Review Article

Clopidogrel resistance and its relevance: Current concepts

Akshyaya Pradhan, Monika Bhandari, Pravesh Vishwakarma, Rishi Sethi

Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh, India

Abstract

Clopidogrel is the most widely used P2Y12 receptor inhibitor (P2Y12i) as a part of dual antiplatelet therapy along with aspirin. Clopidogrel is a pro-drug and is metabolized to its active metabolite by the hepatic enzyme cytochrome P4502C19 (CYP2C19). This active metabolite is responsible for the antiplatelet action of clopidogrel. Recent studies have demonstrated that single nucleotide polymorphisms in the CYP2C19 gene, including CYP2C19*2,*3,*4, and *5 alleles, result in reduced production of the active metabolite of clopidogrel, and hence reduced inhibition of platelet aggregation. This in turn enhances the incidence of stent thrombosis and recurrent cardiovascular (CV) events. We report a case of coronary stent thrombosis due to clopidogrel resistance proven by CYP2C19 genotyping. We then review the literature on clopidogrel resistance and its impact on CV outcomes. Subsequently, we discuss the methods of diagnosis of resistance, evidence from clinical trials for tailoring clopidogrel therapy, the role of potent P2Y12 inhibitors, the current guidelines, and future directions.

Keywords: Antiplatelet therapy, genetic testing, high-on-treatment platelet reactivity, P2Y12 receptor, platelet function testing, stent thrombosis

Introduction

Clopidogrel is a commonly prescribed P2Y12 inhibitor (P2Y12i) worldwide as a part of a dual antiplatelet therapy (DAPT) in patients presenting with acute coronary syndrome (ACS) and those who undergo percutaneous coronary intervention (PCI) with drug-eluting stent (DES).[1,2] Clopidogrel is a prodrug and requires biotransformation by several hepatic cytochrome P-450 (CYP) isoenzymes including CYP2C19 to become an active metabolite.[3] However, genetic polymorphism of CYP2C19 is associated with poor clopidogrel metabolism, in turn leading to stent thrombosis and other major adverse cardiovascular events (MACE).[4]

Address for correspondence: Dr. Monika Bhandari, Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh, 226003, India.
E-mail: drmonikab@gmail.com

Received: 05-09-2023 **Revised:** 18-01-2024
Accepted: 22-01-2024 **Published:** 14-06-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1473_23

Case

A 53-year-old female presented with a diagnosis of ACS to our emergency department. She had a past medical history of hypertension and coronary artery disease (CAD). She had an episode of ACS 3 years back and had undergone PCI to the left anterior descending (LAD) coronary artery with a third-generation DES (size 2.75 mm × 33 mm) during the index hospitalization. Her left ventricular ejection fraction during the hospitalization was 38%. She had been prescribed DAPT in the form of aspirin and clopidogrel at discharge along with other secondary prevention therapies. The patient was fully compliant with therapy and was doing well until the present episode of ACS. Her electrocardiogram showed a new onset right bundle branch block and cardiac enzymes were negative. The patient underwent coronary angiography which revealed thrombus in the LAD stent with approximately 50–70% stenosis (with thrombus) just distal to the stent edge. Thrombosuction was performed and the lesion was predilated with a 2.5 × 12 mm compliant balloon. Following this, a 2.5 × 22 mm sirolimus-eluting DES (ORSIRO, Biotronik

How to cite this article: Pradhan A, Bhandari M, Vishwakarma P, Sethi R. Clopidogrel resistance and its relevance: Current concepts. J Family Med Prim Care 2024;13:2187-99.

Inc., Berlin, Germany) was deployed overlapping with the previous stent. The stent was post-dilated using a 2.75 × 12 mm non-compliant coronary balloon. The end result was satisfactory without any residual stenosis or thrombus with a TIMI III flow. She was prescribed ticagrelor in place of clopidogrel and was investigated for clopidogrel resistance as she had stent thrombosis despite receiving optimal clopidogrel therapy for the past 3 years. The calculated DAPT score of the patient was 2, which indicates a high ischemic risk and that could be the possible reason for the extended DAPT with clopidogrel. She had heterozygous single nucleotide polymorphism (SNP) (CYP2C19*2, SNP ID rs4244285), which is associated with decreased response to clopidogrel therapy.

Discussion

Stent thrombosis is an uncommon but serious complication of coronary artery stents, especially DES, that often presents as myocardial infarction (MI) or death. The incidence of stent thrombosis in recent DES trials is somewhere between 0.58 and 1.3%.[5,6] The factors associated with stent thrombosis include diabetes mellitus (DM), MI at presentation, bifurcation lesion, in-stent restenotic lesion, old age, black race, procedure-related factors such as stent malposition, greater stent length, post-procedure renal dysfunction, non-compliance to antiplatelet drugs, and antiplatelet resistance.[7,8]

Antiplatelet resistance is an independent predictor of stent thrombosis, even several years after implantation of DES. In this patient, stent thrombosis may have been caused by several risk factors including MI at index event and antiplatelet resistance. Recent studies have shown that adequate antiplatelet effects are not achieved in 5–45% of the patients taking aspirin and in 4–30% of patients taking clopidogrel.[9,10]

Clopidogrel has been the most commonly prescribed antiplatelet agent along with aspirin as a part of DAPT. It is a prodrug and requires activation by the hepatic cytochrome P-450 system to become an active metabolite.[3] This active metabolite then inhibits platelet aggregation by irreversibly binding to platelet adenosine diphosphate (ADP) receptor P2Y12.

Clopidogrel resistance is defined as a <10% decrease in platelet aggregation in response to 5 μmol/l ADP in comparison to pre-treatment levels. There are several putative mechanisms for clopidogrel resistance.[10]

Extrinsic mechanisms of resistance include inappropriate or under-dosing, drug–drug interaction, and non-compliance. However, the intrinsic mechanisms include genetic causes (polymorphism of P2Y12 receptor and CYP3A enzymes), increased release of ADP, and alternate pathways of platelet activation. The alternate pathways include catecholamine-mediated platelet aggregation, P2Y12-mediated platelet aggregation, and upregulation of P2Y12-independent pathways (thrombin, thromboxane A2, and collagen-mediated).[11]

Genetic polymorphisms of the cytochrome P-450 isoenzymes can alter the clopidogrel metabolism. Polymorphism with loss-of-function (LOF) alleles CYP2C19*2 (681G>A) is known to be responsible for poor clopidogrel metabolism both in heterozygous and homozygous patients.[12–14] The CYP2C19 carries out 45% of the first step in the biotransformation of clopidogrel.[15] This gene is located within the cytochrome P-450 gene region on chromosome 10q24. The CYP2C19*2 alleles, along with *3, *4, and *5, are termed LOF alleles and are shown to have decreased enzymatic activity. The CYP2C19*2 allele is the most prevalent variant allele in Caucasian, African-American, and Asian populations. However, the CYP2C19 * 3 allele occurs more frequently in Asian populations (~10%).[16] In a recent South Asian cohort, the frequency of CYP2C19*2 allele was around 41% in patients with ACS.[17] Mega *et al.*[4] have demonstrated that carriers of at least one CYP2C19 reduced-function allele had a 32.4% relative reduction in the active clopidogrel metabolite in comparison to non-carriers ($P < 0.001$). Low circulating levels of active clopidogrel metabolite result in a diminished antiplatelet response with treatment culminating in higher major adverse CV events including stent thrombosis.[4,18]

