Kardiologia Polska
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

POLISH HEART JOURNAL

Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon

ISSN 0022–9032

e-ISSN 1897–4279

Can CYP2C19 genotyping improve antiplatelet therapy efficacy in real-life practice? Recent advances

Authors: Udaya S Tantry, Sahib Singh, Lekshmi Narayan Raghavakurup, Kevin P Bliden, Paul A Gurbel

Article type: Review

Received: July 31, 2024

Accepted: July 31, 2024

Early publication date: August 1, 2024

Can CYP2C19 genotyping improve antiplatelet therapy efficacy in real-life practice? Recent advances

Udaya S Tantry, Sahib Singh, Lekshmi Narayan Raghavakurup, Kevin P Bliden, Paul A Gurbel

Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital of Baltimore and Lifebridge Health System, Baltimore, United States

Correspondence to:
Paul A. Gurbel, MD,
Sinai Center for Thrombosis Research and Drug Development,
Sinai Hospital of Baltimore,
Baltimore, MD, 21209,
phone: 410 367 25 90,
e-mail: pgurbel@lifebridgehealth.org

ABSTRACT

Clopidogrel remains the most widely used $P2Y_{12}$ receptor inhibitor worldwide and is often used in combination with aspirin for secondary prevention in patients with arterial disease. The drug is associated with a wide response variability with one on three patients exhibiting little or no inhibition of adenosine diphosphate-induced platelet aggregation. It is a prodrug that is mainly metabolized by hepatic cytochrome P450 (CYP) 2C19. Patients who carry a *CYP2C19 loss-of-function (LoF)* allele have reduced metabolism of clopidogrel that is associated with reduced platelet inhibition compared to non-carriers that is associated with increased risk for thrombotic event occurrences, particularly, stent thrombosis. The United States Food and Drug Administration (US FDA) issued a black box warning in the clopidogrel label highlighting the importance of presence of *CYP2C19 LOF* allele during the insufficient metabolism of clopidogrel and availability of other potent $P2Y_{12}$ inhibitor for the treatment in CYP2C19 poor metabolizers. Clinical trials have conclusively demonstrated greater anti-ischemic benefits of prasugrel/ticagrelor in the treatment of patients carrying the *CYP2C19 LoF* allele. However, uniform use of these more potent $P2Y_{12}$ inhibitors has been associated with greater bleeding and cost, and lower adherence. The latter information provides a strong rationale for personalizing $P2Y_{12}$ inhibitor therapy based on the laboratory determination of *CYP2C19* genotype. However, cardiologists have been slow to take up pharmacogenetic testing possibly due to lack of provider and patient education, clear cardiology guidelines and, and lack of positive results from adequately sized randomized clinical trials. However, current evidence strongly supports genotyping of patients who are candidates for clopidogrel. Physicians should strongly consider performing genetic tests to identify *LoF* carriers and treat these patients with more pharmacodynamically predictable $P2Y_{12}$ inhibitors than clopidogrel.

Key words: clopidogrel, CYP2C19, genotyping, P2Y12 receptor, platelets, stent thrombosis

Therapy with a $P2Y_{12}$ receptor blocker added to aspirin remains the cornerstone pharmacologic therapy in patients with arterial diseases to prevent recurrent ischemic event occurrences [1]. Continuous downstream intracellular signaling from the $P2Y_{12}$ receptor is essential for sustained platelet activation and aggregation, and subsequent stable platelet-rich thrombus generation at the site of vascular injury causing thrombotic event occurrences [2]. Antithrombotic efficacy observed in multiple randomized clinical trials provided the strong rationale to add a $P2Y_{12}$ receptor blocker to aspirin therapy [1]. Despite the availability of more potent $P2Y_{12}$ receptor blockers such as prasugrel and ticagrelor, clopidogrel remains the dominant $P2Y_{12}$ inhibitor used in patients with arterial diseases.

Clopidogrel is an oral, selective platelet $P2Y_{12}$ receptor blocker. It is a second generation thienopyridine prodrug. Following intestinal administration, 85% of clopidogrel is hydrolyzed predominantly by hepatic carboxylesterase I to an inactive carboxylic acid metabolite - SR26334 and the remaining 15% is rapidly metabolized in a two-step process by hepatic CYP enzymes to an unstable active thiolactone metabolite. CYP2C19 plays a major role in clopidogrel metabolism in both steps [3]. In modeling studies, the active thiolactone metabolite is predicted to destabilize interactions of the G-coupled oligomeric $P2Y_{12}$ receptor with adenosine diphosphate (ADP) by binding permanently to the free thiol of Cys97 and thereby preventing ADP-induced platelet activation and aggregation for the life of platelets [2, 4].

