLJ, De Wit GA, Algra A. Statins primary prevention. BMJ 2011;342.
47. Stevanovic J, Pompen M, Le HH, Rozenbaum MH, Tieleman RG, Postma MJ. Apixaban NVAF Netherlands. PLoS One 2014;9:e103974.

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

CHAPTER 13

A Genotype-Guided P2Y12 inhibitor De-Escalation Strategy in Acute Coronary Syndrome: Observational Evidence from the POPULAR-GUIDE PCI

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ABSTRACT

Background and Aims

A genotype-guided de-escalation strategy - switching from a potent P2Y12 inhibitor to clopidogrel - may represent an effective and safe approach to reducing bleeding risk in patients with acute coronary syndrome (ACS). This analysis aimed to evaluate the safety and effectiveness of routine genetic testing to guide antiplatelet therapy in clinical practice.

Methods

In this investigator-initiated, prospective, multicentre implementation study, patients were divided into a standard care cohort, where antiplatelet therapy was prescribed at the physician's discretion (with a potent P2Y12 inhibitor as the default choice), and a genotype-guided cohort. In the genotype-guided group, physicians were recommended to switch to clopidogrel in noncarriers of *CYP2C19* loss-of-function alleles during hospital admission. The primary endpoints were major adverse cardiac events (MACE), defined as a composite of cardiovascular death, myocardial infarction, or stroke, and major or non-major clinically relevant bleeding (Bleeding Academic Research Consortium types 2, 3, or 5), at one year of follow-up. Hazard ratios were adjusted for baseline differences between cohorts using multivariable Cox regression.

Results

A total of 9,907 patients were included in the analysis. Of these, 1,208 (12%) were included in the genotype-guided cohort, while 8,699 (88%) were assigned to the standard care cohort. MACE occurred in 107 patients (8.9%) in the genotype-guided cohort and 897 patients (10.3%) in the standard care cohort ($_{adj}$HR 1.05; 95% CI 0.85-1.29**;** P = 0.64). Major or non-major clinically relevant bleeding was reported in 146 patients (12.1%) in the genotype-guided cohort compared to 1,384 patients (15.9%) in the standard care cohort ($_{adj}$HR 0.79; 95% CI 0.67–0.94; P = 0.01).

Conclusion

In patients with ACS receiving antiplatelet therapy, implementation of a *CYP2C19* genotype-guided de-escalation strategy in clinical practice significantly reduced major and non-major clinically relevant bleeding compared to standard care at 12 months, without increasing ischemic events.

INTRODUCTION

Acute coronary syndrome (ACS) continues to be a significant cause of morbidity and mortality worldwide, necessitating effective strategies to reduce ischemic events in affected patients.[1] Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, is the cornerstone of secondary prevention in these patients.[2] While the more potent P2Y12 inhibitors ticagrelor and prasugrel offer enhanced protection against ischemic events, their use is associated with an increased risk of bleeding, a complication that significantly impacts patient outcomes and is associated with increased morbidity and mortality.[3,4]

The challenge of balancing ischemic and bleeding risks has driven the development of personalized treatment strategies, including the adoption of de-escalation strategies.[5] These strategies involve switching from potent P2Y12 inhibitors to less potent alternatives, such as clopidogrel, to mitigate bleeding risks without compromising ischemic protection. A promising approach to optimize this balance in patients with ACS is a genotype-guided de-escalation strategy. Genetic testing for the *CYP2C19* genotype, which encodes the enzyme essential for clopidogrel activation, enables tailored treatment by identifying patients with loss-of-function (LOF) alleles. These individuals are more likely to experience high on-treatment platelet reactivity (HTPR) to clopidogrel, which in turn is associated with increased ischemic risk.[6] Patients without these genetic variants (normal metabolizers), who comprise approximately 70% of the European population, may safely switch to clopidogrel, reducing both bleeding risks and healthcare costs.[7,8] The POPular Genetics trial demonstrated the efficacy and safety of a *CYP2C19* genotype-guided de-escalation strategy in a randomized setting, showing reduced bleeding without an evident increase in ischemic events among patients with ST-segment elevation myocardial infarction (STEMI).[9] Despite these findings and recommendations from various expert opinion groups, the implementation of this strategy in clinical practice remains low, resulting in limited evidence from real-world settings.[10–12] The controlled nature of clinical trials often excludes high-risk populations and does not account for the complexities of routine clinical practice, raising questions about the generalizability of these results.

To address this gap, our study examines the implementation of a genotype-guided de-escalation strategy in a real-world ACS population. This analysis aims to provide insights into the safety and effectiveness of routine genetic testing to guide antiplatelet therapy, focusing on bleeding and ischemic outcomes in an all-comers cohort at one year follow-up. By bridging the evidence gap between clinical trials and real-world practice, our findings aim to inform broader adoption of personalized antiplatelet therapy strategies.

METHODS

Study design

The POPular GUIDE PCI was an investigator-initiated, prospective, observational, multicentre study. It was conducted as an implementation initiative within the ongoing FORCE-ACS (Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome) Registry (NCT03823547), which includes nine non-interventional and interventional cardiac centres in the Netherlands.[13] The research protocol of the FORCE-ACS registry was approved by the institutional review boards of all participating medical centres. Enrolment procedures have been prescribed previously.[13] All patients included in the registry have provided either written or digital informed consent.

Study Population and Data Collection

Patients aged 18 years or older are eligible for enrolment in the FORCE-ACS registry upon admission with a suspected ACS, including unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or STEMI. The registry has no exclusion criteria. Data was prospectively collected by members of the investigation team during a follow-up of three years. Follow-up was conducted via electronic health record (EHR) review and questionnaires administered at predefined intervals: 1, 12, 24, and 36 months after admission. The questionnaires included specific questions about ischemic and bleeding events, assessed quality of life, and gathered information on drug use and any changes in antiplatelet therapy.

Treatment Procedures

Since 2015, patients with (suspected) ACS were consecutively enrolled in the FORCE-ACS registry. Antithrombotic treatment followed local protocols, comprising a loading dose of aspirin, a potent P2Y12 inhibitor, and heparin, in line European Society of Cardiology guidelines.[14] In June 2021, the implementation of the genotype-guided de-escalation strategy was initiated using on-site testing facilities in the St. Antonius Hospital, Nieuwegein, the Netherlands. Details on the genotype guided de-escalation have been described previously.[15] Initially, *CYP2C19* genotyping was performed using the Genomadix point-of-case assay which required buccal swap samples. In March 2022, the implementation protocol was updated to include on-site *CYP2C19* genotyping using genomic DNA extracted from venous blood in the central laboratory. The local protocol required that every patient with ACS underwent *CYP2C19* genotype testing immediately after admission, with STEMI patients primarily tested via the point-of-care system and NSTEMI patients predominantly tested in the central laboratory. Patients carrying at least one *CYP2C19* LOF allele (*2 or *3), categorized as intermediate (IM) or poor metabolizers (PM), remained on ticagrelor or prasugrel. In non-carriers ([ultra-]rapid [UM/RM] or normal metabolizers [NM]), attending physicians received an automated notification to switch antiplatelet therapy from ticagrelor to clopidogrel, starting with a 600 mg loading dose followed by 75 mg daily. Ultimate prescribing decisions were left to the physician's discretion.

As of 2023, three of the other participating sites adopted off-site genetic testing using blood samples, following the same de-escalation protocol. At these sites, de-escalation to clopidogrel was performed during the patient's next follow-up visit.

Study Endpoints

The study had two primary endpoints: major adverse cardiac events (MACE), defined as a composite of cardiovascular death, myocardial infarction (MI), or stroke within 12 months of hospital admission, and major or non-major clinically relevant bleeding, classified according to the Bleeding Academic Research Consortium (BARC) types 2, 3, or 5. The secondary endpoint, net adverse cardiac events (NACE), was defined as a composite of all-cause death, MI, stroke, stent thrombosis and major bleeding (BARC 3 or 5). All the individual components of the primary endpoints were adjudicated by coordinating investigators of the FORCE-ACS registry.

P2Y12 inhibitor adherence was assessed by classifying medication changes into two groups: alterations, defined as any change in the prescribed P2Y12 inhibitor after hospital discharge, and disruptions, defined as discontinuation of P2Y12 inhibitor therapy for more than 14 days. Reasons for drug alterations were also documented.

Statistical analysis

Patients were categorized into two cohorts: a standard care cohort, where P2Y12 inhibitors were prescribed at the treating physician's discretion, and a genotype guided cohort, where patients underwent *CYP2C19* genotype testing with treatment recommendations tailored to the test results. Patients, in whom the *CYP2C19* genotype was already known at admission, were also included in the genotype-guided group. For this analysis, only patients with a final diagnosis of ACS, for whom antiplatelet therapy was indicated, were included.

Although this study is observational and based on ongoing registry data, a pre-specified sample size calculation was performed to ensure adequate power for detecting clinically meaningful differences between groups. We estimated the required sample size based on an assumed incidence of major or non-major clinically relevant bleeding of 11.0% in the standard-treatment group and 8.0% in the genotype-guided group, derived from a prior pilot analysis and the results of the POPular Genetics.[16] Using an alpha level of 0.05 and a power of 80%, we calculated that 1,125 patients in the genotype-guided group would be necessary to demonstrate superiority. To account for a 5% attrition rate, the final planned sample size was set at 1,181.

Continuous variables were summarized as medians with interquartile ranges (IQR) or means with standard deviations (SD), while categorical variables were presented as frequencies and percentages. Comparisons between the standard care and genotyped cohorts were conducted using Mann-Whitney U tests or t-tests for continuous variables and Chi-square or Fisher's Exact tests for categorical variables. The primary analysis utilized a Cox proportional hazards model to estimate hazard ratios (HRs) with 95% confidence intervals. Potential confounders were included in the multivariable model based on clinical relevance (age, hypercholesterolemia, prior myocardial infarction, prior CABG, prior stroke, peripheral

artery disease, atrial fibrillation, discharge diagnosis, use of diuretics, triple therapy, ACE inhibitors or ATII receptor blockers, proton pump inhibitors, PCI during admission, high bleeding risk, and complex PCI). Similar Cox proportional-hazards models were used for the analysis of subgroups defined according to age (<75 years or ≥75 years), sex (male or female), diabetes mellitus (yes/no), renal function (<60 or >60 mL/min/1.73 m^2), clinical presentation (NSTEMI, or STEMI), high bleeding risk (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy [PRECISE-DAPT] <25 or ≥25) and complex PCI (yes/no), defined as the use of three or more stents, treatment of three or more lesions, stent length exceeding 60 mm, left main stenting, bifurcation stenting, or prior stent thrombosis. Time-to-event analyses were performed using Kaplan-Meier curves. The proportional hazards assumption was assessed using Schoenfeld residuals.

To account for baseline differences and reduce confounding in the comparison of outcomes, propensity score matching was performed using clinically relevant covariates. Matching followed a one-to-three protocol without replacement, applying the nearest neighbour method with a calliper of 0.2 standard deviations of the logit of the propensity score. Additional sensitivity analyses were conducted to refine the assessment of the genotype-guided strategy's treatment effect in three different populations, one excluding patients treated with oral anticoagulants at discharge, one excluding those patients in whom the recommended choice of P2Y12 inhibitor based on the genetic test result was not followed and one only including patients that underwent PCI during admission.

Patients were evaluated from hospital admission until death, withdrawal of consent, or the last contact date. All statistical analyses were conducted R studio version 3.6.1 (Vienna, Austria).

RESULTS

Patient characteristics

A total of 9,907 patients, enrolled between January 2015 and December 2023, were included in the analysis (**Figure 1**). Of these, 1,208 (12%) were included in the genotype-guided cohort, while 8,699 (88%) comprised the standard care cohort. The mean age of the overall population was 66 years (SD ±11.8), 2,827 (29%) were women, and 70% (N = 6,896) underwent PCI during hospital admission. Patients in the genotype-guided cohort exhibited a higher prevalence of prior bleeding events and STEMI as the index diagnosis, whereas the standard care cohort had a greater prevalence of prior MI, prior PCI, prior CABG, prior stroke, atrial fibrillation and peripheral artery disease (Table 1).

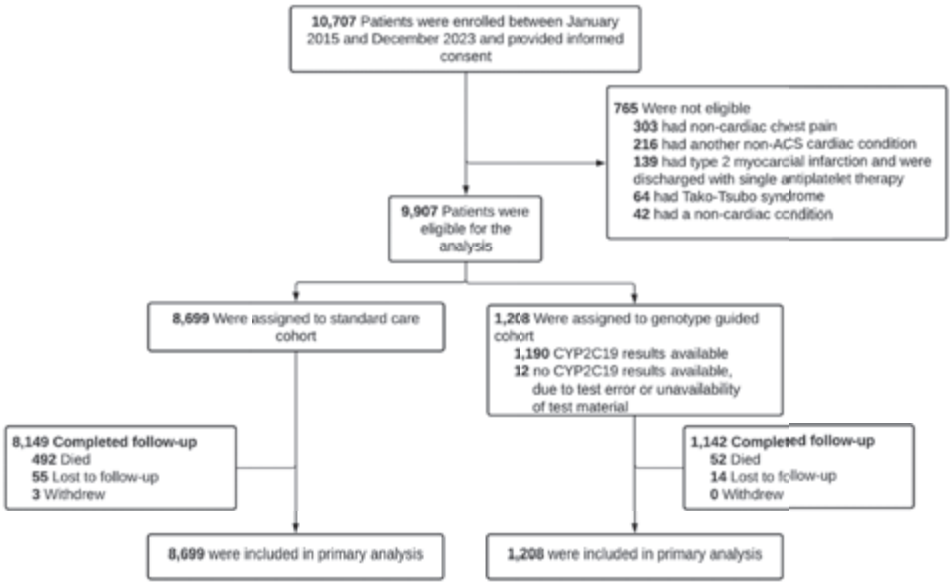

Figure 1. Study Flowchart

ACS = acute coronary syndrome

Treatment and Management

Coronary angiography was performed in 96% of genotype-guided patients and 95% of standard care patients (**Table 1**). PCI was more frequently performed in the genotype-guided cohort (75%) compared to the standard care cohort (69%). More patients in the genotype-guided cohort underwent a complex PCI-procedure (11.6% vs. 14.2%, *P* = 0.008).