Genotype analysis in our patient revealed the presence of heterozygous LOF alleles of CYP2C19*2. This in all clinical likelihood led to an inadequate platelet inhibition resulting in stent thrombosis. It has been shown that in patients with heterozygous CYP2C19*2 alleles, higher doses of clopidogrel can overcome genetic resistance and improve platelet inhibition.[19] However, higher doses of clopidogrel cannot overcome the resistance and are not an option for CYP2C19*2 homozygous patients. These patients should receive novel P2Y12 inhibitors like ticagrelor or prasugrel. Ticagrelor and prasugrel have been shown to have a greater and more consistent inhibition of platelet aggregation in comparison to standard clopidogrel doses.[20,21] The presence of heterozygous polymorphism appears to be the predominant reason that our patient presented with very late (>1 year) stent thrombosis.

Clinical experience with the use of platelet function testing (PFT) for tailoring clopidogrel therapy

Because clopidogrel resistance is a potential cause of stent thrombosis and adverse cardiac events, studies have attempted to individualize antiplatelet therapy in patients undergoing PCI based on platelet function and genetic testing. Five major studies have assessed the impact of PFT to guide clopidogrel therapy in patients with high-on-treatment platelet reactivity (HTPR) [Table 1 and Figure 1].

The initial experience came from the Gauging Responsiveness with a VerifyNow Assay: Impact on Thrombosis and Safety (GRAVITAS) trial. The study utilized a differential dosing of clopidogrel (75 or 150 mg) in patients undergoing PCI based on PFT. The study results failed to show the benefit of an intensified clopidogrel treatment in either overcoming HTPR or improving patient outcomes after PCI [Table 1].[22] The failure

of the study was ascribed to many potential reasons—a higher HTPR cutoff value (platelet reactivity unit [PRU] >230) taken in GRAVITAS that led to >40% of clopidogrel low responders, the selection of a stable cohort of patients with a very low event rate, and the test assay lacking a predictive value in the observational arm. A subsequent secondary analysis of the trial revealed that

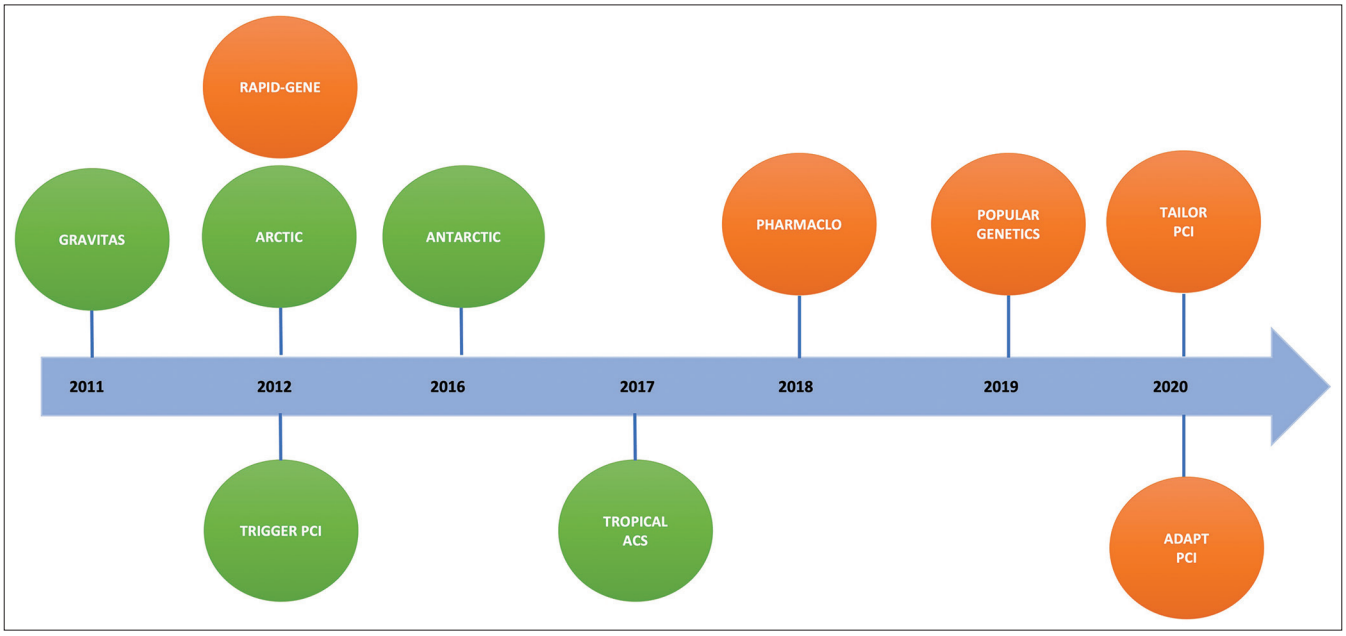

Figure 1: The landmark trials that have utilized PFT and genetic testing to tailor clopidogrel therapy following ACS/PCI. The green circles represent trials that have utilized PFT while the orange circle represents studies utilizing genotyping to guide clopidogrel therapy

Table 1: Comparison of clinical studies attempting tailored antiplatelet therapy based on platelet reactivity testing. *Platelet reactivity was assessed by VerifyNow assay (Accumetrics, San Diego, California) in all four studies and Multiplate Analyzer in one