A pivotal study conducted in patients undergoing elective stenting in 2003 demonstrated the wide pharmacodynamic response variability to clopidogrel. Most importantly, a limited or an absence of inhibition of ADP-induced platelet aggregation was demonstrated in nearly one in three patients. This phenomenon was first described as clopidogrel “non-responsiveness” or clopidogrel “resistance” [5]. Later, it was suggested that high post-treatment platelet reactivity (HPR) to ADP is more appropriate to describe this phenomenon and more useful to correlate with recurrent ischemic event occurrences [6]. In this line, multiple translational and observational research studies linked HPR to recurrent ischemic events such as myocardial infarction (MI) and stent thrombosis in patients treated with coronary stenting. Several lines of evidence strongly suggested that variable and insufficient active metabolite generation were the primary explanation for clopidogrel response variability and nonresponsiveness, respectively [7]. Functional variability in hepatic cytochromes, particularly CYP2C19 has been reported as a major cause of clopidogrel response variability. CYP2C19 isoenzyme activity is strongly influenced by carriage of single nucleotide polymorphisms (SNPs). In addition, epigenetic factors such as demographic variables, comorbidities, and drug-drug interaction at the CYP level further influence platelet reactivity in patients treated with clopidogrel independent of SNP carriage [8].

A genome wide association study (GWAS) study conducted in healthy volunteers demonstrated that *loss-off function (LoF)* polymorphisms of *CYP2C19 (*2 and *3)* were associated with decreased clopidogrel active metabolite exposure and less platelet inhibition [9]. In a replication study of clopidogrel-treated patients treated who underwent percutaneous coronary intervention (PCI), carriers of the *LoF CYP2C19*2* allele had ∼2.4× higher cardiovascular (CV) event occurrence at 1 year compared with non-carriers [9]. The influence of *CYP2C19 LoF* carrier status on clopidogrel-induced platelet inhibition has been shown to be most significant among poor metabolizers who carry two *LoF* alleles compared to patients carrying one *LoF* allele [10]. Similarly, an increased risk of the composite endpoint of CV death, MI, or stroke among carriers of one *LoF* allele (1.6×) and carriers of two *LoF* alleles (1.8×), as compared with non-carriers, was demonstrated in a collaborative meta-analysis of trials primarily involving PCI-treated patients (91%). The same meta-analysis demonstrated a dose-dependent association of *LoF* carriage with a 2.67 times increased risk of stent thrombosis among carriers of one *LoF* allele and 3.97 times increased risk of stent thrombosis among carriers of two *LoF* alleles as compared with non-carriers

[11]. The influence of the *gain-of-function allele (GoF) (CYP2C19*17)* on ADP-induced platelet function and post-PCI clinical events is less compared to that of *CYP2C19 LoF* alleles.

The prevalence of *LoF* and *GoF* alleles differ significantly by ethnicities. *LoF* allele carriage is more frequent in Asians, particularly East Asians, whereas *GoF* allele carriage occurs more frequently among Europeans and Africans [12, 13]. The genotype based CYP2C19 metabolizer status indicating CYP2C19 enzyme activity and their prevalence in different ethnicities are presented in the Table 1. However, despite the higher prevalence of *LoF* allele carriage, East Asian patients demonstrate a lower risk for post-PCI ischemic event occurrences along with elevated risk for bleeding. The latter phenomenon has been described as "East Asian Paradox" [14].

The pharmacodynamic effects of ticagrelor and prasugrel are not significantly influenced by *CYP2C19* genetic polymorphisms. These agents are associated with less response variability, greater platelet inhibition and low rates of HPR. In the genetic sub-studies of major randomized clinical trials, treatment with prasugrel and ticagrelor was associated with significantly lower MACE rates compared to clopidogrel in patients carrying a *LoF* allele [15, 16].

The International Clopidogrel Pharmacogenomics Consortium (ICPC) developed a pharmacogenomic polygenic response score (PgxRS) to study the impact of 31 candidate gene polymorphisms on platelet reactivity in coronary artery disease (CAD) patients treated with clopidogrel [17]. Earlier it was suggested that antithrombotic efficacy can be improved by treating patients with HPR or with *LoF* carriage with prasugrel or ticagrelor. It was also postulated that the reservation of potent $P2Y_{12}$ inhibitors for the latter patients as compared to uniform treatment of all patients with prasugrel or ticagrelor would be associated with greater safety [18]. Multiple subsequent studies have demonstrated that the anti-ischemic effects of clopidogrel are comparable to those of potent $P2Y_{12}$ receptor inhibitors in *LoF* non-carriers. These observations have provided a strong rationale for patients with *CYP2C19 LoF* carriage, as determined by laboratory testing, to be selectively treated with prasugrel or ticagrelor [18].