Among the genotype-guided cohort, 69% of patients (838 of 1,208) were identified as non-carriers. At discharge, clopidogrel was prescribed to 60% of patients in the genotype-guided cohort (N = 723) and ticagrelor in 35% (N=422). In the standard care cohort, 29% of patients were treated with clopidogrel (N=2,505) and 63% with ticagrelor (N=5,494). Among loss-of-function carriers in the genotype-guided group (n = 370), 312 (84%) were treated with ticagrelor or prasugrel, while the remainder predominantly received clopidogrel, mainly due to concomitant oral anticoagulant use.

The rate of P2Y12 treatment alterations was significantly lower in the genotype-guided cohort compared to the standard care cohort (98 [8.1%] vs. 1243 [14.3%], *P* < 0.001). Similarly, dyspnoea leading to treatment alterations was reported less frequently in the genotype-guided cohort (36 [3.0%] vs. 517 [5.9%], P < 0.001). No significant difference was observed in treatment disruption between the two groups (36 [2.4%] vs. 517 [3.2%], *P* = 0.236).

Table 1. Baseline table for the genotype guided cohort compared to the standard care cohort

Characteristics	Genotype Guided Cohort (N = 1,208)	Standard Care cohort (N = 8,699)	*p-value*
Age (mean [SD])	65.51 (11.39)	66.43 (11.90)	0.012
Female sex (%)	318 (26.3)	2509 (28.8)	0.075
BMI (mean [SD])	27.68 (4.79)	27.41 (4.44)	0.057
CYP2C19 LOF carrier (%)	370 (30.6)	-	-
Hypertension (%)	644 (53.6)	4741 (55.9)	0.139
Dyslipidaemia (%)	960 (79.5)	4736 (54.4)	<0.001
Diabetes Mellitus (%)	245 (20.3)	1801 (20.9)	0.696
Previous MI (%)	197 (16.3)	1788 (20.6)	0.001
Previous PCI (%)	208 (17.2)	1764 (20.3)	0.014
Previous CABG (%)	67 (5.5)	684 (7.9)	0.005
Prior stroke (%)	82 (6.8)	774 (8.9)	0.017
Atrial fibrillation (%)	44 (3.6)	713 (8.2)	<0.001
PAD (%)	55 (4.6)	660 (7.6)	<0.001
Kidney failure (%)	41 (3.4)	329 (3.8)	0.558
Previous bleeding event (%)	127 (11.0)	500 (5.9)	<0.001
GRACE-score >140 (%)	190 (15.7)	1430 (16.4)	0.559
PRECISE-DAPT >25 (%)	320 (26.6)	2606 (30.4)	0.008
Discharge diagnosis			
STEMI (%)	628 (52.0)	3443 (39.6)	<0.001
NSTEMI (%)	458 (37.9)	4163 (47.9)	
IAP (%)	59 (4.9)	702 (8.1)	
Treatment			
CAG during admission (%)	1163 (96.4)	8242 (94.8)	0.021
PCI during admission (%)	905 (74.9)	5991 (68.9)	<0.001
DES stent (%)	838 (69.4)	5532 (63.6)	<0.001
CAG access site			0.007
Radial (%)	963 (79.7)	6706 (77.1)	
Femoral (%)	189 (15.6)	1402 (16.1)	
Brachialis (%)	1 (0.1)	32 (0.4)	
Vessel disease			
0-VD (%)	53 (4.4)	546 (6.3)	0.012
1-VD (%)	478 (39.6)	2689 (30.9)	<0.001
2-VD (%)	342 (28.3)	1740 (20.0)	<0.001
3-VD (%)	280 (23.2)	1648 (18.9)	0.001
Graft dysfunction (%)	22 (1.8)	239 (2.7)	0.074
Bifurcation stenting (%)	33 (3.3)	119 (1.7)	<0.001

Table 1. Continued

Left main stenting	29 (2.4)	144 (1.7)	0.064
Complex PCI (%)	172 (14.2)	1010 (11.6)	0.008
Aspirin (%)	992 (82.1)	7420 (85.3)	0.004
Clopidogrel (%)	723 (60.0)	2505 (28.8)	<0.001
Prasugrel (%)	3 (0.3)	46 (0.6)	0.177
Ticagrelor (%)	422 (34.9)	5494 (63.2)	<0.001
Vitamin-K antagonist (%)	46 (3.8)	654 (7.5)	<0.001
DOAC (%)	134 (11.1)	779 (9.0)	0.019
Oral anticoagulation (%)	180 (14.9)	1432 (16.5)	0.182
Triple therapy (%)	8 (0.7)	407 (4.7)	<0.001
Beta-blocker (%)	866 (71.7)	6171 (70.9)	0.59
ACE inhibitor or AT-II antagonist (%)	827 (68.5)	6342 (72.9)	0.001
Lipid lowering drugs (%)	1117 (92.5)	7920 (91.0)	0.102
PPI (%)	1127 (93.3)	7314 (84.1)	<0.001

Data are n (%) unless stated otherwise. Missing data were observed for BMI (4.3%), access site (6.3%) and bifurcation stenting (19.3%); for all other variables, missing data were less than 3%. ACE = angiotensin-converting enzyme; AT-II = angiotensin-II; IQR = interquartile range; BMI= body mass index; CABG = coronary artery bypass grafting; CAG = coronary angiography; DES = drug eluting stent; CV = cardiovascular; IQR = interquartile range; kg = kilogram; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SD = standard deviation; VD = vessel disease.

Comparison of Central Laboratory and Point-Of-Care Testing

The median time from hospitalization to test result was significantly shorter for patients tested using point-of-care testing (POCT) compared to the central laboratory (0 days [IQR 0–1] vs. 2 days [IQR 2–4], $P < 0.001$, **Table 2**). Similarly, the median time from hospitalization to de-escalation was shorter with POCT (1 day [IQR 1–2] vs. 3 days [IQR 2–6], $P < 0.001$).

At the site with on-site testing facilities, POCT demonstrated faster turnaround times, with a median of 0 days (IQR 0–1) from hospitalization to test result compared to 2 days (IQR 2–3) for the central laboratory ($P < 0.001$). De-escalation also occurred more rapidly for POCT patients (median 1 day [IQR 1–2]) compared to those tested via the central laboratory (3 days [IQR 2–5], $P < 0.001$). At the sites with off-site testing facilities only, delays were more pronounced with central laboratory testing. The median time from hospitalization to test result was 4 days (IQR 2–6), and de-escalation occurred at a median of 16 days (IQR 9–22).

Table 2. Comparison of central laboratory and point-of-care testing across between sites with both on-site and off-site testing facilities, and sites with only off-site facilities.

	Central Lab (N = 238)*	**POCT (N = 917)***	
Total (N = 1,155)*	Days (median [IQR])	Days (median [IQR])	*P*-value
Days from hospitalization to test result	2 [2, 4]	0 [0, 1]	<0.001
Days from hospitalization to de-escalation	3 [2, 6]	1 [1, 2]	<0.001
Days from test result to de-escalation	1 [1, 3]	1 [1, 1]	<0.001
Onsite test facilities (N = 1,108)			
Days from hospitalization to test result	2 [2, 3]	0 [0, 1]	<0.001
Days from hospitalization to de-escalation	3 [2, 5]	1 [1, 2]	<0.001
Days from test result to de-escalation	1 [0, 2]	1 [1, 1]	0.082
Off-site test facilities (N = 47)			
Days from hospitalization to test result	4 [2, 6]		
Days from hospitalization to de-escalation	16 [9, 22]		
Days from test result to de-escalation	13 [7, 19]		

*The date and time of test results were unavailable for 53 patients (37 from the central lab and 16 from POCT patients). IQR = interquartile range, POCT = point-of-care testing

Clinical Outcomes

Primary outcomes

During the median follow-up duration of 365 days (mean 348 days, IQR: 365–365 days), MACE occurred in 107 of 1,208 patients (8.9%) in the genotype guided cohort and 897 of 8,699 patients (10.3%) in the standard care cohort ($_{adj}$HR, 1.05; 95% confidence interval [CI], 0.85-1.29; P = 0.64) (**Figure 2A** and **Table 3**). Major or non-major clinically relevant bleeding occurred in 146 patients (12.1%) in the genotype guided cohort and 1,384 patients (15.9%) in the standard care cohort ($_{adj}$HR, 0.79; 95% CI, 0.67-0.94; P = 0.01, **Figure 2B**), with consistent results observed across other bleeding classifications (**Supplementary Appendix Table 1**). Kaplan-Meier analysis demonstrated similar results, showing no significant difference in MACE, but a highly significant reduction in major or non-major clinically relevant bleeding (log-rank P = 0.0006).

Secondary Outcomes

NACE occurred in 137 patients (11.3%) in the genotype guided cohort and 1,253 patients (14.4%) in the standard care cohort ($_{adj}$HR, 0.91, 95% CI, 0.76-1.09; P = 0.31). The incidences of the individual components of all composite end point are shown in **Table 2**. The rate of death from any cause was 4.3% in the genotype guided cohort and 5.7% in the standard care cohort ($_{adj}$HR, 1.08; 95% CI, 0.80-1.44, P = 0.63). The incidence of myocardial infarction was 3.6% in the genotype guided cohort and 4.9% in the standard care cohort ($_{adj}$HR 0.87; 95% CI, 0.63-1.19, P = 0.38). There was no difference in the incidence of stent thrombosis (0.8% vs. 0.9%, $_{adj}$HR 0.81, 95% CI, 0.41-1.61 P = 0.55).

Major bleeding (BARC 3 or 5) occurred in 2.6% of patients in the genotype guided cohort and 3.7% in the standard care cohort ($_{adj}$HR, 0.80, 95% CI, 0.55-1.17; *P* = 0.25). The rate of BARC 2 bleeding was 10.3% in the genotype guided cohort and 13.0% in the standard care cohort ($_{adj}$HR 0.83, 95% CI 0.69-1.01, *P* = 0.06).

Table 3. Clinical outcomes of the genotype guided compared with the standard care cohort.

Outcomes	Genotype guided Cohort (N = 1,207)	Standard Care Cohort (N = 8,699)	Unadjusted		Adjusted	
			HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
MACE	107 (8.9%)	897 (10.3%)	0.85 (0.70-1.04)	0.12	1.05 (0.85-1.29)	0.64
BARC 2, 3 or 5	146 (12.1%)	1384 (15.9%)	0.74 (0.63-0.88)	0.0007	0.79 (0.67-0.94)	0.01
NACE	137 (11.3%)	1253 (14.4%)	0.77 (0.655-0.92)	0.004	0.91 (0.76-1.09)	0.31
All-cause death	52 (4.3%)	492 (5.7%)	0.76 (0.57-1.01)	0.05	1.08 (0.80-1.44)	0.63
CV death	43 (3.6%)	368 (4.2%)	0.84 (0.61-1.15)	0.27	1.30 (0.94-1.81)	0.11
MI	44 (3.6%)	423 (4.9%)	0.74 (0.54-1.01)	0.06	0.87 (0.63-1.19)	0.38
Stroke	33 (2.7%)	177 (2.0%)	1.34 (0.92-1.94)	0.12	1.46 (0.99-2.14)	0.06
Ischemic Stroke	14 (1.2%)	94 (1.1%)	1.27 (0.72-2.24)	0.41	1.56 (0.83-2.94)	0.17
Stent Thrombosis	10 (0.8%)	75 (0.9%)	0.96 (0.48-1.85)	0.90	0.81 (0.41-1.61)	0.55
BARC 2	124 (10.3%)	1132 (13.0%)	0.78 (0.64-0.93)	0.007	0.83 (0.69-1.01)	0.06
BARC 3 or 5	31 (2.6%)	326 (3.7%)	0.68 (0.47-0.98)	0.04	0.80 (0.55-1.17)	0.25
BARC 3	31 (2.6%)	303 (3.5%)	0.73 (0.50-1.06)	0.09	0.85 (0.58-1.24)	0.40

The model was adjusted for age, hypercholesterolemia, prior myocardial infarction, prior CABG, prior stroke, peripheral artery disease, atrial fibrillation, discharge diagnosis, use of diuretics, triple therapy, ACE inhibitors or ATII receptor blockers, proton pump inhibitors, PCI during admission, high bleeding risk, and complex PCI. CV = cardiovascular; MI = myocardial infarction; BARC = Bleeding Academic Research Consortium; HR = hazard ratio; CI = confidence interval. *Hazard ratios are based on an unadjusted model.