Study	No. of patients	Study population	Antiplatelet strategy	Definition of high on platelet reactivity*	Primary endpoints	Results
GRAVITAS[22] (2011)	2800	Post-PCI patients with DES; CCS or ACS	Clopidogrel dose 75 or 150 mg after PFT	PRU>230	Cardiovascular death, non-fatal MI, stent thrombosis at 6 months	The use of a high dose of clopidogrel in patients with high platelet reactivity post-PCI did not reduce primary endpoints
TRIGGER PCI[24] (2012)	423	Post-PCI patients with DES; Chronic stable angina	Patients with HTPR were randomized to receive prasugrel 10 mg vs. clopidogrel 75 mg	PRU>208	Cardiac death or MI at 6 months; Primary safety endpoint of non-CABG related bleeding at 6 months	Premature termination due to futility; Efficacy endpoint event: 1 vs. 0 with clopidogrel and prasugrel, respectively (*P*= NE); Bleeding events: 1.4% vs. 0.5%, respectively
ARCTIC PCI[25] (2012)	2440	Stable angina or non-ST elevation ACS undergoing PCI	Platelet function analysis in post-PCI patients and clopidogrel dose adjustments	PRU>235	Composite of death, MI, stent thrombosis, stroke, or urgent revascularization at 12 months	No significant difference between two groups
ANTARCTIC[27] (2016)	877	ACS (35% STEMI)	PFT-guided P2Y12 adjustment vs. conventional strategy (prasugrel)	PRU≥208 U for HTPR	1-year incidence of CV death, MI, stroke, stent thrombosis, urgent revascularization, or BARC≥2 bleeding	No difference in the two groups either for ischemic or bleeding events
TROPICAL ACS[73] (2017)	2610	ACS (55% STEMI)	Post PCI non-inferiority study of PFT-guided de-escalation vs. conventional strategy (prasugrel)	HTPR>46 U (Multiplate Analyzer)	1-year incidence of CV death, MI, stroke, or BARC≥2 bleeding	Non-inferiority of primary endpoint benefit seen (HR 0.81, *P*=0.0004), *P* value for ischemic events in favor of guided strategy 0.01, and for bleeding it was 0.23

CV=cardiovascular, ACS=acute coronary syndrome, CCS=chronic coronary syndrome, MI=myocardial infarction, PCI=percutaneous intervention, DES=drug-eluting stent; PRI=platelet reactivity index, PRU=platelet reactivity unit, NE= Not evaluated

utilizing a PRU cutoff >208 was predictive of short-term CV events.[23]

The TRIGGER PCI (testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel) trial was done to study whether using prasugrel in clopidogrel non-responders patients would result in better platelet inhibition. Patients with stable CAD undergoing PCI were enrolled. Of the 5245 patients screened, 625 (19%) had HTPR on clopidogrel and were enrolled. The trial was terminated prematurely due to the low rate of ischemic events in both arms. Prasugrel use resulted in improved antiplatelet activity as compared to continuing clopidogrel in these patients. More than 95% of patients switched to prasugrel demonstrated a low PRU even at 6 months in contrast to 70% with HTPR when maintained on clopidogrel. However, there was no difference in clinical outcomes.[24] The lower-than-expected event could be ascribed to the choice of cohort (stable CAD), use of newer generation DES in the later enrollment, and exclusion of patients with periprocedural complications.

The ARCTIC trial also failed to demonstrate the impact of adjusting P2Y12i treatment (based on PFT) on clinical outcomes in 2440 patients with stable angina or NSTE-ACS undergoing PCI. Treatment adjustments included the use of GP IIb/IIIa inhibitors before or during the index procedure, a higher dose of clopidogrel, or switching to prasugrel. In fact, the trial was unique in that it also tested for aspirin resistance simultaneously and intravenous aspirin was administered for HTPR. HTPR was seen in 34.5% of patients with clopidogrel and 7.5% with aspirin in the study. In addition, the trial failed to demonstrate a significant difference in stent thrombosis, stroke, or urgent revascularization.[25] Interestingly, despite dose adjustments, the proportion of patients with HTPR on clopidogrel still remained at 15.4% after a 2-week follow-up warranting further dose adjustment. Prasugrel use was scarce owing to its late availability during the study period. A landmark analysis from the same study excluding patients during their hospital stay and hypothetically including patients from their discharge time yielded similar results.[26] The message was again the same—you can successfully treat and alleviate HTPR as a risk factor but the impact on clinical outcomes may not be relevant.

Similarly, the ANTARCTIC trial randomized 877 elderly patients undergoing PCI across 35 centers in France to a PFT-guided strategy.[27] PFT was performed after 14 days of 5 mg prasugrel therapy and the dose was then adjusted according to the response with a repeat testing after 14 days. The primary endpoint (composite of CV death, MI, stroke, stent thrombosis, urgent revascularization, or BARC >2 bleeding) was not different between guided and unguided arms (28% vs. 28%; $P = 0.69$). The bleeding rates were also not different between arms.

As is evident from Table 1, PFT analysis had its own challenges. The PRU utilized to define HTPR was different in all three studies indicating the absence of a gold standard PRU to define HTPR. Also, all four studies utilized the same assay—VerifyNow assay (Accumetrics, San Diego, California). Whether the use of other standard assays like VASP and Multiplate Analyzer in these studies could have altered the outcome remains speculative.

Genetically proven clopidogrel resistance is a different ball game altogether. The CLOVIS-2 trial sought to examine the effect of higher loading doses of clopidogrel on restoring the antiplatelet effect.[19] The trial randomized 51 patients with genetically proven resistance (eight homozygous and rest heterozygous) to 300 or 900 mg loading doses. Interestingly, the use of a higher loading dose was able to ameliorate the effect of genes in heterozygous patients but not in homozygous patients.

Clinical experience with the use of genomic testing-based tailored regimen for clopidogrel

Because genotyping offers the most conclusive basis for resistance in a patient with recurrent CV events on clopidogrel therapy, researchers have attempted to incorporate genetic testing for improved outcomes [Table 2 and Figure 1]. The RAPID GENE was a proof of concept utilizing a point-of-care (POC) assay for the CYP2C19*2 allele.[28] Based on the presence of the allele, patients were switched to prasugrel from clopidogrel in the intervention arm while no action was taken in the standard arm. The proportion of patients with HTPR (measured by PRU >234) after a week of therapy was significantly lower in the genotyping arm in reference to the standard arm (none vs. 30%; $P = 0.009$). This was despite the similar frequency of the abnormal allele in both arms. Of note, this was not a clinical endpoint-driven study but did prove the feasibility and accuracy of POC genetic testing.

The PHARMCLO trial utilized a POC assay—ST Q3 system which provided genotyping results for ABCB1, CYP2C19*2, and CYP2C19*17 within 70 min.[29] Patients in the standard arm were given P2Y12 inhibitors based on clinical features, while in the pharmacogenomic arm, genotyping results were also taken into consideration. At 12 months of follow-up, among 888 patients, the primary composite endpoint of MACE was significantly lower in the pharmacogenomic arm (15.9% vs. 25.9%; $P < 0.001$). The trial was stopped prematurely however and the distribution of antiplatelet drugs was uneven among both arms.

The POPULAR-GENETICS trial used genotyping to guide de-escalation of P2Y12i therapy after primary PCI for STEMI.[30] About 2488 patients were randomized to receive standard novel P2Y12-based DAPT or genotyping-guided DAPT. In the guided arm, patients who were carriers of CYP2C19*2 or CYP2C19*3 LOF mutation (like our patient) were switched to prasugrel or ticagrelor. Non-carriers (61%) were continued on clopidogrel. At 12 months, the guided arm was non-inferior to the standard arm for primary net clinical adverse events (a composite of ischemic and bleeding events; $P < 0.001$ for non-inferiority). Simultaneously, the primary bleeding outcome (major or minor bleeding defined by PLATO) was curtailed by 22% with guided treatment ($P = 0.04$).