Multiple randomized clinical trials explored the utility of *CYP2C19* genetic testing to personalize $P2Y_{12}$ receptor based dual antiplatelet therapy (DAPT) [19–21]. The TROPICAL ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes) trial primarily demonstrated the utility of de-escalation of prasugrel to clopidogrel therapy based on platelet function testing in ACS patients undergoing PCI. In a genotyping sub-study of TROPICAL ACS, a significant correlation between *CYP2C19*2* and *CYP2C19*17* carrier status with platelet reactivity in patients treated with clopidogrel was demonstrated. However, with respect to the prediction of ischemic and bleeding risk, there was no added benefit of genotyping with the phenotype guided de-escalation approach [22].

In the POPular Genetics trial, patients undergoing PCI for STEMI (n=2,488) who received genotype-guided $P2Y_{12}$ inhibitor treatment had lower Platelet Inhibition and Patient Outcomes (PLATO) major bleeding events (9.8% vs. 12.5%; HR, 0.78; P = 0.04) and similar rates of net adverse clinical events (defined as death from any cause, MI, definite stent thrombosis, stroke, or PLATO major bleeding at 12 months (5.1% vs. 5.9%; P <0.001 for noninferiority) when compared with patients who received uniform ticagrelor or prasugrel therapy [19]. In the TAILOR PCI (Tailored Antiplatelet Therapy Following PCI) Trial a randomized investigation of 5302 CAD patients undergoing PCI, *CYP2C19 LoF* carriers treated with ticagrelor or prasugrel had lower MACE (CV death, MI, stroke, stent thrombosis, and severe myocardial ischemia) rates compared to patients randomized to conventional clopidogrel therapy (4.0% vs. 5.9%; HR, 0.66; P = 0.06) [20]. Interestingly, in a prespecified analysis of this trial that assessed multiple events per patient, the genotype-guided strategy was associated with a significantly lower rate of ischemic events (HR, 0.60; P = 0.01), with no significant difference in major/minor bleeding (HR, 1.36; P = 0.39) [23]. A collaborative study of 3342 patients undergoing PCI in a real-world setting demonstrated a lower rate of major thrombotic events in *LoF* carriers treated with prasugrel or ticagrelor compared to patients treated with clopidogrel (adjusted HR, 0.56), but a similar rate of thrombotic events in in CYP2C19 *LoF* noncarriers (adjusted HR, 1.07) and a similar rate of bleeding with alternative therapy versus clopidogrel in both groups [24]. It was also demonstrated that there was no significant influence of *CYP2C19*17* genotype on post-PCI prescribing decisions or clinical outcomes [25].

Combining *CYP2C19* genotype testing, platelet reactivity and clinical risk factors in a pharmacogenetic-driven algorithm (POPular Risk Score [PRiS]) showed usefulness in tailoring DAPT in patients undergoing drug eluting stenting; in patients with PRiS ≥2, ticagrelor was demonstrated to reduce MACE without an increase in bleeding risk as compared to uniform use of clopidogrel; in patients with PRiS <2, clopidogrel therapy was associated with a bleeding risk with comparable incidence of MACE [26]. This study highlighted the utility of combing genetic testing with platelet function testing and demographic variables to improve patient outcomes.

In addition to CAD patients, the utility of *CYP2C19* genotype testing has been explored in large scale trials of patients with stroke. In the randomized Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE-2 trial), Chinese patients with *CYP2C19 LoF* carriage and with minor ischemic stroke or transient ischemic attack (TIA), when treated with ticagrelor vs clopidogrel had a reduced risk of stroke at 90 days (6.0% vs. 7.6%; HR, 0.77; P = 0.008), and a similar risk of moderate/severe bleeding (0.3% vs. 0.3%) [27] (Table 2). Total bleeding events were more common in the ticagrelor group, and the clinical outcomes were consistent among the intermediate and poor *CYP2C19* metabolizers [28]. Among different subgroups, the benefit of ticagrelor over clopidogrel was seen in patients with normal renal function, single small subcortical infarction (SSSI), non-elevated remnant cholesterol (RC) levels, and without intracranial artery stenosis (ICAS) [29–32]. It is worthwhile mentioning that the time wise assessment in the CHANCE-2 trial showed benefit associated with ticagrelor therapy mainly in the first week, with only small additional benefit in the next 2 weeks and the overall superiority of ticagrelor over clopidogrel persisted at 1 year follow up [33, 34]. In a recent RCT, personalized antiplatelet therapy in acute stroke/TIA patients based on the *CYP2C19 genotype* testing and urinary 11-dehydroxy thromboxane (Tx)B_2 (a marker of aspirin response) levels was associated with favorable neurological function and reduction in bleeding risk compared to a standard treatment [35]. A similar benefit was also shown in another RCT where antiplatelet therapy guided by pharmacogenomics and clinical characteristics was associated with decreased vascular event risk in patients with stroke/TIA [36]. These trials signify the higher recurrent risk of stroke in *CYP2C19 LoF* carriers treated with clopidogrel [37].