Sub-group analyses

Analyses of the primary outcomes were performed in specified subgroups. The results were generally consistent with those in the whole cohort (Supplementary Figure 1). In patients with high bleeding risk (HBR), based on a PRECISE-DAPT of 25 or higher, MACE occurred in 45 of 319 patients (14.1%) in the genotype guided cohort and 499 of 2,606 patients (19.1%) in the standard care cohort ($_{adj}$HR, 0.85; 95% CI, 0.62-1.40; *P* = 0.31, *P*-value for interaction = 0.051). Major or non-major clinically relevant bleeding occurred in 52 of 319 patients (16.3%) in the genotype guided cohort and 572 of 2,606 patients (21.1%) in the standard care cohort ($_{adj}$HR, 0.80; 95% CI, 0.60-1.07; *P* = 0.14).

In patients with complex PCI, MACE occurred in 13 of 172 patients (7.6%) in the genotype guided cohort and 125 of 1,010 patients (12.4%) in the standard care cohort ($_{adj}$HR, 0.77; 95% CI, 0.43-1.40; *P* = 0.39), and major or non-major clinically relevant bleeding occurred in 25 of 172 patients (14.5%) in the genotype guided cohort and 178 of 1,010 patients (17.6%) the standard care cohort ($_{adj}$HR, 0.99; 95% CI, 0.64-1.53; *P* = 0.97).

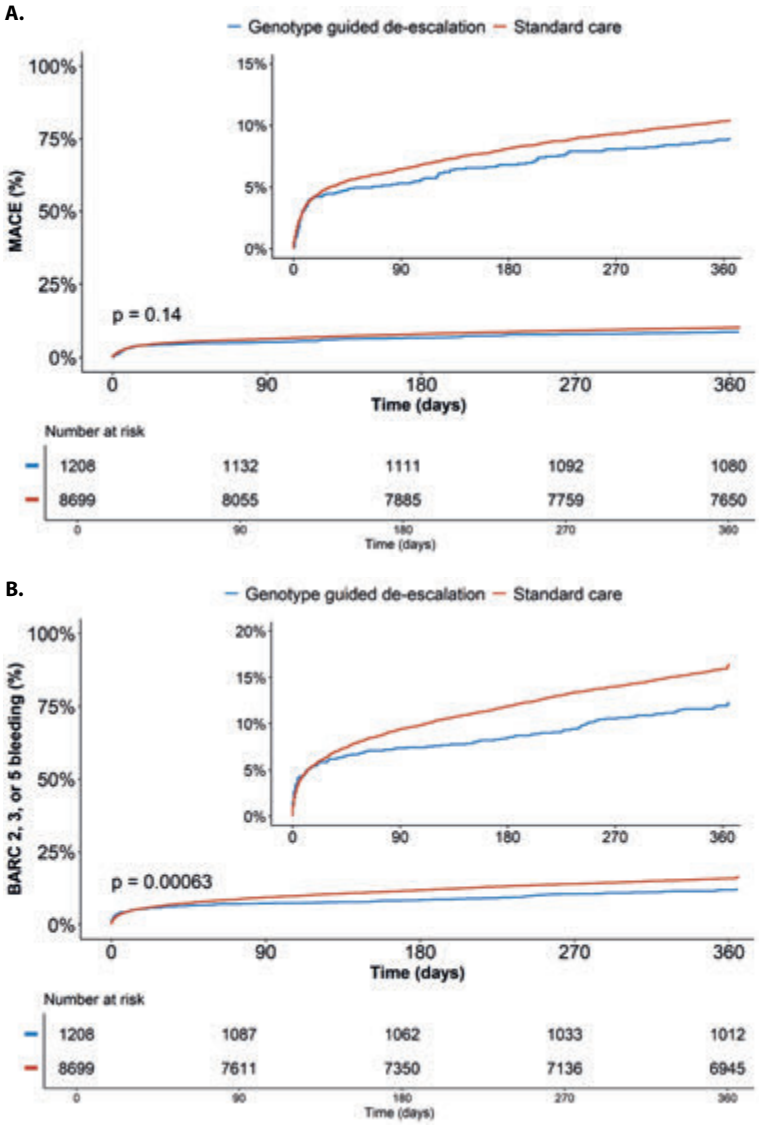

Figure 2. Kaplan-Meier curves for cumulative incidence of (A) the primary ischemic endpoint (cardiovascular mortality, myocardial infarction, or stroke), showing similar event rates between the genotype-guided cohort (blue) and standard care cohort (red), and (B) the primary bleeding endpoint (BARC 2, 3, or 5 bleeding), illustrating lower bleeding rates in the genotype-guided cohort (blue) with increasing divergence over time compared to standard care (red).

Sensitivity analyses

After propensity score matching, 1,207 genotype-guided patients were matched to 3,441 standard care patients, with successful matching confirmed by standardized mean differences below 0.10 (**Supplementary Appendix Table 2**). Results were consistent with those in the overall cohort (**Supplementary Appendix Table 3** and **Supplementary Figure 2**), showing a significant reduction in major or non-major clinically relevant bleeding (12.0% in the genotype guided cohort vs. 16.6% in the standard care cohort, $_{adj}$HR, 0.73; 95% CI, 0.61-0.87, $P = 0.0006$) and comparable event rates for MACE (8.9% in the genotype guided cohort vs. 8.6% in the standard care cohort, $_{adj}$HR, 1.04; 95% CI, 0.83-1.30, $P = 0.74$)

Sensitivity analyses excluding patients on oral anticoagulants (analysing 1,028 genotype-guided vs. 7,276 standard care), those not following the recommended P2Y12 inhibitor (analysing 988 genotype-guided vs 8,699 standard care) and only including patients undergoing PCI (analysing 905 genotype-guided vs. 5,991 standard care), all showed consistent results (**Supplementary Appendix Table 4, 5** and **6**).

DISCUSSION

This study assessed the clinical impact of the implementation of a *CYP2C19* genotype-guided de-escalation strategy in routine practice. At 12 months, among patients admitted with ACS and receiving antiplatelet therapy, the genotype-guided approach significantly reduced major and non-major clinically relevant bleeding compared to standard care. There was no evidence of an increase in the rate of the combined ischemic endpoint, a composite of cardiovascular death, MI, or stroke, between the genotype-guided and standard care cohorts. In addition, the genotype-guided approach significantly reduced P2Y12 inhibitor treatment alterations and dyspnea-related discontinuations compared to standard care, indicating improved adherence and a lower burden of adverse effects. These findings build on our previously published analysis, which evaluated a smaller ACS population lacking power to detect clinical differences.[16] In contrast, the current analysis provides sufficient power to confirm the safety and effectiveness of genotype-guided therapy in routine practice.

The challenge of antiplatelet therapy in patients with ACS lies in achieving an optimal balance between effective platelet inhibition and the minimization of bleeding risk, without compromising protection against ischemic events. Common strategies aiming to achieve this, include shortening the duration of DAPT by discontinuing either aspirin or the P2Y12 inhibitor and continuing single antiplatelet therapy, or de-escalation, whether guided or unguided.[17] In genotype-guided de-escalation, genetic testing is used to identify a patient's *CYP2C19* metabolizer status, allowing clinicians to safely switch normal metabolizers from a more potent P2Y12 inhibitor, such as ticagrelor or prasugrel, to clopidogrel. However, determining the optimal approach between a genotype-guided de-escalation strategy and P2Y12 monotherapy following a short period of DAPT is challenging, as no direct comparisons have been made in clinical trials. The current ESC ACS guidelines provide a Class IIb, Level of Evidence A

recommendation for P2Y12 receptor inhibitor de-escalation as an alternative strategy to reduce bleeding risk.[2] However, specific recommendations whether de-escalation should be guided or unguided are lacking. Interestingly, the guidelines advise against de-escalation of antiplatelet therapy within the first 30 days after an ACS event but do not cite supporting studies for this recommendation. While very early discontinuation of DAPT (within thirty days after ACS or PCI) has been linked to increased ischemic outcomes, none of the early de-escalation strategies, whether guided or unguided, have demonstrated such risks to date.[9,18–20] Our findings align with those of the POPular Genetics trial, highlighting the safety of early de-escalation (preferably within <48 hours) upon admission, demonstrating no observed increase in ischemic events in the genotype-guided cohort. Additionally, Kaplan-Meier curve analysis of our trial reveals no elevated risk during the first 30 days of follow-up. While subgroup analyses consistently showed a reduction in bleeding across all subgroups, the borderline non-significant P-value for interaction suggests a potential modification of the treatment effect by HBR status. However, MACE event rates were similar in non-HBR patients (7.0% vs. 6.5%), with confidence intervals crossing one. Notably, the non-HBR subgroup included a large number of patients (888 in the genotype-guided cohort vs. 6,093 in the standard care cohort), underscoring the statistical power to detect meaningful differences. Based on these results, we conclude that a genotype-guided de-escalation strategy during initial hospital admission is safe for all patients.

While this study represents the largest real-world implementation of a *CYP2C19*-guided de-escalation strategy, other large-scale initiatives have successfully integrated *CYP2C19* genotype-guided antiplatelet therapy into clinical practice. These initiatives often employ escalation strategies, where clopidogrel is used by default, and patients with *CYP2C19* LOF alleles are escalated to ticagrelor or prasugrel. For example, a study by the IGNITE Network, which included an cohort of 3,342 patients across nine United States centres, reported an increased risk for adverse cardiovascular events—including death, MI, ischemic stroke, stent thrombosis, or hospitalization for unstable angina—with clopidogrel in patients carrying a LOF allele.[21] Importantly, no difference in cardiovascular risk was observed between clopidogrel and alternative therapies in patients without a LOF allele, aligning with the results from our study and that of the POPular Genetics.[22] This data from the IGNITE network demonstrate that escalation strategies can improve ischemic outcomes without increasing bleeding events, in line with the results of the TAILOR-PCI trial.[23] Although some regard TAILOR-PCI as a negative study, it provided compelling evidence that escalation strategies can optimize patient outcomes, particularly during the first months post-PCI.[23,24] Additionally, a pre-specified analysis of cumulative ischemic events further supports the benefits of this strategy.[25]

While escalation strategies may reduce ischemic events, their cost-effectiveness is limited, as the default choice, clopidogrel, is significantly more affordable than ticagrelor. In contrast, the cost-saving potential of a de-escalation strategy is more substantial, as instead of treating every patient with ticagrelor/prasugrel as the default, around 70% can be de-escalated to the cheaper clopidogrel.[8,26] Nonetheless, the broader implementation of this strategy still faces notable challenges. Currently, hospitals bear the cost of genetic testing, while insurers benefit from reduced medication expenses. This imbalance

limits adoption, as hospitals are unlikely to fund testing independently. National reimbursement of genetic testing could address this issue, enabling broader implementation and amplifying the cost-saving potential through economies of scale. Further integration requires addressing logistical barriers such as accessibility and turnaround time. Collaborative efforts between researchers, clinicians, and policymakers are critical to ensure equitable access.

A key challenge in optimizing antiplatelet therapy is that variability in response to clopidogrel extends beyond genetic factors. The ABCD-GENE score, which incorporates age, BMI, diabetes, kidney function, and *CYP2C19* genotype, provides a comprehensive tool for stratifying patients at risk for high platelet reactivity (HPR) and adverse ischemic outcomes.[27] Patients with an ABCD-GENE score ≥10 showed trends toward improved outcomes with alternative P2Y12 inhibitors compared to clopidogrel, particularly among carriers of *CYP2C19* LOF alleles.[28] This highlights the necessity for tailored approaches, balancing patient-specific ischemic and bleeding risks. Integrating genetic results within the broader clinical context, including procedural complexity and patient comorbidities, will enhance the precision of antiplatelet therapy strategies.

A key strength of our study is the demonstration of comparable outcomes for both ischemic and bleeding events to those observed in the POPular Genetics trial. The hazard ratios for BARC 2, 3, or 5 bleeding closely align with our adjusted and unadjusted models. Notably, the sensitivity analysis in PCI patients only confirmed consistent bleeding reduction, reinforcing the efficacy of a genotype-guided strategy in ACS patients undergoing PCI. Furthermore, our findings underscore the importance of implementation studies, as randomized trial populations are typically younger and at lower risk. Our study enrolled an older population (66 vs. 62 years) with higher mortality (5.5% vs. 1.5%), better reflecting real-world conditions. Our results further demonstrate that de-escalation is safe and effective in a broad ACS population, unlike the POPular Genetics trial, which focused solely on STEMI patients. An important observation is that approximately 29% of patients in the standard care group received clopidogrel, nearly half of whom were also treated with oral anticoagulation, compared with only 7% in the POPular Genetics trial. This high clopidogrel use would theoretically attenuate bleeding differences between groups, yet we still observed a bleeding reduction comparable to that seen in POPular Genetics. This finding likely reflects the inherent limitations of the observational study design but also supports the robustness of the bleeding benefit associated with genotype-guided de-escalation.