Table 2: Comparison of clinical studies attempting tailored antiplatelet therapy based on genotype testing

Study	No. of patients	Study population	Antiplatelet strategy	Primary endpoints	Results
RAPID-GENE [28] (2012)	200	Stable angina or ACS undergoing PCI	Genotyping for CYP2C19*2 allele with a POC testing machine. Carriers were given 10 mg prasugrel daily and non-carriers and patients in the standard treatment group were given 75 mg clopidogrel daily	Proportion of allele carriers with HTPR (defined by PRU>234) after 1 week of DAPT	30% of standard care group had HTPR compared to none in genotyping group ($P = 0.0092$)
PHARMCLO[29] (2018)	888	ACS	Use of bedside ST Q3 system for genotyping of ABCB1 3435, CYP2C19*2 & CYP2C19*17 alleles. Patient randomized to P2Y12 inhibitor based on genotyping plus clinical features versus clinical features alone	Combination of CV death and occurrence of non-fatal MI, non-fatal stroke, and major bleeding (BARC definition>3)	42% reduction in primary endpoint with pharmacogenomic approach compared with clinical approach. 0.58; 95% CI: 0.43–0.78; $P<0.001$). More patients were prescribed ticagrelor with pharmacogenomic approach while prasugrel prescription was equal in both arms
POPULAR Risk Score Study[31] (2019)	1127	Elective PCI with stent implantation	Composite score based on platelet reactivity (VerifyNow P2Y12 assay), CYP2C19 genotyping, and clinical risk factors. High risk was prescribed prasugrel	Combination of all-cause death, MI, stroke, or stent thrombosis	At 1 year lower incidence of primary endpoint in guided arm (3.7% vs. 8.4%, $P<0.001$). Bleeding was also lower in guided arm (1.3% vs. 4%; $P<0.001$). 27% were switched to prasugrel
POPULAR Genetics[30] (2019)	2488	Primary PCI with stent implantation	Genotype-guided group – carriers of CYP2C19*2 or CYP2C19*3 LOF alleles (by TaqMan StepOnePlus assay or Spartan RX POC assay) received ticagrelor or prasugrel, and non-carriers received clopidogrel. Standard arm received a novel P2Y12 inhibitor; Non-inferiority design	1. Death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding 2. PLATO major or minor bleeding at 12 months	Net clinical adverse events were lower in the genotype arm vis-à-vis standard group (5.1% vs. 5.9%; $P<0.001$ for non-inferiority); Bleeding was also significantly lower by 22% in the genotype-guided arm (P=0.04)
TAILOR PCI[32] (2020)	5302	Patients undergoing PCI for ACS or CCS	Genotype-guided P2Y12 inhibitor vs. conventional (no genotyping) clopidogrel therapy	Composite of CV death, MI, stroke, stent thrombosis, and severe recurrent ischemia at 12 months	No significant difference in the two groups
ADAPT PCI[33] (2020)	504	Patients undergoing PCI for ACS or CCS	Point-of-care genotyping of CYP2C19 major alleles (*2, *3, *17) via salivary swab or usual care to guide antiplatelet therapy	Prescription rate of prasugrel or ticagrelor in each arm	Higher prescription rate of novel P2Y12i in genotyped arm (30% vs. 21%; $P=0.03$). In the patients with LOF allele, 535 were started on ticagrelor/prasugrel while rest 47% were continued on clopidogrel

ACS=acute coronary syndrome; PCI=percutaneous coronary intervention; CCS=chronic coronary syndrome; PRU=platelet reactivity unit; HTPR=high-on-treatment platelet reactivity; DPAT=dual antiplatelet therapy

The POPULAR RISK SCORE STUDY utilized a risk score (see below) for tailoring P2Y12i regimen following non-urgent PCI with a DES implantation.[31] In the guided arm, patients with a popular risk score >2 were switched to prasugrel from clopidogrel. Prasugrel dose was altered to 5 mg in patients with age >75 and body weight <60 kg. The primary endpoint was a combination of all causes of death, non-fatal MI, non-fatal ischemic stroke, and definite stent thrombosis. The control arm was a cohort previously published from a POPULAR study from the same institute (from 2005 to 2007 who were given clopidogrel). Almost, one-fourth of the patients in the guided cohort were switched to prasugrel. The primary ischemic endpoint was significantly lower in the guided arm (8.4% vs. 3.7%, $P < 0.001$) as was the bleeding rate (4.0% vs. 1.3%, $P < 0.001$).

The latest in series TAILOR PCI however did not show benefits of genotype-guided P2Y12 therapy.[32] This large randomized controlled trial (RCT) was designed to better define the effectiveness of genotype-guided PY12 therapy versus standard care in patients undergoing PCI. Patients with LOF carriers of CYP2C19 (by POC Spartan RX assay) were prescribed ticagrelor while non-carriers were prescribed clopidogrel. Clopidogrel was prescribed in the standard arm and patients underwent genotyping at studyend. The primary endpoint was the incidence of MACE at 12 months. There was a 34% non-significant reduction in MACE at 12 months in the genotyping arm (4.0% vs. 5.9%; heart rate [HR] 0.66; $P = 0.06$). The secondary endpoints including bleeding were not different between both arms. The trial was underpowered to detect <50% relative risk (RR) reduction and event rates were also low leading to the recalculation of sample size. The open-label design was another challenge and provision of P2Y12i drug by health insurance plan rather than trialists themselves may have affected drug allocation too.

The ADAPT PCI study randomized 504 patients to genotype-guided care versus usual care.[33] CYP2C19 alleles (*2,*37 *17) were genotyped from saliva by a rapid POC assay. The study population was predominantly male and had an ACS indication for PCI. The prescription of novel P2Y12 inhibitor was higher in the genotype arm compared to the usual care arm (30% vs. 21%; $P = 0.03$). It was not a clinical endpoint-driven study though.

PFT and genotyping: Current consensus

The recommended assays for monitoring platelet inhibition based on the available evidence are the VerifyNow P2Y12 assay, the multiplate device with ADP kit, and the VASP assay. The two most commonly involved gene polymorphisms involved in clopidogrel metabolism are CYP2C19*2 and CYP2C19*17. The LOF of CYP2C19 results in decreased enzyme function while gain of function mutation later results in increased enzyme function. Both PFT and genotyping are not recommended in non-revascularized patients.[34,35] In stable angina patients after PCI and ACS patients post-PCI, it is not recommended on a routine basis. It may be considered (Class IIa recommendation) if the results are likely to change the P2Y12 inhibitor strategy (high thrombotic risk, patients with unexpected stent thrombosis despite being compliant to clopidogrel therapy, history of stent thrombosis, complex PCI in high-risk patient, PCI in the setting of last remaining vessel or unprotected left main stem PCI involving the bifurcation, total stent length >60 mm and treatment of chronic total occlusion). In patients not undergoing PCI, PFT is not recommended.[34] However, the final decision to decide on the P2Y12 therapy should incorporate both clinical, angiographic, procedural, and socio-economic variables.

