Impact of CYP2C19 loss-of-function variants on outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: rationale and study design of the WOEST-3 genetic substudy

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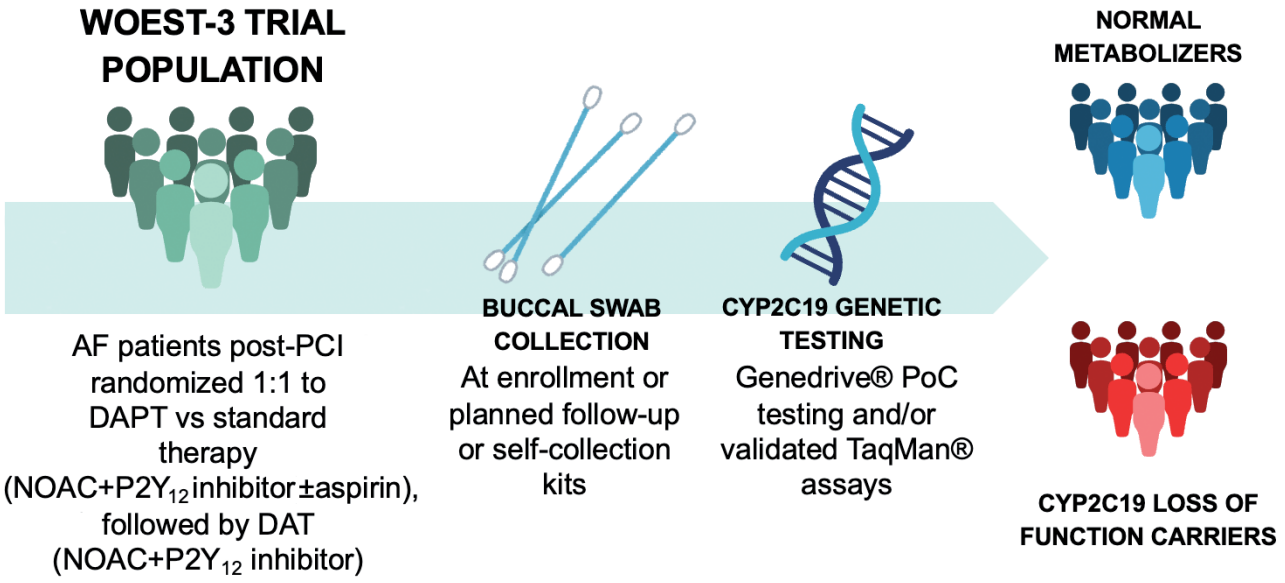
GRAPHICAL ABSTRACT



ABSTRACT

Background: The impact of CYP2C19 loss-of-function (LOF) variants on clopidogrel efficacy in atrial fibrillation (AF) patients undergoing percutaneous coronary intervention (PCI) remains uncertain. While clopidogrel is the preferred $P2Y_{12}$ inhibitor in combination with oral anticoagulants, approximately one-third of patients carry CYP2C19 LOF alleles, known to reduce platelet inhibition and increase ischemic risk.

Methods: The WOEST-3 genetic substudy is an observational pharmacogenetic investigation embedded within the randomized WOEST-3 trial (NCT04436978). Patients with AF undergoing PCI and providing additional consent for genetic testing will be included. CYP2C19 *2, *3, *4, *8 and *35 genotypes will be determined using both Genedrive® (Genedrive Diagnostics Ltd, Manchester, UK) point-of-care and laboratory-based assays. Genetic results will remain blinded to investigators and clinicians to avoid treatment bias. The primary endpoint is a 6-month composite of death, myocardial infarction, stroke, systemic embolism, and stent thrombosis. Approximately 30% of patients are anticipated to carry CYP2C19 LOF alleles. The study will determine whether concomitant direct oral anticoagulants therapy mitigates the impact of reduced clopidogrel activation in these carriers or whether genetic variability continues to confer excess ischemic risk.

Conclusions: This protocol paper describes the rationale and design of a genetic substudy aimed at clarifying the prognostic relevance of CYP2C19 genotype in AF patients undergoing PCI and informing the design of future genotype-guided antithrombotic trials.