Limitations

We recognize several limitations of our study. Our study's real-world design allowed physicians to decide whether to follow genotype recommendations, introducing variability in adherence to the strategy. Also, due to the non-randomized nature of the study, this resulted in baseline differences between both cohorts that could potentially confound the results. While adjustment methods, including propensity score matching, successfully balanced both cohorts, residual confounding related to the selection of antiplatelet therapy cannot be entirely ruled out. The observed differences in hazard ratios before

and after adjustment indicate that part of the observed association was influenced by confounding. However, after adjusting for confounders, our primary findings remained consistent. While the strategy is implemented in multiple hospitals, the majority of most patients in the genotype guided group were enrolled in one site. Patients in the other sites were more often later de-escalated due to offsite genotyping. While most patients still were de-escalated within three weeks, it may have affected ischemic and bleeding outcomes during this period. Nevertheless, it is unlikely that this has affected the overall results of the study since offsite genotyping was only used in a minority of the patients. Lastly, a considerable proportion of patients were treated with oral anticoagulation, reflecting the broader ACS population. Although triple therapy use was higher in the standard care cohort, potentially influencing bleeding risk, we adjusted for this in our models. Moreover, sensitivity analyses excluding patients on oral anticoagulation confirmed consistent results.

CONCLUSION

In conclusion, in patients with ACS receiving antiplatelet therapy, implementing of a *CYP2C19* genotype-guided de-escalation strategy in clinical practice significantly reduced major and non-major clinically relevant bleeding compared to standard care at 12 months, without an increase in ischemic events, including cardiovascular death, MI, or stroke.

REFERENCES

1. Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, et al. European Society of Cardiology: the 2023 Atlas of Cardiovascular Disease Statistics. Eur Heart J [Internet]. 2024 Oct 7;45(38):4019–62. Available from: https://academic.oup.com/eurheartj/article/45/38/4019/7741182
2. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023 Aug;44(38):3720–826.
3. Marquis-Gravel G, Dalgaard F, Jones AD, Lokhnygina Y, James SK, Harrington RA, et al. Post-Discharge Bleeding and Mortality Following Acute Coronary Syndromes With or Without PCI. J Am Coll Cardiol [Internet]. 2020 Jul;76(2):162–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109720353262
4. Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van De Werf F, et al. Validation of BARC Bleeding Criteria in Patients with Acute Coronary Syndromes the TRACER Trial. J Am Coll Cardiol. 2016;67(18):2135–44.
5. Capodanno D, Mehran R, Krucoff MW, Baber U, Bhatt DL, Capranzano P, et al. Defining Strategies of Modulation of Antiplatelet Therapy in Patients With Coronary Artery Disease: A Consensus Document from the Academic Research Consortium. Circulation. 2023 Jun;147(25):1933–44.
6. Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, et al. Cytochrome P-450 Polymorphisms and Response to Clopidogrel. N Engl J Med. 2009;360(4):354–62.
7. Nguyen AB, Cavallari LH, Rossi JS, Stouffer GA, Lee CR. Evaluation of race and ethnicity disparities in outcome studies of CYP2C19 genotype-guided antiplatelet therapy. Front Cardiovasc Med [Internet]. 2022 Aug 23;9. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2022.991646/full
8. Claassens DMF, van Dorst PWM, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, et al. Cost Effectiveness of a CYP2C19 Genotype-Guided Strategy in Patients with Acute Myocardial Infarction: Results from the POPular Genetics Trial. Am J Cardiovasc Drugs. 2022;22(2):195–206.
9. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Van't Hof AWJ, Van Der Harst P, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med. 2019;381(17):1621–31.
10. Pereira NL, Cresci S, Angiolillo DJ, Batchelor W, Capers Q, Cavallari LH, et al. CYP2C19 Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association. Circulation [Internet]. 2024 Aug 6;150(6):e129–50. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001257
11. Angiolillo DJ, Galli M, Alexopoulos D, Aradi D, Bhatt DL, Bonello L, et al. International Consensus Statement on Platelet Function and Genetic Testing in Percutaneous Coronary Intervention. JACC Cardiovasc Interv [Internet]. 2024 Nov;17(22):2639–63. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1936879824011142
12. van den Broek WWA, Ingraham BS, Pereira NL, Lee CR, Cavallari LH, Swen JJ, et al. Genotype-Guided Antiplatelet Therapy. J Am Coll Cardiol [Internet]. 2024 Sep;84(12):1107–18. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0735109724078938
13. Chan Pin Yin DRPPPP, Vos GJAJA, van der Sangen NMRR, Walhout R, Tjon Joe Gin RM, Nicastia DM, et al. Rationale and Design of the Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) Registry: Towards "Personalized Medicine" in Daily Clinical Practice. J Clin Med [Internet]. 2020 Sep 30;9(10):3173. Available from: https://www.mdpi.com/2077-0383/9/10/3173

14. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2016 Jan;37(3):267–315.
15. Azzahhafi J, Broek WWA van den, Chan Pin Yin DRPP, Harmsze AM, van Schaik RHN, ten Berg JM. The Clinical Implementation of CYP2C19 Genotyping in Patients with an Acute Coronary Syndrome: Insights From the FORCE-ACS Registry. J Cardiovasc Pharmacol Ther [Internet]. 2023 Jan 29;28. Available from: https://journals.sagepub.com/doi/10.1177/10742484231210704
16. Azzahhafi J, van den Broek WWA, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, Bofarid S, et al. Real-World Implementation of a Genotype-Guided P2Y12 Inhibitor De-Escalation Strategy in Acute Coronary Syndrome Patients. JACC Cardiovasc Interv [Internet]. 2024 Sep;17(17):1996–2007. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1936879824009130
17. Laudani C, Greco A, Occhipinti G, Ingala S, Calderone D, Scalia L, et al. Short Duration of DAPT Versus De-Escalation After Percutaneous Coronary Intervention for Acute Coronary Syndromes. JACC Cardiovasc Interv. 2022 Feb;15(3):268–77.
18. Natsuaki M, Watanabe H, Morimoto T, Yamamoto K, Obayashi Y, Nishikawa R, et al. An Aspirin-Free Versus Dual Antiplatelet Strategy for Coronary Stenting: STOPDAPT-3 Randomized Trial. Circulation. 2024 Feb;149(8):585–600.
19. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet. 2017;390(10104):1747–57.
20. Watanabe H, Morimoto T, Natsuaki M, Yamamoto K, Obayashi Y, Ogita M, et al. Comparison of Clopidogrel Monotherapy After 1 to 2 Months of Dual Antiplatelet Therapy With 12 Months of Dual Antiplatelet Therapy in Patients With Acute Coronary Syndrome. JAMA Cardiol [Internet]. 2022 Apr 1;7(4):407. Available from: https://jamanetwork.com/journals/jamacardiology/fullarticle/2789701
21. Beitelshees AL, Thomas CD, Empey PE, Stouffer GA, Angiolillo DJ, Franchi F, et al. CYP2C19 Genotype-Guided Antiplatelet Therapy After Percutaneous Coronary Intervention in Diverse Clinical Settings. J Am Heart Assoc [Internet]. 2022 Feb 15;11(4). Available from: https://www.ahajournals.org/doi/10.1161/JAHA.121.024159
22. Claassens DMF, Bergmeijer TO, Vos GJA, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to CYP2C19 Genotype. Circ Cardiovasc Interv [Internet]. 2021 Apr;14(4). Available from: https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.120.009434
23. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes after Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA- J Am Med Assoc. 2020;324(8):761–71.
24. Parcha V, Heindl BF, Li P, Kalra R, Limdi NA, Pereira NL, et al. Genotype-Guided P2Y 12 Inhibitor Therapy After Percutaneous Coronary Intervention: A Bayesian Analysis. Circ Genomic Precis Med [Internet]. 2021 Dec;14(6). Available from: https://www.ahajournals.org/doi/10.1161/CIRCGEN.121.003353
25. Ingraham BS, Farkouh ME, Lennon RJ, So D, Goodman SG, Geller N, et al. Genetic-Guided Oral P2Y12 Inhibitor Selection and Cumulative Ischemic Events After Percutaneous Coronary Intervention. JACC Cardiovasc

Interv [Internet]. 2023 Apr;16(7):816–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1936879823004053

26. van den Broek WWA, Azzahhafi J, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, Dijksman LM, et al. Cost-effectiveness of Implementing a Genotype-Guided De-Escalation Strategy in Patients with Acute Coronary Syndrome. Eur Hear J - Cardiovasc Pharmacother [Internet]. 2024 Nov 13; Available from: https://academic.oup.com/ehjcvp/advance-article/doi/10.1093/ehjcvp/pvae087/7899955
27. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, ten Berg JM, et al. Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC Cardiovasc Interv. 2020;13(5):606–17.
28. Thomas CD, Franchi F, Rossi JS, Keeley EC, Anderson RD, Beitelshees AL, et al. Effectiveness of Clopidogrel vs Alternative P2Y12 Inhibitors Based on the ABCD-GENE Score. J Am Coll Cardiol [Internet]. 2024;83(15):1370–81. Available from: https://www.jacc.org/doi/abs/10.1016/j.jacc.2024.02.015

SUPPLEMENTARY DATA

Please scan the QR code for the supplementary data.

General Discussion and Summary

GENERAL DISCUSSION

Antithrombotic therapy is a rapidly evolving field, continuously shaped by emerging evidence and shifting paradigms. In the 1980s, aspirin became the cornerstone of treatment for acute coronary syndrome (ACS), and by the mid-1990s, the addition of a P2Y12-receptor inhibitor marked the beginning of the dual antiplatelet therapy (DAPT) era.[1,2] The safer alternative clopidogrel, introduced shortly thereafter, became widely adopted and was incorporated into the guidelines nearly a decade later. In 2010, the U.S. Food and Drug Administration (FDA) issued a black box warning on clopidogrel, cautioning that patients carrying a *CYP2C19 *2* or **3* loss-of-function allele may not derive full therapeutic benefit.[3] Despite this warning, and the growing body of evidence linking impaired metabolism to adverse cardiovascular outcomes, clopidogrel remained on the most widely prescribed P2Y12-receptor inhibitors, with routine genetic testing rarely implemented in clinical practice. This misalignment underscores the persistence of a "one-size-fits-all" approach, overlooking the fact that clopidogrel—a prodrug requiring CYP2C19-mediated activation—may be significantly less effective in certain individuals.

Today, DAPT with aspirin and a potent P2Y12-receptor inhibitor (ticagrelor or prasugrel) remains the standard of care for ACS patients undergoing percutaneous coronary intervention (PCI). However, this standardized strategy overlooks important interpatient variability—differences in genetic profile, comorbidities, procedural characteristics, and bleeding risk—that can significantly affect treatment response. Growing evidence suggests that personalizing antithrombotic therapy may offer improved clinical outcomes by optimizing the balance between ischemic protection and bleeding risk.[4,5] This thesis addresses the challenges of optimizing antithrombotic strategies through a three-part approach: first, by establishing the rationale for personalized antithrombotic therapy and reviewing current evidence and strategies (**Part I**); second, by evaluating the clinical impact of genetic polymorphisms on cardiovascular outcomes and treatment response using data from multiple large-scale clinical trials as well as smaller, mechanistic studies involving laboratory-based testing (**Part II**); and third, by examining the real-world implementation, clinical effectiveness, and cost-efficiency of a genotype-guided de-escalation strategy in patients with ACS (**Part III**).

Part I outlines the current landscape of personalized antiplatelet therapy, introducing the key concepts underlying the personalization of antithrombotic treatment. **Chapter 2** explores the current state of personalized antithrombotic therapy by weighing the advantages and limitations of genotype-guided strategies and approaches that assess interindividual variability in treatment response. It provides an overview of available monitoring methods, including coagulation assays and platelet function tests, aimed at identifying patients with high on-treatment platelet reactivity. Although these tools offer valuable insights, their routine clinical use remains limited, likely reflecting the lack of robust clinical evidence for improved outcomes.[6] The chapter emphasizes that personalization can be particularly beneficial in selected clinical scenarios—such as escalation in patients at high thrombotic risk (e.g. left main stenting, complex PCI, prior stent thrombosis), or de-escalation in those with elevated bleeding risk. As evidence supporting platelet function and genotype-guided strategies continues to grow, and

point-of-care assays become more accessible, personalized antithrombotic therapy may eventually evolve from an experimental concept to a standard component of care in patients undergoing PCI.

Chapter 3 provides a more detailed overview of genotype-guided antiplatelet therapy, emphasizing how genetic variation contributes to interindividual differences in treatment response. The review focuses primarily on *CYP2C19* polymorphisms, which significantly affect the metabolism and efficacy of clopidogrel. In patients carrying a loss-of-function allele, an escalation strategy—substituting clopidogrel with a more potent agent—may reduce the risk of recurrent ischemic events. This approach was evaluated in the TAILOR-PCI trial, which suggested a potential clinical benefit of genotype-guided escalation, though it did not reach statistical significance, partly due to lower-than-expected event rates.[7] Conversely, in patients treated with ticagrelor or prasugrel, a de-escalation strategy based on genotype can help minimize bleeding risk without compromising efficacy. The POPular Genetics trial demonstrated that such a genotype-guided de-escalation approach safely reduced bleeding events while enabling broader use of the less costly clopidogrel.[8] Although these personalized strategies show promise in optimizing the balance between ischemic protection and bleeding risk, widespread implementation remains limited due to logistical and economic barriers. However, with ongoing technological progress and increasing clinical evidence, broader uptake of genotype-guided therapy may soon become feasible in routine practice.