HTPR and LPR

HTPR with clopidogrel is an independent predictor of adverse thrombotic events, most notably stent thrombosis in patients receiving clopidogrel post-PCI. This has been demonstrated not only in RCTs, observational studies, and case reports but also in multiple independent meta-analyses.[36-38] Sofi *et al.*[36] performed a meta-analysis of 14 studies involving >4500 patients and found that HTPR significantly increased the death/thrombotic events by >5.5 times. With the exclusion of data from four heterogeneous studies, the odds of death/thrombotic events were still significantly higher by 3.5 times (odds ratio [OR]: 3.58; $P < 0.0001$). Brar *et al.*[37], in their meta-analysis of six studies involving > 3000 patients, found that ischemic events (death, MI, and ST) were more frequent in the upper quartile of HTPR. Notably, all six studies used the same POC assay (VerifyNow), and ROC analysis revealed that a PRU >230 U was the best predictor of ischemic events. In a large meta-analysis, Aradi *et al.*[38] evaluated >20,000 patients across 17 studies. The median follow-up was short at 8.5 months but it included studies done with all three standard devices: VerifyNow, Multiplate Analyzer, and VASP assay, unlike the previous study which adds to the strength of the study. Based on exploratory analyses, the HTPR categories were >208 PRU, >46 U, and >50% for VerifyNow, Multiplate Analyzer, and VASP, respectively. The risk of ST with HTPR in the study was 2.73 (RR: 2.03–3.69; $P < 0.00001$) and this was accompanied by a slight decrease in bleeding risk (RR: 0.84; $P = 0.04$). Mortality was also significantly higher in the HTPR group compared with other categories (HR: 1.54; $P < 0.0002$). Similarly, the ADAPT-DES registry enrolled >8500 patients with DES implantation in 11 centers across Germany and the United States who were treated with clopidogrel and had a follow-up of 2 years.[39] HTPR on clopidogrel (detected by VerifyNow assay) was significantly correlated with the risk of stent thrombosis and MI (HR 2.49 and 1.42, respectively). But there was no effect on death. In the same study, HTPR on aspirin was not correlated with ST, MI, or death. Interestingly, HTPR on each drug was inversely associated with bleeding. HTPR also was an independent predictor of both early- and late-stent thrombosis alike.[39] More than half of early ST could be explained by high HTPR. The association between HTPR and CV events is stronger in patients undergoing PCI for ACS rather than in stable CAD.[40] In the ADAPT-DES study, 52% had ACS at presentation. These patients had significantly higher P2Y12 reactivity as measured by VerifyNow assay and a higher proportion of patients with HTPR (defined as PRU >208) compared to non-ACS patients. Out of the total number of patients with ST, two-thirds belonged to the ACS cohort. A greater proportion of patients with ST in the ACS cohort had HTPR but there was no difference in the distribution of HTPR among ST patients in the non-ACS cohort. HTPR was an independent predictor of ST and MI over 2 years but this correlation was higher in the ACS cohort than in the non-ACS cohort.

Studies have shown that novel P2Y12 inhibitors can better overcome HTPR on clopidogrel compared to doubling to clopidogrel dose to 150 mg.[41-44] However, large head-to-head PFT-based trials lack a large body of evidence to suggest that ticagrelor betters prasugrel in lowering the incidence of HTPR.[44-49] This appears to be the case even in the setting of DM.[50-52] Four meta-analyses have shown that HTPR is lower with ticagrelor compared to prasugrel.[53-56] However, some studies suggest the variation is due to the type of PFT assay used rather than the effect of the drug per se.[57-59] However, the small SWAP-3 trial demonstrated that switching to ticagrelor from prasugrel leads to further platelet inhibition and lower PRU as early as 2 h after drug initiation.[59] There was no effect of a loading dose of ticagrelor on the results of the study and there was no increase in HTPR at 1 week.

Bleeding is also a fatal complication in post-PCI patients. The risk of bleeding depends upon the patient's characteristics and the P2Y12i regimen utilized. The presence of low-on-treatment platelet reactivity (LPR) or hyperresponse on clopidogrel therapy may lead to increased bleeding events. A large study of post-PCI patients on clopidogrel reported that in hospitals major bleeding was more common in patients with LPR compared to those with a normal response (OR 3.5, 95% confidence interval [CI] 1.6–7.3; $P = 0.001$).[60] However, for minor bleeding, the difference between groups was not significant. The POBA study also

demonstrated that LPR was a strong and independent predictor of bleeding.[61] In the meta-analysis by Aradi *et al.*[38] too (vide supra), LPR was predictive of bleeding risk by 1.8 times (HR 1.47–2.06; $P < 0.00001$) without any protection for stent thrombosis (HR: 1.06; $P = 0.76$). In the ADAPT-DES trial, patients with bleeding after PCI had significantly lower PRU compared to those without bleeding events.[39] If such patients are prescribed prasugrel or ticagrelor, there will be a high risk of bleeding without any advantage of reduction in thrombotic events. Now, reports correlating LPR on prasugrel and bleeding have also emerged.[62,63] LPR on ticagrelor has now also been reported in a Brazilian study of 44 patients with STEMI on Ticagrelor-based DAPT.[64] Although the study did not report a correlation with bleeding, based on prior data, it is a foregone conclusion.

The concept of LPR and its correlation to bleeding is still evolving although its counterpart HTPR has garnered much attention in the literature. However, it might be appealing in patients experiencing major bleeding on P2Y12i therapy to prevent recurrent bleeding.

The optimal cutoff values for HTPR and LPR are assay-dependent, and the consensus values are summarized in Figure 2.[35,38]

Clopidogrel resistance: Do genes have the final say?

Clinically clopidogrel resistance is a complex interplay of genetic (non-modifiable) as well as non-genetic elements (which can be modulated to some extent). The factors governing clopidogrel response can be broadly classified into genetic factors, cellular factors, and clinical factors. The genetic factors include CYP polymorphism and P2Y12 polymorphism.[65] The cellular factors include platelet turnover rate, up/downregulation of P2Y12 receptor, and up/downregulation of platelet via P2Y12 independent pathways. The clinical factors include age, body mass index (BMI), chronic kidney disease (CKD), DM, drug interactions, intestinal absorption, and compliance. Out of these factors, diabetes, BMI, drug interactions, and compliance are modifiable. Although both DM and HTPR on clopidogrel are related to an increased risk of ischemic events after PCI, whether the HTPR-associated ischemic events vary with DM status is unknown. In the ADAPT-DES diabetes sub-study, mean PRU and HTPR were more common in patients with DM compared to those without DM. Among diabetic patients, a more pronounced effect of HTPR on MACE was seen in lower-risk Type 2 DM patients than in higher-risk patients with Type 1 DM.[66]

Guided P2Y12i therapy: Meta-analysis

A meta-analysis of 15 RCTs involving 61,898 patients compared different P2Y12 strategies in ACS patients. It showed that compared with routine clopidogrel use, a guided selection of P2Y12 inhibitor strategy was associated with a reduction in MACE while the routine use of novel P2Y12i (ticagrelor/prasugrel) was not. Both ticagrelor and prasugrel use led to an increase in bleeding episodes but not with the use of a guided approach. The superior performance of the guided approach was consistent with the *P* scores and had an efficacy profile superior to prasugrel and ticagrelor, while it was slightly inferior to clopidogrel in terms of safety.[67]

Can we predict the risk: A tale of three risk scores!