GUIDELINES ADDRESSING *CYP2C19* GENOTYPE TESTING

In 2010, the US FDA issued a “Boxed Warning” stating that healthcare professionals should consider other antiplatelet medications or alternative dosing in patients who are poor metabolizers of clopidogrel (*CYP2C19 LoF* carriers) [38]. Despite the demonstration of a graded effect of *CYP2C19 LoF* carriage [11], the American Heart Association and American College of Cardiology guidelines for *CYP2C19* genotyping have not changed since 2011 when they recommended against routine genotyping — a class III (i.e., no benefit) recommendation [39]. The 2020 European Society of Cardiology guidelines for the management of ACS recommend *CYP2C19*-guided antiplatelet therapy as an alternative to 12 months of DAPT with prasugrel or ticagrelor [40]. The latter was based on the results from POPular Genetics trial [19]. The 2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline recommended the use of alternative $P2Y_{12}$ inhibitors in *CYP2C19 poor metabolizers* in patients with acute coronary syndromes and/or those undergoing PCI (strong recommendation), and other CV/neurovascular indications (moderate recommendation) [15]. Finally, the 2023 European Society of Cardiology guidelines for the management of acute coronary syndrome briefly mention *CYP2C19* genetic testing for $P2Y_{12}$ therapy de-escalation [41].

The main reason for not giving a strong recommendation for genotyping is that the guidelines require high-quality evidence from more than one large RCT, meta-analyses of high-quality RCTs, or one or more RCT's corroborated by high-quality registry studies for a class I/level A recommendation (i.e., that the test should be performed) [39]. It is difficult to achieve the latter evidence at this time because it is prohibitively costly to conduct the large-scale trial with the size required to reach adequate power. Moreover, trials of personalized therapies are not of interest to most pharmaceutical companies due to concern of market share loss. Finally, it is unethical given the body of evidence currently available to randomize *CYP2C19 LoF* carriers to clopidogrel since they suffer harm. In this scenario, a non-inferiority trial like the POPular Genetics trial, and the integration of evidence across multiple studies in meta-analyses may be the only option but would not likely provide findings conclusive enough to reach a class I recommendation in the minds of the guideline writers [19].

FUTURE PERSPECTIVES

Despite the FDA's boxed warning, robust data implicating a poorer clinical outcome in *LoF* carriers treated with clopidogrel, and the cost-effectiveness of personalizing antiplatelet therapy by genotyping, the implementation of genotype testing into routine clinical practice has been less robust. Furthermore, uniform use of more potent $P2Y_{12}$ inhibitors is associated with greater bleeding and cost, and lower adherence, whereas clopidogrel is effective in the majority of *CYP2C19 LoF* non-carriers patients. Therefore, at this time, the totality of evidence strongly suggests that physicians should perform genetic testing to identify patients with high-risk arterial disease to determine whether they are suitable for clopidogrel therapy. However, current physician preference for $P2Y_{12}$ inhibitors is not genotype guided [42–44]. The current American Heart Association statement supporting genotype-guided antiplatelet therapy may provide an impetus to change current practice [45]. Parenthetically, the seemingly absolute requirements for large RCT results stand against the requirements of guideline writers in other specialties (e.g., oncology) who have been willing to consider the entire hierarchy of evidence.

Real-time PCR (TaqMan system, laboratory-based testing) using genomic DNA from whole blood samples is time consuming and requires certified personnel and a laboratory to perform *CYP2C19* genotyping for clinical use. Point-of-care (POC) genotype testing may have its greatest impact when implemented during the hospital stay when the physician can decide on the genetically predicted optimal choice of $P2Y_{12}$ receptor inhibitor for loading and for maintenance. Development of advanced point of care genetic testing technology with rapid turnaround time has opened the door for personalized antiplatelet therapy strategies. Currently, a POC *CYP2C19* genotyping assay using buccal swabs (Cube, Genomadix, Kanata, ON, Canada, earlier SPRATAN) are available. There is a 99.1% concordance between the Spartan assay and TaqMan genotyping assay results [20]. Genedrive, another POC testing method, is also available [46].