Key words: clopidogrel; coronary artery disease; atrial fibrillation; CYP2C19; antithrombotic therapy.

Introduction

Clopidogrel is a prodrug requiring bioactivation by the polymorphic cytochrome P450 2C19 (CYP2C19) enzyme to generate its active metabolite and irreversibly inhibit the platelet $P2Y_{12}$ receptor.[1] Genetic polymorphisms in CYP2C19 lead to variable enzyme activity, resulting in substantial interindividual differences in clopidogrel responsiveness. The most clinically relevant loss-of-function (LOF) variants, CYP2C19 *2 and *3, are present in up to 30% in Caucasians and up to 50% of Asian populations.[1-6] Carriers of these alleles demonstrate reduced platelet inhibition and an increased risk of major adverse cardiovascular events (MACE), including stent thrombosis (ST), particularly after acute coronary syndrome (ACS).[7-10]

Several randomized clinical trials have evaluated genotype-guided antiplatelet strategies, but their findings have been heterogeneous. The POPular Genetics trial,[11] conducted in ST-segment elevation myocardial infarction patients, demonstrated that genotype-guided de-escalation was non-inferior for ischemic outcomes and significantly reduced bleeding compared with routine potent $P2Y_{12}$ inhibitor use.[12] Similarly, in the TAILOR-PCI trial, which enrolled both acute and stable coronary syndrome patients, genotype-guided escalation in CYP2C19 LOF carriers was associated with a 34% relative reduction in ischemic events compared with standard clopidogrel therapy (HR 0.66; 95% CI, 0.43-1.02), although the difference did not reach statistical significance, largely due to fewer-than-expected endpoint events.[13] These findings collectively support the biological relevance of CYP2C19 polymorphisms but leave uncertainty about the clinical value of genotype-guided therapy across different risk settings. Notably, none included patients requiring long-term oral anticoagulation (OAC).

This knowledge gap is especially relevant for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). These patients are typically older, frailer, and face both elevated thrombotic and bleeding risks.[14] Current guidelines recommend clopidogrel as the $P2Y_{12}$ inhibitor of choice in triple antithrombotic therapy (TAT), given the higher bleeding risk associated with prasugrel and ticagrelor.[12,13] After a brief period of TAT, most patients transition to dual antithrombotic therapy (DAT) consisting of a direct oral anticoagulant (DOAC) plus clopidogrel. Consequently, more than 90% of AF-PCI patients are treated with clopidogrel, despite up to one-third being carriers of CYP2C19 LOF alleles.[12-19] It remains unknown whether concomitant DOAC therapy attenuates the ischemic disadvantage associated with reduced clopidogrel activation.

The WOEST-3 trial (NCT04436978) compares two antithrombotic strategies in AF patients undergoing PCI: a short course of dual antiplatelet therapy (DAT) with temporary discontinuation of OAC *versus* the conventional DAT regimen after limited TAT.[20] The nested WOEST-3 genetic substudy aims at determining whether CYP2C19 LOF carrier status influences ischemic or bleeding outcomes in AF-PCI patients and to clarify whether DOAC co-therapy mitigates the clinical impact of clopidogrel hyporesponsiveness.

The present manuscript describes the rationale and design of an observational pharmacogenetic protocol embedded within the WOEST-3 randomized trial, aiming to explore the prognostic relevance of CYP2C19 genetic variability in AF patients undergoing PCI.

Materials and methods

Study design

The WOEST-3 genetic substudy is an observational pharmacogenetic substudy embedded within the ongoing WOEST-3 trial (ClinicalTrials.gov: NCT04436978), a multicenter, international, open-label, randomized controlled trial comparing 2 antithrombotic strategies in patients with AF undergoing successful PCI. Patients are randomized to receive either a 30-day DAT regimen (aspirin plus a $P2Y_{12}$ inhibitor, with temporary withdrawal of OAC) or guideline-directed therapy consisting of DAT (DOAC + a $P2Y_{12}$ inhibitor) following a limited duration of TAT (DOAC + $P2Y_{12}$ inhibitor plus aspirin).[20] The WOEST-3 genetic substudy will include patients from both randomized arms of the main trial, enabling genotype-stratified comparisons across the full spectrum of antithrombotic strategies studied. Although embedded within a randomized controlled trial, the genetic analysis itself is observational in nature and is designed to evaluate genotype-outcome associations rather than to establish causality. The substudy is designed to evaluate the impact of CYP2C19 *2 and *3 LOF alleles on ischemic and bleeding outcomes during a short- and a mid-

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Availability of data and materials: the datasets used and/or analyzed during the current study are available upon reasonable request from the corresponding author.