The **ABCD-Gene** (age, BMI, CKD, DM, and genotyping) score has been derived based on clinical and genetic factors.[68] The score was developed, externally validated, and clinically implied using three independent prospective cohorts from GRAVITAS, POPULAR, and FAST-MI trials (mostly Caucasian cohorts though!). The score ranges from 0 to 38 points. A score of ≥10 when treated with clopidogrel had the greatest sensitivity and specificity to detect HTPR and adverse ischemic events after PCI [Figure 3]. The platelet reactivity was significantly higher in those with ABCD gene score ≥10 in GRAVITAS and POPULAR studies. Likewise, 1-year clinical outcomes were worse in those with a high score in the FAST-MI trial. When prospective applied to a cohort of 184 East Asian patients undergoing PCI, the score identified HTPR on clopidogrel with moderate diagnostic ability.[69] The score was also prospective applied to the TAILOR-PCI study cohort.[70] Out of 3883 patients prescribed clopidogrel, those with a score >10 had significantly higher primary and secondary ischemic endpoints.

Another risk score is the **Popular** Risk Score which is based on VerifyNow P2Y12 assay (HTPR, PRU ≥236), CYP2C19

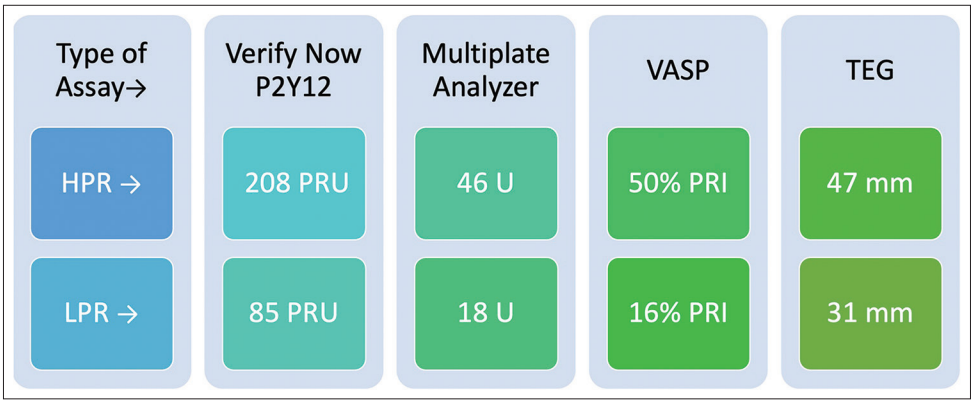

Figure 2: Various cutoffs to define HTPR and LPR[35,38]

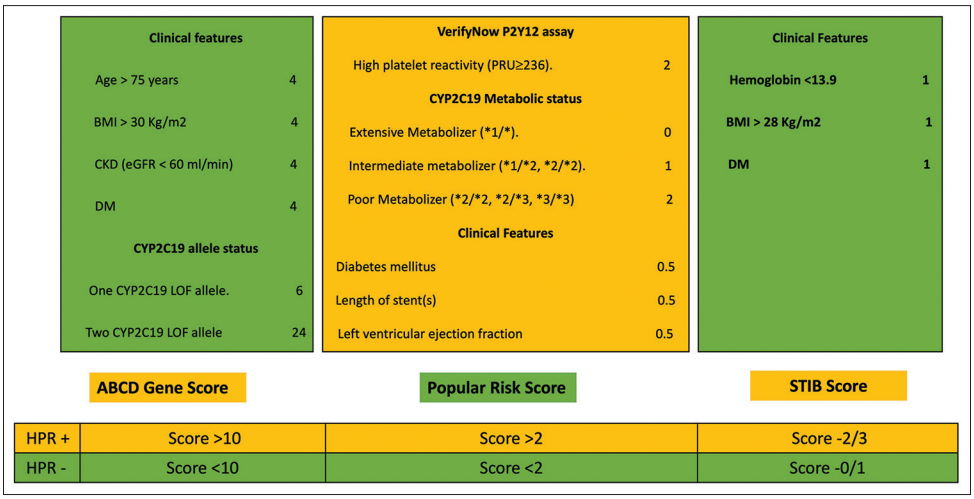

Figure 3: Comparison of three risk scores to predict HTPR on clopidogrel therapy

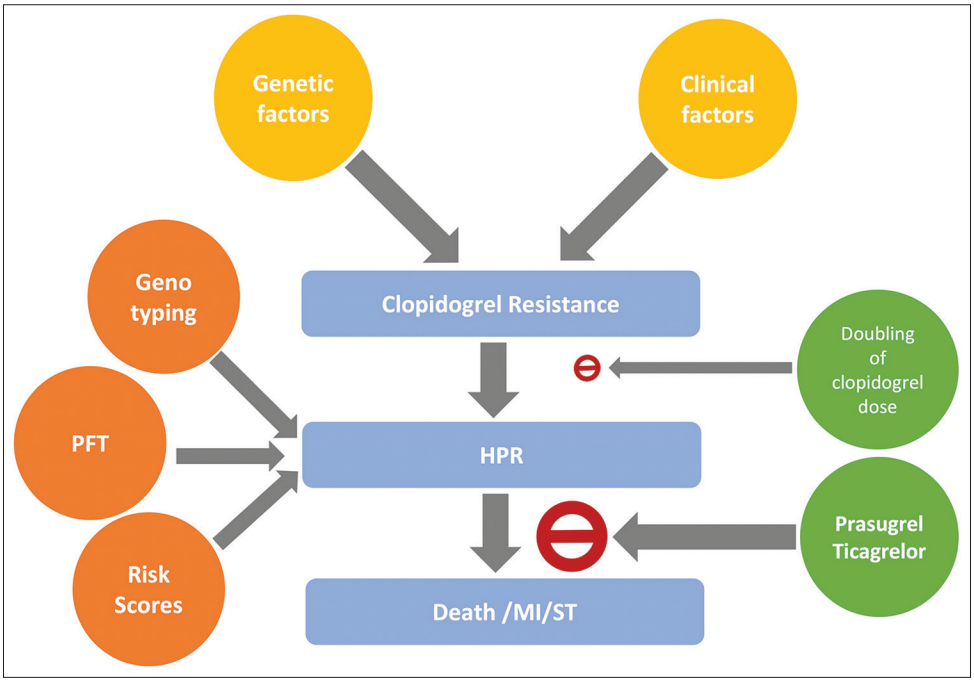

Figure 4: Central illustration of the manuscript. Both genetic and clinical factors interact to produce clinical clopidogrel resistance in a given patient. This leads to HTPR which has been shown in trials and meta-analyses to correlate with death, myocardial infarction, and stent thrombosis. HTPR can be diagnosed by genotyping, PFT, or clinical risk scores. Prasugrel and ticagrelor can overcome HTPR on clopidogrel and prevent ischemic events. Doubling of the clopidogrel has a limited effect only