POC genotyping assay is simple, user friendly and can be performed even in an outpatient doctor's office for quick antiplatelet therapy personalization. In a recent study, the feasibility of a routine bedside *CYP2C19* genetic testing for guiding antiplatelet therapy in a community setting was explored using the SPARTAN System [47]. *CYP2C19* genetic testing was performed in the catheterization laboratory prior to PCI and the results were available within one hour for decision making by the interventional cardiologist. Adherence to the best practice advisory (BPA) by clinicians was noted in 93% of patients undergoing PCI; 87% of *CYP2C19 LoF* allele carriers were prescribed prasugrel or ticagrelor, and 95 % of non-carriers were prescribed clopidogrel [47]. These finding from the community hospital study reinforce the feasibility of routine *CYP2C19* genotyping in large academic centers. In 2024 POC genotyping can be clearly used to rapidly personalize antiplatelet therapy, reserving clopidogrel for the wild type and prasugrel or ticagrelor for the *LoF* carriers.

Article information

Conflict of interest: PAG received consulting fees and/or honoraria from Bayer, Vectura/Otitopic, Janssen, Cleveland Clinic foundation, Wolters Kluwer Pharma, Web MD Medscape, Baron and Budd, Premier Health Care Resource, Baim Institute, and Medforce; institutional research grants from Accriva Diagnostics, AstraZeneca, Bayer, Cronos, Janssen Pharmaceuticals Inc.,

Haemonetics, Hikari Dx, Idorisa, Labcorp Drug Development, Novartis, Prolocor, Recor Medical, Vectura Limited, Zoll Medical Corporation; in addition, Dr. Gurbel has two patents, Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient. Dr. Gurbel was an expert witness in a lawsuit associated with Plavix. Other authors report no conflict of interests.

Funding: This study was funded by Sinai Center for Thrombosis Research and Drug Development.

REFERENCES

1. Gurbel PA, Tantry US. Combination antithrombotic therapies. Circulation. 2010; 121(4): 569–583, doi: 10.1161/circulationaha.109.853085.
2. Gurbel PA, Kuliopulos A, Tantry US. G-protein-coupled receptors signaling pathways in new antiplatelet drug development. Arterioscler Thromb Vasc Biol. 2015; 35(3): 500–512, doi: 10.1161/ATVBAHA.114.303412, indexed in Pubmed: 25633316.
3. Gurbel PA, Tantry US. Drug insight: Clopidogrel nonresponsiveness. Nat Clin Pract Cardiovasc Med. 2006; 3(7): 387–395, doi: 10.1038/ncpcardio0602, indexed in Pubmed: 16810174.
4. Zhang J, Zhang K, Gao ZG, et al. Agonist-bound structure of the human P2Y12 receptor. Nature. 2014; 509(7498): 119–122, doi: 10.1038/nature13288, indexed in Pubmed: 24784220.
5. Gurbel PA, Bliden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003; 107(23): 2908–2913, doi: 10.1161/01.CIR.0000072771.11429.83, indexed in Pubmed: 12796140.
6. Tantry US, Bliden KP, Gurbel PA. What is the best measure of thrombotic risks — pretreatment platelet aggregation, clopidogrel responsiveness, or posttreatment platelet

aggregation? Catheter Cardiovasc Interv. 2005; 66(4): 597–598, doi: 10.1002/ccd.20526, indexed in Pubmed: 16208713.

7. Bonello L, Tantry US, Marcucci R, et al. Working group on high on-treatment platelet reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol. 2010; 56(12): 919–933, doi: 10.1016/j.jacc.2010.04.047, indexed in Pubmed: 20828644.
8. Gurbel PA, Tantry US, Shuldiner AR, et al. Genotyping: one piece of the puzzle to personalize antiplatelet therapy. J Am Coll Cardiol. 2010; 56(2): 112–116, doi: 10.1016/j.jacc.2010.04.008, indexed in Pubmed: 20471192.
9. 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. 2009; 302(8): 849–857, doi: 10.1001/jama.2009.1232, indexed in Pubmed: 19706858.
10. Gurbel PA, Shuldiner AR, Bliden KP, et al. The relation between CYP2C19 genotype and phenotype in stented patients on maintenance dual antiplatelet therapy. Am Heart J. 2011; 161(3): 598–604, doi: 10.1016/j.ahj.2010.12.011, indexed in Pubmed: 21392617.
11. 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(16): 1821–1830, doi: 10.1001/jama.2010.1543, indexed in Pubmed: 20978260.
12. Beitelshees AL, Horenstein RB, Vesely MR, et al. Pharmacogenetics and clopidogrel response in patients undergoing percutaneous coronary interventions. Clin Pharmacol Ther. 2011; 89(3): 455–459, doi: 10.1038/clpt.2010.316, indexed in Pubmed: 21270785.
13. 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(5): 959–967, doi: 10.1002/cpt.2526, indexed in Pubmed: 35034351.
14. Jeong YH, Tantry US, Gurbel P. What is the “East Asian Paradox”? Cardiosource Interventional News. 2012; 1: 38–39.
15. 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. 2009; 119(19): 2553–2560, doi: 10.1161/CIRCULATIONAHA.109.851949, indexed in Pubmed: 19414633.