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term follow-up. Other CYP2C19 variants detected by the genetic testing panel (*4, *8, *35, *17) will be assessed in exploratory analyses only, whereas the primary analyses will focus on the most prevalent and clinically validated LOF alleles (2 and 3). To prevent treatment bias, results of the genetic testing will remain blinded to the investigators, ensuring that $P2Y_{12}$ inhibitor selection is not influenced by genotype knowledge. This design will enable assessment of the impact of CYP2C19 genotype on treatment outcomes while preserving the primary objectives of the WOEST-3 main trial.

Study population

Patients eligible for inclusion in the genetic substudy comprise all individuals enrolled in the WOEST-3 main trial who provide explicit additional written informed consent for genetic testing. Inclusion criteria are age ≥18 years, a diagnosis of AF or atrial flutter with an indication for long-term OAC, and successful PCI. Exclusion criteria are aligned with the main trial protocol and include, but are not limited to, recent ischemic stroke, a history of hemorrhagic stroke, another current indication for OAC, a CHA_2DS_2-VA(Sc) score ≥7, or active bleeding.[20]

Genetic testing

Buccal swabs will be prospectively collected at the time of enrollment by trained study personnel. Samples will be stored in lysis buffer at room temperature for up to 70 days prior to analysis. Genotyping will be performed using the Genedrive® (Genedrive Diagnostics Ltd, Manchester, UK) CYP2C19 ID Kit, a validated Conformité Européenne-marked point-of-care (PoC) molecular diagnostic platform designed for near-patient pharmacogenetic testing. The Genedrive® system uses polymerase chain reaction amplification with allele-specific fluorescent probes to detect CYP2C19 variants directly from buccal swab lysates, without the need for prior DNA extraction or purification. The Genedrive® CYP2C19 ID Kit identifies multiple loss-of-function alleles (*2, *3, *4, *8, *35) and the gain-of-function allele (*17), which affect CYP2C19 enzyme activity.[21,22] PoC analyses will be performed centrally. Participating sites will collect and ship samples to these centers for batch analysis within 70 days of collection. As local investigators do not have access to the PoC devices or the analytical interface, genotyping results will remain blinded to all enrolling sites. This centralized workflow ensures analytical consistency, maintains blinding, and prevents treatment bias.

In a subset of patients, venous blood samples will be obtained during the periprocedural period for paired blood-based genotyping to allow cross-validation of the PoC analysis.[23] Samples will be drawn into ethylene-diamino tetra-acetic acid tubes, preferably via existing intravenous lines, and processed using the TaqMan® single nucleotide polymorphism (SNP) Genotyping Assay (Applied Biosystems, Waltham, MA, USA). Although this assay is labeled for *Research Use Only* and is therefore not considered a clinical gold standard, it represents a widely adopted and reliable method for SNP detection in research settings. In the event of discordant results between buccal swab-based Genedrive® testing and blood-based TaqMan® assays, the blood-based genotyping will be considered the reference standard. Discrepant samples will undergo repeat testing where feasible to exclude technical error.

For patients already enrolled, sampling will occur during follow-up visits or via mailed self-collection kits with written instructions. Returned buccal swabs will be analyzed at Erasmus University Medical Center (Rotterdam, The Netherlands) following the center's validated diagnostic workflow. Each sample will be tested using two independent methods – INFINITI® Microarray (AutoGenomics, Vista, CA, USA) and TaqMan® OpenArray® Genotyping on the QuantStudio™ 12K Flex system (Thermo Fisher Scientific, Waltham, MA, USA) – to ensure accuracy and cross-validation of CYP2C19 results. This extended analysis aligns with the use of the Genedrive® point-of-care test within the study, allowing direct comparison between rapid and laboratory-based approaches. All samples will be processed within an ISO 15189-accredited pharmacogenomics laboratory and labeled with anonymized WOEST-3 codes for data protection and traceability. Patients will be classified as LOF carriers (*2/*3/*4/*8 and/or *35 alleles) or normal (*1/*1, *1/*17) and ultrarapid (*17/*17) metabolizers (no LOF variants).