Building on this, **Chapter 4** discusses the potential benefits and limitations of genotype-guided antithrombotic therapy specifically in elderly patients with ACS, a population that poses unique clinical challenges due to increased bleeding risk and often under-treatment. While earlier analyses suggest clopidogrel may be a safe alternative to ticagrelor in elderly non-carriers of *CYP2C19* loss-of-function alleles, the evidence remains limited and underpowered to draw firm conclusions.[9] As such, although genotyping may support treatment de-escalation in select elderly patients, further dedicated studies are needed before clear clinical recommendations can be made for this vulnerable group.

Part II presents studies evaluating the impact of different genetic polymorphisms on clinical outcomes in patients with ACS. In **Chapter 5,** the clinical relevance of *CYP2C9* loss-of-function polymorphisms in patients with ACS treated with clopidogrel is examined. Using combined data from the POPular Genetics and POPular AGE trials, the study compared thrombotic and bleeding outcomes in carriers versus non-carriers of *CYP2C9*2* or **3* alleles.[8,10] The results showed no significant differences in clinical outcomes between the groups, suggesting that *CYP2C9* genotype does not meaningfully affect the efficacy or safety of clopidogrel in this context. Given the small number of poor metabolizers, no conclusions could be drawn for homozygous carriers, but the overall findings do not support routine *CYP2C9* testing in guiding antiplatelet therapy.

Chapter 6 investigates whether genetic variants in *CYP3A4* and *CYP3A5* affect clinical outcomes in STEMI patients treated with ticagrelor. Using data from the POPular Genetics trial, the study analysed the association of *CYP3A4*22* and *CYP3A5* expressor status with thrombotic events, bleeding complications, and ticagrelor-related dyspnoea. No statistically significant differences were observed between genotype groups for thrombotic or bleeding endpoints, nor for the occurrence of dyspnoea. These findings suggest that, unlike *CYP2C19* in clopidogrel-treated patients, *CYP3A4* and *CYP3A5* polymorphisms do not

appear to have a clinically relevant impact on the efficacy or safety of ticagrelor. While pharmacogenetic testing has shown value in guiding clopidogrel use, its role in patients treated with ticagrelor remains limited based on current evidence.

Shifting focus to treatment strategy, **Chapter 7** presents an individual patient data meta-analysis evaluating the efficacy and safety of de-escalation of dual antiplatelet therapy (DAPT) in patients with ACS undergoing PCI. The analysis pooled data from four major randomized controlled trials—including TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS, and TALOS-AMI—comprising over 10,000 patients.[8,11–13] De-escalation strategies, which involved switching from a potent P2Y12-receptor inhibitor to a less potent agent, were associated with a significant reduction in both ischemic events (2.3% vs. 3.0%) and bleeding events (6.5% vs. 9.1%) at one year compared to standard DAPT. While major bleeding and all-cause mortality did not differ significantly, the overall safety profile favoured de-escalation. Interestingly, unguided de-escalation was more effective in reducing bleeding than guided strategies, with no compromise in ischemic protection. These findings support de-escalation as a safe and effective approach for balancing bleeding and thrombotic risk in ACS patients post-PCI.

Continuing the exploration of genotype-guided strategies, **Chapter 8** presents an individual participant data meta-analysis comparing *CYP2C19*-guided antiplatelet therapy to conventional treatment in ACS patients undergoing PCI. Drawing on data from two large randomized trials (TAILOR-PCI and POPular Genetics), the study included over 6,700 patients to evaluate the effects of genotype-guided escalation and de-escalation on clinical outcomes.[7,8] While overall MACE and bleeding rates were not significantly different between guided and conventional groups, genotype-guided therapy reduced myocardial infarction and net adverse cardiovascular events (NACE). Importantly, guided de-escalation significantly reduced bleeding and NACE without compromising ischemic protection, particularly in the early post-PCI period. In contrast, guided escalation showed no added benefit compared to standard care. These findings highlight the potential clinical value of genotype-guided de-escalation as a safer and more effective strategy in selected patients.

Shifting to a precision-medicine approach in complex patient populations, **Chapter 9** examines platelet reactivity in patients undergoing PCI who are treated with a novel oral anticoagulant (NOAC) and have a high ABCD-GENE score, indicating impaired clopidogrel response.[14] In this randomized pharmacodynamic study (SWAP-AC-2), patients with a ABCD-GENE score ≥10 were allocated to clopidogrel- or low-dose ticagrelor-based dual antithrombotic therapy (DAT). Low-dose ticagrelor significantly reduced platelet reactivity at both trough and peak levels compared to clopidogrel, as measured by multiple platelet function assays. These effects were observed without major changes in other thrombotic pathways. The study suggests that ticagrelor may offer superior platelet inhibition in NOAC-treated patients with high genetic risk, although clinical outcomes were not assessed. Further randomized trials are warranted to determine whether tailoring DAT using the ABCD-GENE score improves outcomes in this complex and high-risk group.

The previous chapters collectively demonstrate the potential of pharmacogenetic insights and de-escalation strategies to refine antiplatelet therapy and improve patient outcomes across diverse

clinical contexts. While these data provide a strong rationale for personalized treatment, translating such strategies into daily practice remains a key challenge. **Part III** of this thesis focuses on the real-world implementation of genotype-guided antiplatelet therapy by examining its clinical effectiveness, feasibility, and economic implications in contemporary ACS care.

Chapter 10 evaluates the real-world feasibility of implementing *CYP2C19* genotype-guided P2Y12 inhibitor de-escalation. Among 738 genotyped patients treated with ticagrelor, over 80% were eligible for de-escalation to clopidogrel, which was carried out rapidly—often within 24 hours—particularly when point-of-care (POC) testing was used. POC genotyping significantly reduced turnaround time compared to lab-based methods and facilitated earlier treatment adaptation. Importantly, physicians showed high adherence to genotype results, and the strategy resulted in substantial medication cost savings. These findings demonstrate that early genotype-guided de-escalation is operationally feasible and economically favourable, offering a viable strategy for routine clinical use.

Extending these findings, **Chapter 11** compares clinical outcomes of genotype-guided de-escalation with standard DAPT in a real-world cohort from the FORCE-ACS registry.[15] Among 5,321 ACS patients, those undergoing genotyping and de-escalation (N = 406) experienced significantly lower bleeding rates than the standard therapy group, without an increase in ischemic events. While the study was not powered to confirm non-inferiority for thrombotic outcomes, it supports the safety and potential benefit of genotype-guided therapy in clinical practice. These results align with previous trial data and confirm the feasibility of this approach in a broad ACS population, laying the groundwork for future large-scale implementation.

Building on the clinical findings, **Chapter 12** assesses the cost-effectiveness of a genotype-guided de-escalation strategy compared to standard DAPT from the perspective of the Dutch healthcare system. Using a two-part decision-analytic model to simulate lifelong costs and effects, the analysis showed that genotype-guided therapy not only improved quality-adjusted life years but also reduced lifetime healthcare costs. The strategy remained cost-effective under a wide range of sensitivity scenarios, including when drug prices were equalized. These results reinforce the economic and clinical value of personalized antiplatelet therapy and strengthen the case for its broader adoption in ACS care.

Chapter 13 presents the results of a large, prospective, multicentre implementation study evaluating the clinical safety and effectiveness of routine *CYP2C19* genotype-guided antiplatelet therapy in patients with ACS. Among nearly 10,000 patients, those in the genotype-guided cohort experienced significantly fewer major or clinically relevant bleeding events at one year compared to standard care, while rates of MACE were similar between groups. The findings confirm that genotype-guided de-escalation—switching non-carriers of *CYP2C19* loss-of-function alleles from potent P2Y12-receptor inhibitors to clopidogrel—is not only safe but also clinically beneficial in reducing bleeding risk. These results provide compelling real-world evidence that personalized antiplatelet therapy can be effectively and safely implemented in routine ACS care.

FUTURE PERSPECTIVE

Achieving widespread implementation of innovative antithrombotic strategies is essential for improving future patient outcomes. The field of antithrombotic therapy for coronary artery disease is expansive and critically significant, given the substantial number of patients requiring treatment. This prevalence drives extensive research, as summarized in Table 1. A limitation of existing and ongoing studies is that most new strategies are typically compared to the standard DAPT within different populations, making it difficult to directly compare the different strategies with one another. This complexity presents challenges for cardiologists attempting to navigate the multitude of new approaches and for guideline developers striving to establish clear recommendations. Consequently, the general adoption of novel strategies remains low, often hindered by variations in healthcare systems, resource availability, and reimbursement policies across countries. Despite these differences, all strategies share a common goal: improving antithrombotic therapy by optimizing the balance between ischemic and bleeding risk. Most strategies can be divided into two groups: de-escalation or shorter DAPT duration strategies. The most optimal treatment may ultimately combine elements of both.

There is broad consensus that using potent DAPT for 12 months should no longer be the default strategy.[16] Interestingly, despite this agreement, many hospitals still adhere to a 12-month duration. This is notable as the landmark trials that informed our understanding of DAPT primarily investigated its composition, not its duration.[17–19] Nonetheless, previous guidelines adopted 12 months as the standard timeframe. An approach that still continues today, as reflected by the current ESC guideline, which assigns a Class I recommendation to 12 months of DAPT following ACS.[20] While a 12-month duration may appear convenient and logical, it is not necessarily optimal for all patients. Numerous studies consistently show that shorter durations of DAPT or de-escalation to less potent strategies reduce bleeding risks without sacrificing ischemic protection.[21–23] While cumulative evidence supports reducing DAPT duration, it is important to consider that most randomized controlled trials have been conducted in selected populations, often including lower-risk patients compared to routine clinical practice. Moreover, some studies have shown that prolonged DAPT can provide additional protection in higher-risk subgroups.[24,25] These findings emphasize that the key to optimizing DAPT lies not in a uniform strategy, but in tailoring therapy to the individual. Personalization involves two critical components: (i) identifying patients who are most likely to benefit from a specific DAPT duration and (ii) selecting the most appropriate P2Y12-receptor inhibitor based on individual risk profiles.

Patient selection involves distinguishing between those at high bleeding risk (HBR) and those at high ischemic risk without HBR. Patients with HBR derive greater benefit from a less intensive antithrombotic approach. Robust evidence supports the safety of an abbreviated 1–3-month course of DAPT followed by P2Y12-receptor inhibitor monotherapy, significantly reducing bleeding risk.[26,27] Conversely, prolonged DAPT (≥12 months) is most beneficial for patients at high ischemic risk (e.g., those undergoing complex PCI) who do not exhibit features of HBR.[24] The selection of the optimal P2Y12-receptor inhibitor can be further refined using genetic or platelet function testing, as explained in **Chapter 2**, allowing for a more tailored approach to antiplatelet therapy. Among these strategies, genetic testing appears most

promising based on clinical research and the findings presented in this thesis. As shown in **Chapter 10**, a genotype-guided de-escalation strategy was feasible, with rapid implementation and high physician adherence to genotype results. Additionally, **Chapter 11** and **Chapter 13** showed that this strategy was associated with a reduction in bleeding events without increasing ischemic events, with **Chapter 12** providing complementary evidence of its cost-effectiveness.

In the Netherlands, all antithrombotic drugs are reimbursed, which creates a favourable environment for cost-effective strategies such as genotype-guided de-escalation strategy. Despite evidence supporting the benefit of the genetic testing in this context, implementation is not straightforward. Regional initiatives require adjustments to the Diagnosis Treatment Combination ("DBC" in Dutch) system, which is subject to strict maximum capping. This limitation makes it challenging to increase the DBC rates, creating a significant barrier to broader adoption of innovative strategies.

A specific challenge within this case lies in the distribution of costs and benefits. The cost of genetic testing, in the context of the antiplatelet de-escalation strategy, is borne by hospitals, specifically the cardiology departments or the central labs, while the primary savings, a reduction in medication costs, solely benefit the health insurers. This misalignment limits the further implementation of these strategies, as hospitals are unlikely to fund testing independently. National reimbursement of genetic tests would resolve this issue and benefit insurers by enabling broader implementation of these cost-saving strategies. Moreover, a nationwide approach would actually amplify these benefits, as scalability of genetic testing could drive efficiency, reducing testing costs over time, increasing overall savings for insurers.

Efforts are already undertaken to engage with insurers, leveraging the findings presented in this thesis and future study results to advocate for national reimbursement of genetic tests. Such a development would facilitate widespread implementation of genotype-guided de-escalation strategies, ultimately advancing patient care and optimizing resource allocation.

Additionally, efforts should be made to streamline the implementation of genetic testing within healthcare systems. This includes addressing logistical barriers, such as cost, turnaround time, and accessibility, as well as educating healthcare providers on the interpretation and application of genetic data. For example, not every hospital needs to have an on-site point-of-care testing system. Depending on resources and patient volume, hospitals could collaborate with off-site genetic testing laboratories. Although the turnaround time may be longer, patients could still be de-escalated at their next visit, preferably within one month, which would maintain benefits in terms of reducing bleeding risks and improving cost-effectiveness. Collaboration between researchers, clinicians, and policymakers will be essential to overcome these challenges and ensure equitable access to genotype-guided therapies.