16. 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(9749): 1320–1328, doi: 10.1016/S0140-6736(10)61274-3, indexed in Pubmed: 20801498.
17. Lewis JP, Backman JD, Reny JL, et al. Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. Eur Heart J Cardiovasc Pharmacother. 2020; 6(4): 203–210, doi: 10.1093/ehjcvp/pvz045, indexed in Pubmed: 31504375.
18. Gurbel PA, Tantry US. Do platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents?: Platelet function testing and genotyping improve outcome in patients treated with antithrombotic agents. Circulation. 2012; 125(10): 1276–1287, doi: 10.1161/CIRCULATIONAHA.111.031195, indexed in Pubmed: 22412089.
19. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y inhibitors in primary PCI. N Engl J Med. 2019; 381(17): 1621–1631, doi: 10.1056/NEJMoa1907096, indexed in Pubmed: 31479209.
20. 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. 2020; 324(8): 761–771, doi: 10.1001/jama.2020.12443, indexed in Pubmed: 32840598.
21. Pereira NL, Rihal C, Lennon R, et al. Effect of CYP2C19 genotype on ischemic outcomes during oral p2y inhibitor therapy: A meta-analysis. JACC Cardiovasc Interv. 2021; 14(7): 739–750, doi: 10.1016/j.jcin.2021.01.024, indexed in Pubmed: 33744207.
22. Gross L, Trenk D, Jacobshagen C, et al. Genotype-phenotype association and impact on outcomes following guided de-escalation of anti-platelet treatment in acute coronary syndrome patients: The TROPICAL-ACS genotyping substudy. Thromb Haemost. 2018; 118(9): 1656–1667, doi: 10.1055/s-0038-1667337, indexed in Pubmed: 30103241.
23. Ingraham BS, Farkouh ME, Lennon RJ, et al. Genetic-guided oral P2Y inhibitor selection and cumulative ischemic events after percutaneous coronary intervention. JACC

Cardiovasc Interv. 2023; 16(7): 816–825, doi: 10.1016/j.jcin.2023.01.356, indexed in Pubmed: 37045502.

24. Beitelshees AL, Thomas CD, Empey PE, et al. Genotype-Guided antiplatelet therapy after percutaneous coronary intervention in diverse clinical settings. J Am Heart Assoc. 2022; 11(4): e024159, doi: 10.1161/JAHA.121.024159, indexed in Pubmed: 35156424.
25. 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 intervention. Clin Pharmacol Ther. 2021; 109(3): 705–715, doi: 10.1002/cpt.2039, indexed in Pubmed: 32897581.
26. Lyu SQ, Zhu J, Wang J, et al. Utility of a pharmacogenetic-driven algorithm in guiding dual antiplatelet therapy for patients undergoing coronary drug-eluting stent implantation in China. Eur J Clin Pharmacol. 2022; 78(2): 215–225, doi: 10.1007/s00228-021-03224-8, indexed in Pubmed: 34636928.
27. 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. 2021; 385(27): 2520–2530, doi: 10.1056/nejmoa2111749, indexed in Pubmed: 34708996.
28. Xie X, Johnston SC, Wang A, et al. Association of CYP2C19 loss-of-function metabolizer status with stroke risk among Chinese patients treated with ticagrelor-aspirin vs clopidogrel-aspirin: A prespecified secondary analysis of a randomized clinical trial. JAMA Netw Open. 2023; 6(6): e2317037, doi: 10.1001/jamanetworkopen.2023.17037, indexed in Pubmed: 37279000.
29. Wang A, Tian X, Xie X, et al. Ticagrelor-aspirin versus clopidogrel-aspirin among loss-of-function carriers with minor stroke or transient ischemic attack in relation to renal function: A post hoc analysis of the CHANCE-2 trial. Ann Intern Med. 2022; 175(11): 1534–1542, doi: 10.7326/M22-1667, indexed in Pubmed: 36315949.
30. Wang C, Jia W, Jing J, et al. Ticagrelor versus clopidogrel in minor stroke or transient ischemic attack with intracranial artery stenosis: A post hoc analysis of CHANCE-2. J Am Heart Assoc. 2023; 12(21): e031611, doi: 10.1161/JAHA.123.031611, indexed in Pubmed: 37889172.
31. Liu H, Jing J, Wang A, et al. Genotype-guided dual antiplatelet therapy in minor stroke or transient ischemic attack with a single small subcortical infarction. Neurology. 2023;

100(16): e1643–e1654, doi: 10.1212/WNL.0000000000206775, indexed in Pubmed: 36697242.