Clinical endpoints and follow-up

Clinical outcomes will be recorded at 6 weeks and 6 months post-PCI, in alignment with the main WOEST-3 trial follow-up schedule. The primary efficacy endpoint is a composite of ischemic events, including all-cause death, myocardial infarction (MI), stroke, systemic embolism, and probable or definite ST, assessed at 6 months after successful PCI. Secondary endpoints will include ischemic events across different antithrombotic therapy combinations and durations during the 6-week period following successful PCI. Bleeding events will be evaluated at both 6 weeks and 6 months, according to the International Society on Thrombosis and Haemostasis and Bleeding Academic Research Consortium criteria.[24] A net clinical benefit endpoint will be calculated as the composite of the primary ischemic and safety endpoints. Additionally, the study will assess whether procedural complexity, defined by anatomical and technical factors such as treatment of 3 vessels, implantation of ≥3 stents, treatment of ≥3 lesions, total stent length exceeding 60 mm, bifurcation requiring two stents, or chronic total occlusion as the target lesion, modifies the effect of CYP2C19 genotype on ischemic risk.

Data collection, sample size calculation, statistical analysis

Efficacy and safety outcomes will be assessed at both 6 weeks and 6 months following randomization and documented in an electronic case report form. Data collection will be based on the review of medical records, patient-reported questionnaires detailing clinical events, adherence to the assigned treatment, and quality of life measured using the EQ-5D-5L instrument at 6 weeks, 3 months, and 6 months of follow-up. Adherence data will be incorporated into secondary and sensitivity analyses to evaluate their potential impact on clinical outcomes. When needed, follow-up may include telephone contact with the patient and retrieval of supplementary medical documentation. Although DOAC type and dose are not strictly mandated by protocol, edoxaban is the recommended agent within the parent trial and is expected to represent the predominant exposure. Pre-specified subgroup analyses according to DOAC type and dosing regimen will be performed to account for potential treatment heterogeneity. Missing genotyping data will be explicitly reported. Primary analyses will include only patients with valid genetic results. Sensitivity analyses

will be conducted to assess the potential impact of missing data on outcome estimates.

The sample size calculation has been performed using a web-based power calculator (https://clincalc.com/stats/samplesize.aspx). The expected number of ischemic events was estimated using contemporary data from patients with atrial fibrillation undergoing PCI treated with oral anticoagulation, including the post hoc analysis of the AUGUSTUS trial, which reports clinical outcomes in a modern AF population after ACS or PCI.[25] These data demonstrate that thrombotic events, including myocardial infarction, stent thrombosis, and ischemic stroke, continue to occur during follow-up despite DOAC-based dual therapy. The assumption of an approximately three-fold relative increase in risk associated with CYP2C19 LOF variants is supported by robust prior pharmacogenetic evidence in PCI populations treated with clopidogrel, as demonstrated in outcome studies.[2,22] In contemporary AF-PCI management, aspirin is typically discontinued early, leaving clopidogrel as the sole antiplatelet agent in addition to oral anticoagulation. While oral anticoagulants reduce thrombin generation, they do not provide platelet inhibition comparable to aspirin. Therefore, impaired clopidogrel metabolism may remain clinically relevant in this setting, although the extent to which concomitant anticoagulation mitigates the pharmacogenetic effect remains uncertain. Considering the prevalence of CYP2C19 LOF variants,[1-6] a sample size of at least 800 patients will be required to achieve statistical significance for detecting differences in outcomes.[26] Continuous variables will be summarized using means ± standard deviation or medians with interquartile ranges, as appropriate. Between-group comparisons will be conducted using independent samples t-tests or Mann-Whitney U tests for non-normally distributed data. For paired observations, paired t-tests or Wilcoxon signed-rank tests will be used. Categorical variables will be compared using the Chi-square or the Fisher's exact test, depending on sample size and expected frequencies. Time-to-event analyses will be analyzed using Kaplan-Meier survival curves, with group comparisons performed using the log-rank test. Hazard ratios and 95% confidence intervals will be estimated using Cox proportional hazards regression models, adjusting for potential confounding variables (*e.g.*, age, sex, clinical presentation, procedural complexity, comorbidities and concomitant medications known to induce or inhibit CYP2C19 activity). In a predefined subset of patients, cross-validation of genotyping methods will be conducted to evaluate agreement between PoC buccal swab testing (Genedrive®) and blood-based genotyping (TaqMan® assay). Concordance will be assessed using Cohen's kappa (κ) coefficient, with $\kappa > 0.80$ indicating substantial agreement. Sensitivity, specificity, and overall accuracy of the Genedrive® system will be calculated relative to the TaqMan® assay as the reference standard. All analyses will be performed using validated statistical software, and a two-sided p-value <0.05 will be considered statistically significant unless otherwise specified. For additional information please see also the Appendix.