metabolizer status [Extensive (*1/*1), Intermediate (*1/*2,*1/*3), poor (*2/*2,*2/*3,*3/*3)], DM, adjoining stent length 30 mm, left ventricular ejection fraction <30%.[31] According to this algorithm, a score >2 indicates HTPR and a switch to prasugrel/ticagrelor is advised. Meanwhile, a score <2 indicates that clopidogrel therapy should be sufficient. As described earlier, the score was applied successfully in a guided cohort of 1128 patients.[31]

The **STIB** score was proposed in the STIB (Stent Thrombosis in Belgium) trial.[71] It is a simple clinical and biological score that can predict clopidogrel resistance at the bedside obviating the need for either PFT or genotyping. It is based on adding three parameters, namely BMI >28 kg/m^2, Hb <13.9 g/dl, and diabetes. The probability of HTPR or clopidogrel resistance ranges from 38.5 to 77.8% depending on the presence of one, two, or three factors.

The usual GRACE and CRUSADE scores have also been utilized to personalize antiplatelet therapy. In a prospective registry of >3300 ACS patients from the United Kingdom, patients were stratified into high, low, and intermediate categories of both scores.[72] In the guided arm, patients with low GRACE (<108) or high CRUSADE (>40) scores or those requiring concomitant

oral anticoagulation were given clopidogrel while the rest were given ticagrelor. Clopidogrel was the standard of care in the unguided arm. At 3 years of follow-up, a guided strategy led to a significant reduction of MACE (13.7% vs. 19.7%; HR 0.61; $P < 0.001$) without any significant difference in bleeding.

"De-escalation" of antiplatelet therapy: A success story

As alluded to before, newer antiplatelet agents provide consistent and more potent platelet inhibition.[20,21] However, bleeding was also higher with newer agents in both pivotal studies. Because the post-procedural phase of ACS has high ischemic risk, some studies have attempted to use novel antiplatelet agents in the early post-procedural phase after PCI for ACS and subsequent "de-escalation" or switch to clopidogrel. This strategy aims to overcome early ischemic risk while curtailing long-term bleeding risk.

In the TROPICAL-ACS study, PFT was utilized to guide de-escalation.[73] A total of 2610 patients were randomized to either prasugrel-based DAPT for 12 months or de-escalation from prasugrel to clopidogrel after 14 days of prasugrel-based DAPT. Patients with HTPR (PRU >46 IU) were continued on prasugrel while those with low reactivity were switched to clopidogrel. At 1 year, the de-escalation strategy was non-inferior to the standard strategy for the primary endpoint (composite of CV death, MI, stroke, and bleeding BARC >2). There was an 18% decrease in bleeding events (BARC >2) but there was no increase in ischemic events despite the de-escalation of DAPT.

The TOPICS trial tested a strategy for unguided de-escalation in 646 patients with ACS.[74] Patients were randomized to either standard DAPT for 12 months or switched to DAPT. In the switch arm, patients were switched from novel P2Y12i-based DAPT to clopidogrel-based DAPT 1 month following ACS without any testing. There was a significant 50% reduction in the primary endpoint at 1 year. This was driven primarily by a decline in BARC >2 bleeding (70% ↓; $P < 0.01$) and there was no increase in ischemic events. The factors that can be considered for de-escalation include prior major bleeding and/or hemorrhagic stroke, anemia, and clinically significant bleeding on DAPT.

Guidelines

ACC/AHA/SCAI guidelines for PCI[75] recommended that genetic testing might be considered to identify patients at high risk of poor clinical response to clopidogrel therapy [Class IIB(c)] and when the patient is predisposed to inadequate clopidogrel response with genetic testing, alternative P2Y12 therapy may be considered [Class IIB(c)]. However, routine use of genetic testing was not recommended (Class III).

2014 ACC/AHA guidelines for ACS/NSTEMI[76] also did not recommend routine genetic testing for platelet function.

As per 2014 Expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in PCI[34] clinical presentation and patient characteristics should guide the choice of P2Y12 inhibitors during and after PCI: prasugrel or ticagrelor is preferred for ACS while clopidogrel is recommended in PCI for stable angina. In patients suspected to have high clinical and/or procedural risk for adverse outcomes (thrombosis or bleeding) with recommended P2Y12 inhibitors, platelet function testing may help the decision-making (IIB). It recommended VerifyNow P2Y12 assay, the Multiplate device with ADP kit, and VASP assay for monitoring platelet inhibition.

According to the 2019 Updated Expert consensus statement on platelet function and genetic testing for guiding P2Y12 receptor inhibitor treatment in PCI,[35] in patients with stable CAD undergoing PCI, PFT is not recommended to escalate (switch to a more potent P2Y12 inhibitor) or de-escalate (DAPT cessation) is not recommended. However, PFT may provide useful prognostic information on CV risk prediction (for both bleeding and ischemic events) in stable CAD patients undergoing PCI. Routine CYP2C19 genotyping to escalate treatment in LOF allele carriers (especially *2 and *3) during clopidogrel treatment is also not recommended but may be considered in specific clinical scenarios (heterozygous and homozygous allele carriers). Similarly in ACS patients undergoing PCI, PFT to escalate treatment in patients with HTPR on clopidogrel is not recommended on a routine basis but may be considered in specific clinical scenarios. But PFT to screen for HTPR (on clopidogrel) when DAPT de-escalation is planned may be considered in specific clinical scenarios (bleeding events, high bleeding risk, and socioeconomic indications) as an alternative to DAPT. Routine genotyping to escalate and de-escalate treatment in LOF allele carriers is not recommended due to lack of dedicated studies.