32. Wang A, Tian X, Xie X, et al. Effects of remnant cholesterol on the efficacy of genotype-guided dual antiplatelet in CYP2C19 loss-of -function carriers with minor stroke or transient ischaemic attack: a post-hoc analysis of the CHANCE-2 trial. eClinicalMedicine. 2024; 67: 102357, doi: 10.1016/j.eclinm.2023.102357.
33. Pan Y, Meng X, Jin A, et al. Time course for benefit and risk with ticagrelor and aspirin in individuals with acute ischemic stroke or transient ischemic attack who carry CYP2C19 loss-of-function alleles: A secondary analysis of the CHANCE-2 randomized clinical trial. JAMA Neurol. 2022; 79(8): 739–745, doi: 10.1001/jamaneurol.2022.1457, indexed in Pubmed: 35727586.
34. Meng X, Wang A, Tian X, et al. One-Year outcomes of early therapy with ticagrelor vs clopidogrel in loss-of-function carriers with stroke or TIA trial. Neurology. 2024; 102(3): e207809, doi: 10.1212/WNL.0000000000207809, indexed in Pubmed: 38181311.
35. Han M, Jia W, Wu Y, et al. Short-term efficacy and safety of personalized antiplatelet therapy for patients with acute ischaemic stroke or transient ischaemic attack: A randomized clinical trial. Br J Clin Pharmacol. 2023; 89(9): 2813–2824, doi: 10.1111/bcp.15775, indexed in Pubmed: 37159861.
36. Zhang X, Jiang S, Xue J, et al. Personalized antiplatelet therapy guided by clopidogrel pharmacogenomics in acute ischemic stroke and transient ischemic attack: A prospective, randomized controlled trial. Front Pharmacol. 2022; 13: 931405, doi: 10.3389/fphar.2022.931405, indexed in Pubmed: 36744212.
37. Cargnin S, Ferrari F, Terrazzino S. Impact of CYP2C19 genotype on efficacy and safety of clopidogrel-based antiplatelet therapy in stroke or transient ischemic attack patients: an updated systematic review and meta-analysis of non-east asian studies. Cardiovasc Drugs Ther. 2023 [Epub ahead of print], doi: 10.1007/s10557-023-07534-0, indexed in Pubmed: 38038819.
38. FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-reduced-effectiveness-plavix-clopidogrel-patients-who-are-

poor#:~:text=FDA%20recommends%20that%20healthcare%20professionals,is%20reduced%20in%20these%20patients (accessed: July 30, 2024).

39. Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA focused update of the guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline). J Am Coll Cardiol. 2011; 57(19): 1920–1959, doi: 10.1016/j.jacc.2011.02.009, indexed in Pubmed: 21450428.
40. Collet JP, 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. 2021; 42(14): 1289–1367, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
41. Byrne RA, Rossello X, Coughlan JJ, et al. et al.. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J. 2023; 44(38): 3720–3826, doi: 10.1093/eurheartj/ehad191, indexed in Pubmed: 37622654.
42. Koshy AN, Giustino G, Sartori S, et al. Ticagrelor or prasugrel versus clopidogrel in patients undergoing percutaneous coronary intervention for chronic coronary syndromes. EuroIntervention. 2023; 18(15): 1244–1253, doi: 10.4244/EIJ-D-22-00654, indexed in Pubmed: 36660810.
43. Ijaz SH, Baron SJ, Shahnawaz A, et al. Utilization trends in platelet adenosine diphosphate P2Y12 receptor inhibitor and cost among medicare beneficiaries. Curr Probl Cardiol. 2023; 48(5): 101608, doi: 10.1016/j.cpcardiol.2023.101608, indexed in Pubmed: 36690313.
44. Wang Y, Cavallari LH, Brown JD, et al. Assessing the clinical treatment dynamics of antiplatelet therapy following acute coronary syndrome and percutaneous coronary intervention in the US. JAMA Netw Open. 2023; 6(4): e238585, doi: 10.1001/jamanetworkopen.2023.8585, indexed in Pubmed: 37067798.
45. Pereira NL, Cresci S, Angiolillo DJ, et al. Genetic Testing for Oral P2Y12 Inhibitor Therapy: A Scientific Statement From the American Heart Association. Circulation. 2024 [Epub ahead of print], doi: 10.1161/CIR.0000000000001257, indexed in Pubmed: 38899464.
46. Multi-partner grant awarded for the validation of Genedrive® CYP2C19 ID Kit in time critical NHS settings. http://www.genedriveplc.com/press-releases/gdr_-_devote_(16.06.23).pdf (accessed: July 30, 2024).