Ethical consideration

The WOEST-3 trial and the nested genetic substudy are being conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Council on Harmonisation and have been approved by the relevant institutional ethics committees of all participating sites. CYP2C19 genotype results will remain blinded to both investigators and patients in this substudy to preserve the integrity of the randomized trial design and avoid treatment bias, as the aim is to evaluate the prognostic impact of genetic variants rather than to guide therapy. Unblinding could introduce confounding and compromise the validity of outcome comparisons. In particular, awareness of the CYP2C19 genotype might lead investigators to prescribe a more potent $P2Y_{12}$ inhibitor in addition to a DOAC, thereby increasing bleeding risk without a proven ischemic benefit in this population. As the clinical utility of genotype-guided antithrombotic therapy in AF patients undergoing PCI remains unproven, withholding genetic results during the study period is ethically justified. All findings will be disclosed after study completion.

Discussion

The clinical significance of CYP2C19 genetic variability in AF-PCI patients remains uncertain. Most evidence linking CYP2C19 LOF alleles to adverse outcomes comes from populations without OAC, where impaired conversion of clopidogrel leads to high platelet reactivity and increased ischemic risk.[10,21,27] In patients receiving a DOAC, however, the pathophysiological context differs. DOACs inhibit thrombin generation, reducing both fibrin formation and thrombin-mediated platelet activation, which may offset the effects of diminished $P2Y_{12}$ receptor blockade.[24,28-30]

This manuscript describes a prespecified study protocol describing the rationale, design, and planned analyses of the genetic substudy and does not report clinical outcome data. The WOEST-3 genetic substudy is designed to determine whether CYP2C19 LOF variants affecting clopidogrel metabolism retain prognostic relevance under contemporary DOAC-based therapy. Its embedded design within a randomized clinical trial ensures that $P2Y_{12}$ inhibitor selection and overall treatment allocation occur independent of the genotype, as genetic results remain concealed from investigators and treating physicians. This approach prevents treatment bias and allows a reliable assessment of genotype–outcome associations.

Previous genotype-guided trials in non-AF populations offer important perspective for interpreting the present study. Both POPular Genetics and TAILOR-PCI evaluated CYP2C19-guided antiplatelet strategies, although their designs and patient populations differed substantially. POPular Genetics, conducted in patients with ST-segment elevation myocardial infarction, showed that a genotype-guided de-escalation approach (prescribing ticagrelor or prasugrel for LOF carriers and clopidogrel for non-carriers) was non-inferior for ischemic outcomes and significantly reduced bleeding compared with routine potent $P2Y_{12}$ inhibitor use.[12] In contrast, TAILOR-PCI enrolled patients with both acute and stable coronary syndromes and tested a genotype-guided escalation strategy (ticagrelor for LOF carriers, clopidogrel for non-carriers) against standard clopidogrel therapy. Although a consistent trend toward lower ischemic risk was observed among LOF carriers, the trial did not meet its primary endpoint.[13] Importantly, all control patients, including those with ACS, were treated with clopidogrel rather than a potent $P2Y_{12}$ inhibitor; while this