In the broader context, exploring the role of pharmacogenomics beyond antiplatelet therapy could open new opportunities for personalized medicine in cardiovascular care. For example, genetic testing may guide the use of other medications commonly prescribed for CAD, such as beta-blockers or lipid-lowering agents. As briefly covered in **Chapter 3**, recent years have provided convincing evidence

supporting the benefits of pharmacogenetic panel testing. The results of the PREPARE (PREemptive Pharmacogenomic testing for preventing Adverse drug Reactions) study implemented a 12-gene pharmacogenetic panel (including *CYP2C19*) combined with guideline recommendations across seven European countries, including 6,944 patients who initiated treatment with one of 39 drugs with established pharmacogenetic recommendations.[28] Genotype-guided prescribing reduced clinically relevant adverse drug reactions from 29% in the usual care group to 21% in the genotype-guided group (OR 0.70 [95% CI 0.61–0.79]; $p < 0.0001$). These results highlight the feasibility and clinical impact of panel testing across diverse healthcare systems.

Studies have repeatedly shown that 95–99% of the population carries one or more genetic variants requiring adjustments in drug choice or dosage, reinforcing the need for broader genetic testing.[29,30] Combined with advances in genetic testing platforms that can analyse millions of markers simultaneously, these developments make a compelling case for transitioning from single-gene testing to a panel-based approach. The integration of digital health tools, such as electronic decision support systems, could streamline the incorporation of genetic information into clinical decision-making.

Taken together, these findings advocate for a wider use of pharmacogenetic testing in the future, transitioning from single-gene to panel-based pharmacogenetic testing. However, key questions remain regarding which patient groups derive the greatest benefit and the overall cost-effectiveness of such an approach, warranting further investigation.

While the genotype de-escalation strategy primarily targets ACS patients, genetic testing also holds significant potential for chronic coronary syndrome (CCS) patients, a group in which genetic strategies remain underexplored. The ongoing Pharmacodynamic Outcomes in CCS Patients Treated With an Individualized Treatment Strategy (POPular STRATEGY PD, NCT05773989), initiated at St. Antonius Hospital, aims to optimize antithrombotic therapy in patients following elective PCI. This trial compares a genotype-guided P2Y12 monotherapy strategy (clopidogrel for noncarriers and ticagrelor or prasugrel for carriers) with standard DAPT, seeking to reduce bleeding risk and pill burden while maintaining therapeutic efficacy.

Another important area for exploration is the impact of genotype-guided therapy on patient-reported outcomes measures, such as quality of life and treatment satisfaction. Including these metrics in future studies will offer a more comprehensive understanding of the benefits and challenges associated with personalized treatment approaches. This is currently being investigated using data from the FORCE-ACS Registry, as part of a recently funded ZonMw initiative (Project ID: 10140312310016, Personalized Dual Antiplatelet Therapy and its Impact on Quality of Life in the FORCE-ACS Registry), and aims to enhance understanding of how personalized treatment affects patient-reported outcome measures (PROMs).

In conclusion, the future of antithrombotic therapy lies in personalization, using patient-specific characteristics, such as genetics, to tailor treatment strategies with the aim of improving patient outcomes, minimizing adverse events, and optimizing cost-effectiveness. We are already moving away

from a one-size-fits-all approach, and through continued collaboration across stakeholders, investment in innovations, and a commitment to equitable healthcare delivery, the widespread implementation of personalized antiplatelet therapy can ultimately be realized.

Table 1. Ongoing studies investigating different DAPT strategies

Trial acronym	NCT number	Intervention	Control
ADEN	NCT05577988	Single APT with aspirin in LOF carriers; Single APT with clopidogrel 75mg od in noncarriers	Single APT with ticagrelor 90mg bid or prasugrel 10mg od
Dan-DAPT	NCT05262803	Standard arm: DAPT with ticagrelor 90mg bid/prasugrel 10mg od in LOF carriers, clopidogrel 75mg od in noncarriers (6 months); Short arm: DAPT with ticagrelor 90mg bid/prasugrel 10mg od in LOF carriers, clopidogrel 75mg od (3 months)	DAPT with prasugrel 10mg od /ticagrelor 90mg bid (6 months)
GUARANTEE	NCT03783351	DAPT with ticagrelor 90mg bid in LOF carriers, clopidogrel 75mg od in noncarriers	DAPT with clopidogrel 75mg od or ticagrelor 90mg bid based on clinical presentation
TARGET SAFE	NCT03287167	1-month DAPT followed by aspirin monotherapy (HBR patients)	6-month DAPT
TAILOR-DAPT	NCT03848572	Customization of DAPT duration based on PRECISE-DAPT score	
SMART-CHOICE 4	NCT05066789	Prasugrel monotherapy after 1-month DAPT	12-month DAPT
LEGACY	NCT05125276	Monotherapy with potent P2Y12 inhibitor after PCI	12-month DAPT
PREMIUM	NCT05709626	Monotherapy with potent P2Y12 inhibitor after PCI	12-month DAPT
TARGET FIRST	NCT04753749	1-month DAPT followed by P2Y12 monotherapy	12-month DAPT
ULTIMATE-DAPT	NCT03971500	DAPT for 1 month, followed by 11 months of placebo + target vessel failure	12-month DAPT
CAGEFREE II	NCT04731156	1-month DAPT followed by ticagrelor monotherapy for 5 months	12-month DAPT

REFERENCES

1. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet (London, England). 1988 Aug;2(8607):349–60.
2. Schömig A, Neumann FJ, Kastrati A, Schühlen H, Blasini R, Hadamitzky M, et al. A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents. New England Journal of Medicine. 1996 Apr;334(17):1084–9.
3. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug | FDA [Internet]. [cited 2022 Apr 29]. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-poor#ds
4. Galli M, Benenati S, Capodanno D, Franchi F, Rollini F, D'Amario D, et al. Guided versus standard antiplatelet therapy in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis. The Lancet. 2021 Apr;397(10283):1470–83.
5. Galli M, Benenati S, Franchi F, Rollini F, Capodanno D, Biondi-Zoccai G, et al. Comparative effects of guided vs. potent P2Y12 inhibitor therapy in acute coronary syndrome: a network meta-analysis of 61 898 patients from 15 randomized trials. European Heart Journal. 2022 Mar 7;43(10):959–67.
6. Angiolillo DJ, Galli M, Alexopoulos D, Aradi D, Bhatt DL, Bonello L, et al. International Consensus Statement on Platelet Function and Genetic Testing in Percutaneous Coronary Intervention. JACC: Cardiovascular Interventions. 2024 Nov;17(22):2639–63.
7. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes after Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2020;324(8):761–71.
8. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. New England Journal of Medicine. 2019;381(17):1621–31.
9. Claassens DMF, Gimbel ME, Bergmeijer TO, Vos GJA, Hermanides RS, van der Harst P, et al. Clopidogrel in noncarriers of CYP2C19 loss-of-function alleles versus ticagrelor in elderly patients with acute coronary syndrome: A pre-specified sub analysis from the POPular Genetics and POPular Age trials CYP2C19 alleles in elderly patients. International Journal of Cardiology. 2021;334:10–7.
10. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, 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. The Lancet. 2020 Apr;395(10233):1374–81.
11. Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. The Lancet. 2017;390(10104):1747–57.

12. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, et al. Durable Polymer Versus Biodegradable Polymer Drug-Eluting Stents After Percutaneous Coronary Intervention in Patients with Acute Coronary Syndrome: The HOST-REDUCE-POLYTECH-ACS Trial. Circulation. 2021 Mar;143(11):1081–91.
13. Kim CJ, Park MW, Kim MC, Choo EH, Hwang BH, Lee KY, et al. Unguided de-escalation from ticagrelor to clopidogrel in stabilised patients with acute myocardial infarction undergoing percutaneous coronary intervention (TALOS-AMI): an investigator-initiated, open-label, multicentre, non-inferiority, randomised trial. The Lancet. 2021;398(10308):1305–16.
14. Angiolillo DJ, Capodanno D, Danchin N, Simon T, Bergmeijer TO, ten Berg JM, et al. Derivation, Validation, and Prognostic Utility of a Prediction Rule for Nonresponse to Clopidogrel: The ABCD-GENE Score. JACC: Cardiovascular Interventions. 2020;13(5):606–17.
15. Chan Pin Yin DRPPPP, Vos GJAJA, van der Sangen NMRR, Walhout R, Tjon Joe Gin RM, Nicastia DM, et al. Rationale and Design of the Future Optimal Research and Care Evaluation in Patients with Acute Coronary Syndrome (FORCE-ACS) Registry: Towards "Personalized Medicine" in Daily Clinical Practice. Journal of Clinical Medicine. 2020 Sep 30;9(10):3173.
16. Valgimigli M, Landi A, Angiolillo DJ, Baber U, Bhatt DL, Bonaca MP, et al. Demystifying the Contemporary Role of 12-Month Dual Antiplatelet Therapy After Acute Coronary Syndrome. Circulation. 2024 Jul;150(4):317–35.
17. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. New England Journal of Medicine [Internet]. 2001 Aug 16;345(7):494–502. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa010746
18. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine. 2009 Sep;361(11):1045–57.
19. 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;357(20):2001–15.
20. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. European Heart Journal. 2023 Aug;44(38):3720–826.
21. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y12inhibitor in patients after percutaneous coronary intervention: A systematic review and meta-analysis. Circulation. 2020;142(6):538–45.
22. Valgimigli M, Mehran R, Franzone A, da Costa BR, Baber U, Piccolo R, et al. Ticagrelor Monotherapy Versus Dual-Antiplatelet Therapy After PCI: An Individual Patient-Level Meta-Analysis. JACC Cardiovascular interventions. 2021 Feb;14(4):444–56.
23. Valgimigli M, Gragnano F, Branca M, Franzone A, da Costa BR, Baber U, et al. Ticagrelor or Clopidogrel Monotherapy vs Dual Antiplatelet Therapy After Percutaneous Coronary Intervention. JAMA Cardiology. 2024 Mar;
24. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PhG, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. New England Journal of Medicine. 2014 Dec;371(23):2155–66.
25. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. New England Journal of Medicine. 2015 May 7;372(19):1791–800.

26. Valgimigli M, Frigoli E, Heg D, Tijssen J, Jüni P, Vranckx P, et al. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. New England Journal of Medicine. 2021;385(18):1643–55.
27. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. New England Journal of Medicine. 2019;381(21):2032–42.
28. Swen JJ, van der Wouden CH, Manson LE, Abdullah-Koolmees H, Blagec K, Blagus T, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. The Lancet. 2023 Feb;401(10374):347–56.
29. Bush WS, Crosslin DR, Owusu-Obeng A, Wallace J, Almoguera B, Basford MA, et al. Genetic variation among 82 pharmacogenes: The PGRNseq data from the eMERGE network. Clinical pharmacology and therapeutics. 2016 Aug;100(2):160–9.
30. McInnes G, Lavertu A, Sangkuhl K, Klein TE, Whirl-Carrillo M, Altman RB. Pharmacogenetics at Scale: An Analysis of the UK Biobank. Clinical pharmacology and therapeutics. 2021 Jun;109(6):1528–37.

APPENDIX

Nederlandse samenvatting

Impact section

Lists of publications

Curriculum vitae

Dankwoord

NEDERLANDSE SAMENVATTING

Coronaire hartziekten vormen een grote uitdaging voor de volksgezondheid. Jaarlijks worden in Nederland ruim 60.000 patiënten opgenomen met een hartinfarct, ook wel bekend als een acuut coronair syndroom (ACS). Hiervan ondergaan circa 40.000 patiënten een percutane coronaire interventie (PCI) ondergaan. ACS ontstaat meestal door het scheuren of eroderen van een atherosclerotische plaque in de kransslagaders. Dit kan leiden tot de vorming van een stolsel dat de bloedstroom blokkeert, waardoor de hartspier een zuurstoftekort krijgt. Wanneer de onderliggende vaatwand (subendotheliale matrix) bloot komt te liggen, worden bloedplaatjes en de stollingscascade geactiveerd. De geactiveerde bloedplaatjes geven signaalstoffen (agonisten) af, zoals ADP en tromboxaan A_2, die de stolling verder stimuleren. Dit versterkt de aggregatie en resulteert in een stabiel stolsel. In tegenstelling tot stolsels bij diepveneuze trombose of longembolieën, die voornamelijk uit fibrine bestaan, zijn stolsels bij ACS rijk aan bloedplaatjes. Dit benadrukt de centrale rol van plaatjes in de pathofysiologie van ACS en het belang van effectieve plaatjesremming ter preventie van recidiverende ischemische events.