47. Gurbel PA, Bliden K, Sherwood M, et al. Development of a routine bedside CYP2C19 genotype assessment program for antiplatelet therapy guidance in a community hospital catheterization laboratory. J Thromb Thrombolysis. 2024; 57(4): 566–575, doi: 10.1007/s11239-024-02953-8, indexed in Pubmed: 38480590.

Table 1. Genotyping based CYP2C19 metabolizer status and their prevalence in different ethnicities

Common *CYP2C19* genotypes	**Phenotype (Metabolized status)**	**Prevalence in different ethnicities**
**17/*17, *17/*1*	Rapid metabolizer (RM)	34% Caucasians, 30% African Americans, 4% Asians
**1/*1*	Normal metabolizer (NM)	
**1/*2*	Intermediate metabolizer (IM)	24% Caucasians, 30% African Americans, 46% Asians
**2/*2*	Poor metabolizer (PM)	2% Caucasians. 3.5% African Americans, 10% Asians

Table 2. Studies supporting genotyping in clopidogrel treated patients

Study, (ref #)	**Study design**	**Intervention**	**Primary endpoints**	**Key results**
Shuldiner et al. [9]	Genome Wide Association study in Amish healthy subjects, n = 429	Clopidogrel for 7 days Clopidogrel-treated patients	Platelet aggregation in patients with *CYPC19*2* allele	*CYP2C129*2* carriage strongly associated with diminished anti-platelet response, accounting for 12% of the variation in platelet aggregation

	Outcome study in patients undergoing coronary intervention, n = 237			to ADP ($P = 4.3 \times 10^{-11}$) *CYP2C19*2* carriers vs non- carriers have higher risk for 1-year CV event or death (20.9% vs. 10%; HR, 2.42; 95% CI, 1.18–4.99; *P* = 0.02)
POPular Genetics [20]	RCT in patients undergoing primary PCI with stent implantation, n = 2488	Personalized $P2Y_{12}$ inhibitor therapy based on early *CYP2C19* genetic testing (genotype-guided group) vs. blanket therapy with ticagrelor/ prasugrel (standard-treatment group) for 12 months	All cause death, MI, definite stent thrombosis, stroke, or PLATO major bleeding at 12 months PLATO major or minor bleeding	5.1% vs. 5.9%, absolute difference 0.7 percentage points, 95% CI, –2 to 0.7; *P* <0.01 for non-inferiority 9.8% vs. 12.5%; HR, 0.78; 95% CI, 0.61 to 0.98; *P* = 0.04
TAILOR-PCI [21]	RCT in patients undergoing PCI for ACS or stable CAD, n = 5302	Point-of-care genotype guided group: *CYP2C19* LoF carriers: ticagrelor or prasugrel and noncarriers: clopidogrel vs. conventional group: clopidogrel	CV death, MI, stroke, stent thrombosis and severe recurrent ischemia at 12 months[a] Major bleeding[a]	4.0% vs. 5.9%; HR, 0.66; 95% CI, 0.43–1.02; *P* = 0.06 1.9% vs. 1.6%; HR, 1.22;

				95% CI, 0.60–2.51; *P* = 0.58
Pereira et al. [22]	Meta-analysis of 7 RCTs: 77% had PCI and 98% had ACS, n =15 949	Ticagrelor and prasugrel vs. clopidogrel in: *CYP2C19* LoF carriers *CYP2C19* LoF non-carriers	CV death, MI, stroke, stent thrombosis, and severe recurrent ischemia	7% vs. 10.3%; RR, 0.70; 95% CI, 0.59–0.83 8.8% vs. 9.2%; RR, 1.0; 95% CI, 0.80–1.25
CHANCE 2 trial [27]	Chinese patients with a minor IS or TIA who carried *CYP2C19* LoF alleles, n = 6412	Ticagrelor with aspirin vs. clopidogrel with aspirin for 90 days	New stroke within 90 days Severe or moderate bleeding within 90 days	6.0% vs. 7.6%; HR, 0.77; 95% CI, 0.64–0.94; *P* = 0.008 0.3% vs. 0.3%; HR, 0.82 95% CI, 0.34–1.98; *P* = 0.66

*The primary analysis was in patients with *CYP2C19* LoF variants where ticagrelor or prasugrel was compared to clopidogrel

Abbreviations: ACS, acute coronary syndromes; ADP, adenosine diphosphate; CAD, coronary artery disease; CHANCE, clopidogrel in high-risk patients with acute nondisabling cerebrovascular events; CI, confidence interval; CV, cardiovascular; CYP, cytochrome 450; HR, hazard ratio; IS, ischemic stroke; LoF, loss of function; MI, myocardial infraction; PCI, percutaneous coronary intervention; PLATO, platelet inhibition and patient outcomes; RCT, randomized clinical trial; RR, relative risk; TIA, transient ischemic stroke