was consistent with guideline-recommended therapy for a chronic coronary syndrome, it represented undertreatment for ACS patients and may have attenuated the observable benefit of genotype-guided escalation. However, despite their differing designs and outcomes, both studies suggest that CYP2C19 genotyping may have a clinically relevant role in optimizing antiplatelet therapy. Meta-analyses pooling data from genotype-guided trials suggest that CYP2C19-guided strategies may reduce ischemic events without increasing bleeding, particularly in ACS populations.[22,31] However, these studies exclusively involved patients treated with antiplatelet therapy alone.[11,31,32] Extending this investigation to AF–PCI patients is essential, as concomitant DOAC therapy modifies both thrombotic and bleeding pathways and may alter the clinical expression of clopidogrel hypo-responsiveness. Two mechanistic scenarios are plausible. If DOAC therapy attenuates the impact of CYP2C19 LOF alleles, clinical outcomes may be similar across genotypes, suggesting that genotyping offers limited additional value and that treatment decisions can rely primarily on established clinical predictors. Conversely, if LOF carriers experience higher rates of ischemic events despite anticoagulation, this would confirm that platelet inhibition remains a key determinant of outcome and justify future studies assessing tailored post-PCI strategies, such as replacing clopidogrel with aspirin or a (low-dose) potent $P2Y_{12}$ inhibitor in genetically predisposed patients, provided the bleeding risk remains acceptable. In either case, the findings will clarify whether pharmacogenetic testing provides actionable information for guiding discharge therapy and risk stratification in AF-PCI patients.

Limitations

This substudy has several limitations. Genotyping is performed using different sample collection and analytical methods across centers, which may introduce minor variability despite predefined cross-validation procedures and centralized quality control. Heterogeneity in DOAC type and dosing may further contribute to treatment variability, although subgroup and sensitivity analyses are planned to mitigate this potential confounding. As an observational investigation embedded within a randomized trial, the study is designed to assess genotype–outcome associations but cannot establish causality between CYP2C19 genotype and clinical events. Although comprehensive data collection allows adjustment for major clinical confounders, residual confounding cannot be fully excluded.

The estimated three-fold relative increase in ischemic risk among loss-of-function carriers used for sample size calculation represents the upper range of previously reported associations derived primarily from PCI populations treated with dual antiplatelet therapy. This assumption may overestimate the true effect size in AF patients receiving DOAC-based regimens. Accordingly, the substudy should be interpreted as exploratory and hypothesis-generating rather than definitively powered for clinical superiority testing. Finally, the follow-up duration of 6 months focuses on the period of highest thrombotic and bleeding risk after PCI and may not capture late events beyond this time window.[22]

Conclusions

The WOEST-3 genetic substudy is designed to provide the first systematic evaluation of the clinical relevance of CYP2C19 LOF alleles in patients with atrial fibrillation undergoing PCI. By integrating pharmacogenetic testing within a randomized trial framework while maintaining complete blinding of genotype results, the study offers a unique opportunity to explore the association between CYP2C19 variants and clinical outcomes without influencing treatment decisions. The findings of this substudy will inform whether CYP2C19 LOF carriers experience an excess ischemic risk despite concomitant DOAC therapy or whether oral anticoagulation mitigates the impact of reduced clopidogrel activation. In either scenario, the results will provide critical hypothesis-generating evidence to support the design of future prospective trials evaluating genotype-guided antithrombotic strategies and optimizing the balance between ischemic and bleeding risks in this high-risk population.