De standaardbehandeling bestaat uit duale antiplaatjestherapie (DAPT) met aspirine en een P2Y12-remmer. Aspirine remt de tromboxaan A_2-gemedieerde aggregatie, terwijl P2Y12-remmers de ADP-gemedieerde activatie tegengaan. Binnen de huidige richtlijnen wordt voor patiënten met ACS die een PCI ondergaan DAPT met aspirine en een krachtige P2Y12-remmer (ticagrelor of prasugrel) aanbevolen. Deze uniforme benadering houdt echter onvoldoende rekening met individuele verschillen, zoals genetisch profiel, comorbiditeit, procedurele kenmerken en het bloedingsrisico. Toenemend bewijs wijst erop dat een meer gepersonaliseerde aanpak van antitrombotische therapie kan leiden tot betere klinische uitkomsten door ischemische bescherming en bloedingsrisico beter in balans te brengen.

Dit proefschrift richt zich op het optimaliseren van antitrombotische strategieën via een drieluik: (deel 1) het onderbouwen van de noodzaak voor gepersonaliseerde therapie en het samenvatten van huidige strategieën, (deel 2) het onderzoeken van de klinische impact van genetische variaties op cardiovasculaire uitkomsten en behandelingseffect, aan de hand van zowel grote klinische studies als kleinschalige laboratoriumonderzoeken, en (deel 3) het bestuderen van de implementatie in de praktijk, de effectiviteit en de kostenefficiëntie van een genotype-geleide de-escalatiestrategie bij patiënten met ACS (deel III).

Deel I geeft een overzicht van de huidige stand van zaken rond gepersonaliseerde antiplaatjestherapie en bespreekt de belangrijkste uitgangspunten voor het personaliseren van antitrombotische behandeling. **Hoofdstuk 2** beschrijft de huidige stand van zaken en weegt de voor- en nadelen van genotype-geleide strategieën af, evenals methoden die de interindividuele variatie in behandelrespons in kaart brengen. Er wordt een overzicht gegeven van beschikbare technieken, waaronder stollingstesten en plaatjesfunctietesten, gericht op het identificeren van patiënten met hoge plaatjesreactiviteit. Hoewel deze testen waardevolle informatie kunnen bieden, is hun routinematige klinische toepassing beperkt, waarschijnlijk vanwege een gebrek aan robuust klinisch bewijs voor verbetering van uitkomsten.

Personalisatie kan echter bijzonder nuttig zijn in geselecteerde situaties, zoals escalatie bij hoog tromboserisico of de-escalatie bij verhoogd bloedingsrisico. Naarmate het bewijs en de beschikbaarheid van point-of-care testen toenemen, kan gepersonaliseerde therapie evolueren van experimenteel concept naar standaardzorg.

Hoofdstuk 3 biedt een gedetailleerd overzicht van genotype-geleide antiplaatjes therapie, met de nadruk op de rol van genetische variatie, met name *CYP2C19*-polymorfismen, op de metabolisering en effectiviteit van clopidogrel. Bij dragers van een zogenoemd loss-of-function-allel (een genetische variant die leidt tot een verminderde werking van het betrokken enzym) kan escalatie naar een krachtiger middel het risico op ischemische events verminderen. Deze benadering werd onderzocht in de TAILOR-PCI-studie, die een mogelijk klinisch voordeel liet zien, maar zonder statistische significantie. Daarentegen kan genotype-geleide de-escalatie bij patiënten behandeld met ticagrelor of prasugrel het bloedingsrisico verlagen zonder verlies van effectiviteit. Onder de-escalatie wordt verstaan dat patiënten die aanvankelijk met een krachtig middel zoals ticagrelor worden behandeld, op basis van hun genetisch profiel veilig kunnen overstappen naar een minder krachtig middel zoals clopidogrel. De POPular Genetics-studie liet zien dat deze aanpak bloedingen reduceert en de inzet van het goedkopere clopidogrel mogelijk maakt bij 60% van de patiënten. Hoewel deze strategieën veelbelovend zijn, worden ze nog beperkt toegepast vanwege logistieke en economische barrières. Technologische vooruitgang en toenemend bewijs kunnen bredere implementatie echter binnen handbereik brengen.

Hoofdstuk 4 bespreekt de toepassing van genotype-geleide therapie bij ouderen met ACS, een kwetsbare populatie met een verhoogd bloedingsrisico en vaak onderbehandeling. Eerdere analyses suggereren dat clopidogrel veilig kan zijn bij oudere patiënten zonder *CYP2C19*-loss-of-function allel, maar de beschikbare data zijn beperkt, wat verdere studies noodzakelijk maakt.

Deel II presenteert studies waarin het effect van verschillende genetische polymorfismen op klinische uitkomsten bij patiënten met ACS wordt onderzocht. In **Hoofdstuk 5** wordt de klinische relevantie onderzocht van *CYP2C9*-loss-of-function-polymorfismen bij patiënten met ACS die met clopidogrel worden behandeld. Op basis van gegevens uit de POPular Genetics- en POPular AGE-studies werden trombotische en bloedingsuitkomsten vergeleken tussen dragers en niet-dragers van het *CYP2C9 *2*- of **3*-allel. Er werd geen significant verschil gevonden in klinische uitkomsten, wat suggereert dat CYP2C9-genotypering geen zinvolle meerwaarde biedt bij het begeleiden van antiplaatjes therapie met clopidogrel. Vanwege het lage aantal homozygote slechte metaboliseerders konden voor deze subgroep geen harde conclusies worden getrokken.

Hoofdstuk 6 onderzoekt het effect van genetische variatie in *CYP3A4* en *CYP3A5* op klinische uitkomsten bij STEMI-patiënten die behandeld worden met ticagrelor. Data uit de POPular Genetics-studie werden geanalyseerd om de relatie tussen *CYP3A4 *22* en *CYP3A5*-expressorstatus en het optreden van trombotische events, bloedingen en dyspneu te onderzoeken. Er werden geen significante verschillen gevonden tussen genotypegroepen, wat suggereert dat deze polymorfismen, in tegenstelling tot *CYP2C19* bij clopidogrelgebruik, geen klinisch relevante impact hebben op de effectiviteit of veiligheid van ticagrelor.

In **Hoofdstuk 7** wordt een meta-analyse van individuele patiëntgegevens gepresenteerd naar de effectiviteit en veiligheid van de-escalatie van DAPT bij patiënten met ACS die een PCI ondergingen. De analyse omvatte meer dan 10.000 patiënten uit vier grote gerandomiseerde studies (TROPICAL-ACS, POPular Genetics, HOST-REDUCE-POLYTECH-ACS en TALOS-AMI). De-escalatiestrategieën, waarbij werd overgestapt van een krachtig naar een minder krachtig P2Y12-remmer, gingen gepaard met een significante reductie van zowel ischemische events (2,3% versus 3,0%) als bloedingen (6,5% versus 9,1%) na één jaar. Hoewel er geen verschil werd gevonden in majeure bloedingen of totale mortaliteit, was het algemene veiligheidsprofiel gunstiger bij de-escalatie. Deze bevindingen ondersteunen de-escalatie als een veilige en effectieve strategie om het evenwicht tussen trombose- en bloedingsrisico te verbeteren bij ACS-patiënten na PCI.

Hoofdstuk 8 gaat verder met de verkenning van genotype-geleide strategieën en presenteert een meta-analyse op basis van individuele patiëntgegevens waarin *CYP2C19*-geleide antiplaatjestherapie wordt vergeleken met de gebruikelijke behandeling bij ACS-patiënten die een PCI ondergaan. De studie combineerde gegevens van twee grote gerandomiseerde trials (TAILOR-PCI en POPular Genetics) en omvatte meer dan 6.700 patiënten. Hoewel er geen significant verschil werd gevonden in de incidentie van MACE (Major Adverse Cardiovascular Events; een gecombineerd eindpunt van ernstige cardiovasculaire events zoals overlijden, myocardinfarct en beroerte) of bloedingen tussen de groepen als geheel, resulteerde genotype-geleide therapie wel in minder hartinfarcten en een lagere incidentie van NACE (Net Adverse Clinical Events; een gecombineerd eindpunt van ernstige cardiovasculaire events en ernstige bloedingen). Genotype-geleide de-escalatie leidde bovendien tot minder bloedingen en NACE zonder verlies aan ischemische bescherming, vooral in de vroege fase na PCI. Genotype-geleide escalatie bood daarentegen geen extra voordeel ten opzichte van standaardzorg. Deze bevindingen benadrukken de klinische waarde van met name genotype-geleide de-escalatie als een veilige en effectieve strategie bij geselecteerde patiënten.

In **Hoofdstuk 9** verschuift de focus naar gepersonaliseerde behandeling bij een specifieke populatie patiënten die worden behandeld met directe orale anticoagulantia (DOAC). Dit zijn middelen die rechtstreeks bepaalde stollingsfactoren remmen en vaak worden voorgeschreven bij hartritmestoornissen. In een gerandomiseerde farmacodynamische studie (SWAP-AC-2) werd onderzocht of patiënten die behandeld worden met een DOAC en een verhoogd risico hebben volgens de ABCD-GENE score (≥10), baat hebben bij een aangepaste behandeling. Patiënten werden gerandomiseerd naar clopidogrel of een lage dosis ticagrelor. Ticagrelor leidde tot een significant sterkere remming van de plaatjesactiviteit, zowel in piek- als dalspiegels, gemeten met verschillende functionele testen. Hoewel klinische uitkomsten niet onderzocht werden gezien de kleine onderzoekspopulatie, suggereert de studie dat ticagrelor mogelijk effectiever is bij NOAC-gebruikers met een ongunstig genetisch profiel. Verdere studies zijn nodig om te beoordelen of een ABCD-GENE-gestuurde benadering daadwerkelijk leidt tot betere uitkomsten bij deze complexe populatie.

De voorgaande hoofdstukken laten zien dat farmacogenetica en de-escalatiestrategieën kunnen bijdragen aan het verfijnen van antiplaatjestherapie en het verbeteren van klinische uitkomsten. Hoewel

het bewijs hiervoor toeneemt, blijft de vertaling naar de dagelijkse praktijk een uitdaging. **Deel III** van dit proefschrift richt zich daarom op de implementatie, haalbaarheid en kosteneffectiviteit van genotype-geleide antiplaatjes therapie in de huidige praktijk.

In **Hoofdstuk 10** wordt de praktische haalbaarheid onderzocht van het toepassen van *CYP2C19*-geleide de-escalatie bij patiënten met ACS. Van de 738 genetisch geteste patiënten bleek meer dan 80% in aanmerking te komen voor overstap naar clopidogrel. De switch van ticagrelor naar clopidogrel kon vaak al binnen 24 uur worden uitgevoerd, vooral wanneer point-of-care testen werden gebruikt. Een point-of-care test wordt vaak op de afdeling zelf uitgevoerd, en leidt tot snellere resultaten dan via een centraal laboratorium. Het gebruik van de point-of-care test leidde tot significant kortere doorlooptijden en zorgde ervoor dat patiënten sneller en vaker het voor hun genetisch profiel passende middel kregen. Artsen volgden de genotype-uitslagen goed op, en de strategie leidde tot aanzienlijke kostenbesparingen op medicatie. Deze bevindingen laten zien dat vroege genotype-geleide de-escalatie uitvoerbaar, effectief en economisch gunstig is.

Hoofdstuk 11 bouwt voort op de in het vorige hoofdstuk beschreven implementatie en richt zich op de klinische uitkomsten van genotype-geleide de-escalatie in vergelijking met standaard DAPT. Hier wordt gebruik gemaakt van data van de FORCE-ACS-registratie, een regionale registratie voor patiënten met een hartinfarct. In deze observationele studie met 5.321 patiënten lieten degenen die genetisch getest werden en de-escalatie ondergingen (N = 406) significant minder bloedingen zien dan patiënten die standaardtherapie ontvingen, zonder dat er een toename was in ischemische events. Hoewel de studie niet was opgezet om non-inferioriteit voor trombotische uitkomsten aan te tonen, bevestigen de resultaten de veiligheid en toepasbaarheid van genotype-geleide therapie in de dagelijkse praktijk. Deze bevindingen liggen in lijn met eerdere resultaten uit gerandomiseerd onderzoek en ondersteunen verdere opschaling van deze aanpak.

Na de beschrijving van de klinische resultaten, richt **Hoofdstuk 12** zich op de kosteneffectiviteit van genotype-geleide de-escalatie ten opzichte van standaard DAPT vanuit het perspectief van het Nederlandse zorgsysteem. Aan de hand van een tweedelig beslismodel werden de verwachte zorgkosten en gezondheidswinst op de lange termijn gesimuleerd. Genotype-geleide therapie bleek niet alleen beter in termen van kwaliteit van leven, maar leidde ook tot lagere zorgkosten. De strategie bleef kosteneffectief onder diverse scenario's, zelfs wanneer de medicatieprijzen voor clopidogrel en ticagrelor werden gelijkgetrokken. Deze resultaten versterken de klinische en economische onderbouwing voor bredere implementatie van gepersonaliseerde antiplaatjes therapie in de Nederlandse zorg.

Tot slot presenteert **Hoofdstuk 13** de resultaten van een grootschalige, prospectieve, multicenter implementatiestudie naar de klinische veiligheid en effectiviteit van routinematige *CYP2C19*-gestuurde therapie bij patiënten met ACS. In deze studie met bijna 10.000 patiënten traden bij de genetisch behandelde groep significant minder ernstige of klinisch relevante bloedingen op na één jaar, terwijl de incidentie van trombotische events vergelijkbaar was met die van standaardzorg. Deze resultaten bevestigen dat genotype-geleide de-escalatie, waarbij niet-dragers van een *CYP2C19* loss-of-function allel overstappen van een krachtig P2Y12-remmer naar clopidogrel, niet alleen veilig is, maar ook klinisch voordeel biedt in het verminderen van bloedingsrisico. Daarmee leveren deze gegevens overtuigend

bewijs dat een gepersonaliseerde antiplaatjes therapie veilig en effectief kan worden toegepast in de dagelijkse zorg voor patiënten met ACS.

IMPACT SECTION

Coronary artery disease remains one of the most common and serious health problems worldwide. Every day, millions of patients depend on antithrombotic therapy, making the optimization of its safety and effectiveness highly relevant for both individual patients and society as a whole. Over the past decades, extensive research has focused on antithrombotic therapy. As discussed in this thesis, many different strategies to optimize the balance between bleeding and ischemic risk have been explored, each with unique advantages and limitations. The number of antithrombotic strategies explored underscore the importance and ongoing challenge in cardiology to continuously improve antithrombotic management. The ultimate goal of these efforts should not be the publication of trial results, but the genuine implementation in daily clinical practice. Yet, the step of implementation is often overlooked or insufficiently prioritized.

This thesis bridges that important gap by following the path from initial clinical trials to real-world implementation. We demonstrated that a *CYP2C19* genotype-guided de-escalation strategy, as validated in randomized trials, can be successfully translated into routine practice, reducing bleeding without increasing ischemic events. Furthermore, we quantified its cost-effectiveness, providing concrete evidence facilitating first reimbursement for genetic testing in our hospital and second formed the basis for regional funding initiatives. The next step is to expand this to a national level, where both the clinical and cost-effectiveness results will serve as a solid foundation for ongoing negotiations. These findings are highly relevant for healthcare professionals, policymakers, and health insurers, as they provide robust clinical and economic evidence to support the broader implementation of personalized antiplatelet therapy. By engaging these stakeholders—through scientific publications, presentations at national and international conferences, and close collaboration with professional societies—this work helped to translate the research findings into improved patient care on both a regional and international scale. Its impact has also been formally recognized by the Dutch Society of Cardiology (NVVC), leading to the inclusion of the following research question in the NVVC Kennisagenda: "Hoe kan antitrombotische therapie worden gepersonaliseerd bij patiënten met coronaire syndromen en percutane klepinterventies?" This integration into a national platform strengthens the potential for broader adoption and knowledge dissemination, further underscoring the scientific and societal relevance of the results presented in this thesis.

Beyond proving the feasibility and cost-effectiveness of genotype-guided therapy, this thesis has shown how translating evidence from clinical trials into daily clinical practice can meaningfully improve patient care. The practical impact of this strategy has been made clearly visible in our coronary care unit, where its implementation resulted in fewer bleeding events and a noticeable reduction in side effects such as dyspnea among a broad population of patients with ACS. In addition, the implementation has generated valuable knowledge products and practical experience, such as the development of clinical protocols and the resolution of real-world challenges, including integrating genotype-guided strategies into electronic patient records and ensuring that test results are neither missed nor misinterpreted. These

insights are highly valuable and can support the successful implementation of personalized antiplatelet therapy in other hospitals and healthcare systems.

In addition to implementation, this thesis also explores new areas of potential improvement in antiplatelet therapy. Specific attention is given to patients requiring oral anticoagulation undergoing percutaneous coronary intervention, a group that presents a unique challenge in balancing bleeding and ischemic risk. Studies like this open the door for future research, further refining the personalization of antithrombotic treatment beyond the current focus on DAPT.

This thesis has objectified the local impact of implementation while setting in motion a broader shift within the field of personalized antithrombotic therapy. With these results, we are not at the finish line but rather on the road toward a future in which antiplatelet therapy in ACS is no longer based on a "one-size-fits-all" principle, but instead moves toward truly personalized care.

LIST OF PUBLICATIONS

van den Broek WWA, ten Berg JM. Is there a benefit for CYP2C19 genotype-guided antiplatelet treatment in elderly acute coronary syndrome patients? Pharmacogenomics [Internet]. 2021 Aug;22(12):727–30.

van den Broek WWA, Azzahhafi J, van Schaik RHN, Ten Berg JM. Genotype-guided antithrombotic therapy. Ned Tijdschr Geneeskd. 2022;166.

van den Broek WWA, van Paassen JG, Gimbel ME, Deneer VHM, ten Berg JM, Vreman RA. Cost-effectiveness of clopidogrel vs. ticagrelor in patients of 70 years or older with non-ST-elevation acute coronary syndrome. Eur Hear J - Cardiovasc Pharmacother. 2022 Dec 15;9(1):76–84.

Raafs AG, Boscutti A, Henkens MTHM, **van den Broek WWA**, Verdonschot JAJ, Weerts J, et al. Global Longitudinal Strain is Incremental to Left Ventricular Ejection Fraction for the Prediction of Outcome in Optimally Treated Dilated Cardiomyopathy Patients. J Am Heart Assoc. 2022 Mar 15;11(6).

van den Broek WWA, ten Berg JM. Is a genotype-guided therapy the optimal strategy to personalize anti-thrombotic management in patients with acute coronary syndrome? Eur Heart J. 2022 Jun 9.

Nugteren MJ, de Borst GJ, **van den Broek WWA**, Ten Berg JM, Kappelle LJ, Ünlü Ç. Recent developments in secondary cardiovascular prevention: the pros and cons of dual pathway inhibition. Ned Tijdschr Geneeskd [Internet]. 2022 Jun 22;166.

Azzahhafi J, Bergmeijer TO, **van den Broek WWA**, Chan Pin Yin DRPP, Rayhi S, Peper J, et al. Effects of CYP3A4*22 and CYP3A5 on clinical outcome in patients treated with ticagrelor for ST-segment elevation myocardial infarction: POPular Genetics sub-study. Front Pharmacol. 2022 Dec 5;13.

van den Broek WWA, Gimbel ME, Chan Pin Yin DRPP, Azzahhafi J, Hermanides RS, Runnett C, et al. Conservative versus Invasive Strategy in Elderly Patients with Non-ST-Elevation Myocardial Infarction: Insights from the International POPular Age Registry. J Clin Med. 2023 Aug 22;12(17):5450.

van den Broek WWA, Mani N, Azzahhafi J, ten Berg JM. CYP2C9 Polymorphisms and the Risk of Cardiovascular Events in Patients Treated with Clopidogrel: Combined Data from the POPular Genetics and POPular AGE Trials. Am J Cardiovasc Drugs. 2023 Mar;23(2):165-172.

Azzahhafi J, **Broek WWA van den**, Chan Pin Yin DRPP, Harmsze AM, van Schaik RHN, ten Berg JM. The Clinical Implementation of CYP2C19 Genotyping in Patients with an Acute Coronary Syndrome: Insights From the FORCE-ACS Registry. J Cardiovasc Pharmacol Ther. 2023 Jan 29;28.

ten Berg JM, **van den Broek WWA**. Another Step Toward CYP2C19 Genotype-Guided Therapy in Treatment With Dual Antiplatelet Therapy. JACC Cardiovasc Interv. 2023 Apr;16(7):826–8.

Kang J, Rizas KD, Park KW, Chung J, **van den Broek W**, Claassens DMF, et al. Dual antiplatelet therapy de-escalation in acute coronary syndrome: an individual patient meta-analysis. Eur Heart J [Internet]. 2023 Apr 17;44(15):1360–70.

Akbulut AC, Arisz RA, Baaten CCFMJ, Baidildinova G, Barakzie A, Bauersachs R, et al. Blood Coagulation and Beyond: Position Paper from the Fourth Maastricht Consensus Conference on Thrombosis. Thromb Haemost. 2023 Aug 13;123(08):808–39.

van den Broek WWA, ten Berg JM, Sibbing D, Rizas KD. Personalized antithrombotic therapy: measuring individual variation and monitoring. In: De Caterina R, Moliterno DJ, Kristensen SD, editors. The ESC Textbook of Thrombosis. Oxford University PressOxford; 2023. p. 355–66.

van Schaik RH, Manolopoulos VG, Daly AK, Niemi M, Zukic B, Patrinos GP, et al. The Sixth European Society of Pharmacogenomics and Personalised Therapy Congress. Pharmacogenomics. 2023 Apr 4;24(5):243–6.

Azzahhafi J, **van den Broek WWA**, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, Bofarid S, et al. Real-World Implementation of a Genotype-Guided P2Y12 Inhibitor De-Escalation Strategy in Acute Coronary Syndrome Patients. JACC Cardiovasc Interv [Internet]. 2024 Sep;17(17):1996–2007.

Gimbel ME, Chan Pin Yin DRPP, **van den Broek WWA**, Hermanides RS, Kauer F, Tavenier AH, et al. Treatment of elderly patients with non-ST-elevation myocardial infarction: the nationwide POPular age registry. Netherlands Hear J. 2024 Feb 28;32(2):84–90.

van den Broek WWA, Gimbel ME, Hermanides RS, Runnett C, Storey RF, Knaapen P, et al. The impact of patient-reported frailty on cardiovascular outcomes in elderly patients after non-ST-acute coronary syndrome. Int J Cardiol. 2024 Jun;405:131940.

Ortega-Paz L, Bor W, Franchi F, **van de Broek WWA**, Rollini F, Giordano S, et al. P2Y12 Inhibition in Patients Requiring Oral Anticoagulation after Percutaneous Coronary Intervention: The SWAP-AC–2 Study. JACC Cardiovasc Interv. 2024 Jun 10;17(11):1356-1370.

Verburg A, Bor WL, Küçük IT, Henriques JPS, Vink MA, Ruifrok W-PT, et al. Temporary omission of oral anticoagulation in atrial fibrillation patients undergoing percutaneous coronary intervention: rationale and design of the WOEST-3 randomised trial. EuroIntervention. 2024 Jul;20(14):e898–904.

van den Broek WWA, Ingraham BS, Pereira NL, Lee CR, Cavallari LH, Swen JJ, et al. Genotype-Guided Antiplatelet Therapy. J Am Coll Cardiol [Internet]. 2024 Sep;84(12):1107–18.

van der Sangen NMR, Azzahhafi J, Chan Pin Yin DRPP, Zaaijer LJG, **van den Broek WWA**, Walhout RJ, et al. Treatment Modifications in Acute Coronary Syndrome Patients Treated with Ticagrelor: Insights from the FORCE-ACS Registry. Thromb Haemost. 2025 Jun;125(6):597-606.

van den Broek WWA, Azzahhafi J, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, Dijksman LM, et al. Cost-effectiveness of Implementing a Genotype-Guided De-Escalation Strategy in Patients with Acute Coronary Syndrome. Eur Hear J - Cardiovasc Pharmacother. 2025 May 2;11(3):230-240.

Sivanesan S, Gąsecka A, van der Sangen NMR, **van den Broek WWA,** Azzahhafi J, Chan Pin Yin DRPP, van de Pol QYF, Walhout RJ, Joe Gin MT, Pisters R, Nicastia DM, de Roest GJ, Vlachojannis GJ, van Bommel RJ, Kikkert WJ, Henriques JPS, Ten Berg JM, Appelman Y. Sex differences in the presentation and management of acute coronary syndrome patients: Insights from the FORCE-ACS registry. Int J Cardiol Heart Vasc. 2025 Dec 10;62:101849.

Galli M, Pereira NL, Lennon RJ, **van den Broek WWA**, Claassens DMF, Bergmeijer TO, Rosenberg Y, Fazzini L, Deneer VHM, Murad MH, Farkouh ME, Rihal C, Ten Berg J, Angiolillo DJ. Genotype-Guided vs Conventional Oral P2Y12 Inhibitors in Acute Coronary Syndrome: A Combined Analysis of TAILOR-PCI and POPular Genetics. JACC Cardiovasc Interv. 2026 Feb 9;19(3):283-296.

van den Broek WWA, Azzahhafi J, van de Pol QYF, Chan Pin Yin DRPP, van der Sangen NMR, Sivanesan S, et al. Genotype-Guided P2Y12-Inhibitor De-Escalation Strategy in Acute Coronary Syndrome: Observational Evidence From the POPular-GUIDE PCI. Circ Cardiovasc Interv. 2026;19:e016084.

CURRICULUM VITAE

Wout Willem Antoon van den Broek was born on August 30, 1996, in Well, the Netherlands. He is a son of Wil van den Broek en Mariet van Kempen†. He completed his secondary school at Raayland College (2008–2014) before starting his medical studies at Maastricht University. He studied in Maastricht for six years and graduated with honors (cum laude) from both the bachelor's and master's programs, in 2017 and 2020 respectively.

In February 2021, Wout commenced his full-time PhD at the Department of Cardiology at St. Antonius Hospital, under the direct supervision of Prof. Dr. J.M. ten Berg. His research focused on personalized antithrombotic therapy in patients with coronary artery disease, the clinical implementation of genetic testing, and the coordination of the regional acute coronary syndrome registry, the FORCE-ACS registry. After completing his PhD in January 2025, he almost spent six months traveling through South America.

In September 2025, Wout returned to St. Antonius Hospital to continue his clinical training as a resident at the department of Cardiology.

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