References

1. Jiang XL, Samant S, Lesko LJ, et al. Clinical pharmacokinetics and pharmacodynamics of clopidogrel. Clin Pharmacokinet 2015;54:147-66.
2. Li X, Liu Y, Zhang Y, et al. Clopidogrel-associated genetic variants on inhibition of platelet activity and clinical outcome for acute coronary syndrome patients. Basic Clin Pharmacol Toxicol 2019;124:84-93.
3. van den Heuvel L, van der Leeuw J, van Dijk EJ, et al. The frequency of CYP2C19 loss-of-function variants in patients with non-cardioembolic ischemic stroke or transient ischemic attack in the Dutch population. Cerebrovasc Dis 2023;52:700-5.
4. Magavern EF, Squire IB, Hall AS, et al. CYP2C19 genotype prevalence and association with recurrent myocardial infarction in British-South Asians treated with clopidogrel. JACC Adv 2023;2:100465.
5. Vidović S, Savić-Radojević A, Plješa-Ercegovac M, et al. Prevalence of five pharmacologically most important CYP2C9 and CYP2C19 allelic variants in the population from the Republic of Srpska in Bosnia and Herzegovina. Arh Hig Rada Toksikol 2021;72:129-34.
6. Carano F, De Iudicibus S, Stocco G, et al. Genetic variability of CYP2D6, CYP2B6, CYP2C9 and CYP2C19 genes across the Italian Peninsula. Ann Hum Biol 2018;45:66-71.
7. 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;11:181-91.
8. Lee CR, Luzum JA, Sangkuhl K, et al. Clinical outcomes and sustainability of using CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. Circ Genom Precis Med 2018;11:e002069.
9. Shen DL, Wang B, Bai J, et al. Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. J Cardiovasc Pharmacol 2016;67:232-6.
10. Janssen PWA, Bergmeijer TO, Ten Berg JM, et al. Tailored $P2Y_{12}$ inhibitor treatment in patients undergoing non-urgent PCI—the POPular Risk Score study. Eur J Clin Pharmacol 2019;75:1201-10.
11. Bergmeijer TO, Janssen PWA, Schipper JC, et al. CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients—rationale and design of the POPular Genetics study. Am Heart J 2014;168:16-22.

12. De Caterina R, Husted S, Wallentin L, et al. Great debate: triple antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting should be limited to 1 week. Eur Heart J 2022;43:3512-27.
13. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J Acute Cardiovasc Care 2024;13:55-161.
14. Desai A, Gupta A, Patel P, et al. Risk of stroke vs intracerebral hemorrhage in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention: a systematic review and meta-analysis of randomized controlled trials comparing dual vs triple antithrombotic therapy. J Stroke Cerebrovasc Dis 2021;30:105654.
15. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509-24.
16. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24.
17. 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;394:1335-43.
18. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-34.
19. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019;41:407-47.
20. Verburg A, Geisler T, Ten Berg JM, 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;20: e898-e904.
21. Pereira NL, Rihal CS, So D, et al. CYP2C19 genetic testing for oral P2Y12 inhibitor therapy: a scientific statement from the American Heart Association. Circulation 2024;149.
22. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. JAMA 2010;304:1821-30.
23. Burke KA, Tuteja S, Zhao H, et al. Development and validation of a rapid point-of-care CYP2C19 genotyping platform. J Mol Diagn 2025;27:209-15.
24. Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis. Circ Res 2016;118:1409-24.
25. Bahit MC, Lopes RD, Wojdyla DM, et al. Apixaban or warfarin and aspirin or placebo after acute coronary syndrome or percutaneous coronary intervention in patients with atrial fibrillation and prior stroke: a post hoc analysis from the AUGUSTUS trial. JAMA Cardiol 2022;7:682-9.
26. Petrović J, Pešić V, Lauschke VM. Frequencies of clinically important CYP2C19 and CYP2D6 alleles are graded across Europe. Eur J Hum Genet 2020;28:88-94.
27. 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 2018;71:1869-77.
28. Heestermans M, Verhamme P, Weitz JI, et al. Anticoagulants: a short history, their mechanism of action, pharmacology, and indications. Cells 2022;11:3210.
29. Schwarb H, Tsakiris DA. New direct oral anticoagulants (DOAC) and their use today. Dent J (Basel) 2016;4:5.
30. Pereira NL, Farkouh ME, So D, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral $P2Y_{12}$ inhibitor therapy: a meta-analysis. JACC Cardiovasc Interv 2021;14: 739-50.
31. Ingraham BS, Tuteja S, Mega JL, et al. Genetic-guided oral $P2Y_{12}$ inhibitor selection and cumulative ischemic events after percutaneous coronary intervention. JACC Cardiovasc Interv 2023;16:816-25.
32. Parcha V, Kalra R, Arora P, et al. Genotype-guided $P2Y_{12}$ inhibitor therapy after percutaneous coronary intervention: a Bayesian analysis. Circ Genom Precis Med 2021;14:e003353.

Online supplementary material:
Online Appendix. Outcomes definition.