The 2018 ESC/EACTS guidelines on myocardial revascularization recommend that de-escalation of P2Y12 inhibitor treatment (switching from prasugrel or ticagrelor to clopidogrel) guided by PFT may be considered as an alternative DAPT strategy in ACS patients deemed unsuitable for 12-month potent platelet inhibition [Class IIB recommendation[77]]. The 2020 ESC guidelines for the management of ACS without ST persistent elevation similarly permit selective de-escalation may be based on clinical judgment or guided by PFT/CYP2C19 genotyping.[78]

Resistance to novel P2Y12 inhibitor: A fact or fiction

The story of antiplatelet resistance does not end at clopidogrel. Recent reports have emerged on HTPR with novel P2Y12 inhibitors. The incidence of HTPR on novel antiplatelet agents is anywhere between 10 and 20%.[79,80] Intravenous morphine and STEMI at presentation were the two major predictors of HTPR on ticagrelor.[81,82] The mechanisms of resistance are not fully elucidated but appear to be related to gastrointestinal absorption for ticagrelor at least.[81]

Implications for Practice

The primary care physician is more often than not entrusted with the care of CAD and post-PCI patients despite the incremental

availability of dedicated cardiac care services. DAPT remains the cornerstone for the management of post-PCI and ACS patients. Clopidogrel has been a widely used P2Y12i for the past two decades with a vast body of experience and clinical data. However, the wide variability in its antiplatelet action can lead to ischemic events in many patients and bleeding events in some. Resistance to antiplatelet activity of clopidogrel can be detected by PFT or genotyping. On the other hand, novel P2Y12i like prasugrel and ticagrelor are more potent with stable antiplatelet action compared to clopidogrel but have higher bleeding risk. Hence, the attractive concept of using PFT and genotyping to guide P2Y12i therapy is to maximize ischemic benefits and minimize bleeding. Although guided antiplatelet has had mixed success in RCTs, meta-analysis and guidelines do support its use in selected clinical scenarios when patients are at high ischemic or bleeding risk. The practicing clinician needs to be aware of the various clinical tests and risk prediction tools that he can utilize to suspect or diagnose resistance to clopidogrel and use the novel P2Y12i or vice versa when the situation demands. Figure 4 displays the complex interaction among clinical, genetic and platelet function leading to clopidogrel resistance.

Future Directions

A host of trials are ongoing to shed further light on tailoring P2Y12i therapy with or without the use of PFT/genotyping. The GUARANTEE Trial (NCT03783351) plans to enroll 4009 post-PCI patients. The study has two arms: conventional clopidogrel or ticagrelor therapy versus genotype-guided P2Y12i arm. Those with the CYP2C19*2/*3 allele will get ticagrelor or prasugrel, while those with the wild-type CYP2C19 allele will get clopidogrel 75 mg. The endpoint being evaluated is the frequency of MACCE over 1 year. The VERONICA Trial (NCT04654052) will involve 634 patients of ACS. It is a prospective randomized and multicenter trial to establish a de-escalation strategy of P2Y12 inhibitors based on PFT using VerifyNow. The main endpoint of the study is the incidence of net adverse clinical events (NACE), including death from vascular cause, non-fatal MI, or non-fatal stroke, bleeding BARC type ≥2 over 12 months. TAILOR DAPT study (NCT05732701) trial aims to investigate the benefits of using PRECISE-DAPT score-based decision-making to guide the duration of DAPT in post-PCI patients compared to standard care. This will be a single-blinded RCT involving 2788 patients undergoing PCI with contemporary stenting. Apart from the PRECISE-DAPT score, PCI complexity, and clinical presentation will be used to guide the DAPT duration. The primary endpoint will be NACE including a composite of all causes of death, MI, stroke, stent thrombosis, or BARC 2, 3, or 5 bleeding at 1 year. TAILOR BLEED (NCT05681702) will compare two DAPT de-escalation strategies. After a novel P2Y12 (prasugrel or ticagrelor) based DAPT for 30 days of PCI for stable CAD and 90 days post-PCI in ACS, patients will be offered either clopidogrel-based DAPT or novel P2Y12-based monotherapy. The primary outcome measure will be thrombus formation at 30 days defined by Total Thrombus formation Analysis System (T-TAS). GENEPAD (NCT04619927) is a phase 4 trial in patients with peripheral arterial disease to evaluate the ability of genotype-guided antithrombotic therapy to reduce adverse clinical events comprising MI, stroke, transient ischemic attack, major adverse limb events (acute or chronic limb ischemia) and death. In the experimental arm, poor metabolizers will get a combination of aspirin and rivaroxaban 2.5 mg bid, intermediate metabolizers will get clopidogrel 75 mg bid, and normal metabolizers will get clopidogrel 75 mg od. Clopidogrel 75 mg once daily will serve as the comparator.

Conclusions

Currently, all the guidelines recommend newer antiplatelets (prasugrel and ticagrelor) in preference to clopidogrel as a part of DAPT in post-PCI patients, especially in the setting of ACS unless there is a contraindication. However, clopidogrel is still a widely used P2Y12 inhibitor in the post-PCI setting. In clinical practice, several factors including thrombotic risk, bleeding risk, and socio-economic background may influence the antiplatelet regimen in an individual patient. HTPR with clopidogrel therapy is not uncommon and has been correlated with ischemic events including stent thrombosis. The occurrence of bleeding on a potent P2Y12 inhibitor is the opposite scenario in which the use of PFT and genetic testing may be desirable. Although the use of PFT/genotyping studies to tailor antiplatelet regimens may be an attractive option, the absence of unequivocal results of multiple RCTs obviates their routine use in clinical practice. Nevertheless in a setting where the thrombotic risk seems to be higher than the bleeding risk, guided platelet therapy is desirable. Similarly in the setting of high-risk PCI and in the setting of ACS where initially newer antiplatelets are used and the patient has a high bleeding risk or has financial constraints, de-escalation may be done using PFT or gene testing based on local availability and feasibility. LPR has now been correlated with bleeding events while using P2Y12 inhibitors and the utility of this concept is evolving. Further studies in this regard will throw more light on the field of individualization or personalization of P2Y12 receptor inhibition in CAD patients treated with PCI.

Author contributions

AP and MB prepared the concept sheet. PV performed the literature review. AP and MB prepared the first draft. RS critically reviewed the manuscript and suggested changes. AP and MB prepared the final version and AP made the journal search. AP made the online submission.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bertrand ME, Rupprecht H-J, Urban P, Gershlick AH. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared

with ticlopidine in combination with aspirin after coronary stenting: The clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624–9.

2. Mehta SR, Yusuf S, Peters RJG, 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 2001;358:527–33.
3. Savi P, Herbert JM, Pflieger AM, Dol F, Delebassee D, Combalbert J, *et al.* Importance of hepatic metabolism in the antiaggregating activity of the thienopyridine clopidogrel. Biochem Pharmacol 1992;44:527–32.
4. 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;360:354–62.
5. Schuhlen H, Kastrati A, Pache J, Dirschinger J, Schomig A. Incidence of thrombotic occlusion and major adverse cardiac events between two and four weeks after coronary stent placement: Analysis of 5,678 patients with a four-week ticlopidine regimen. J Am Coll Cardiol 2001; 37:2066–73.
6. De la Torre-Hernandez JM, Alfonso F, Hernandez F, Elizaga J, Sanmartin M, Pinar E, *et al.* Drug-eluting stent thrombosis: Results from the multicenter Spanish registry ESTROFA (Estudio ESpanol sobre TROmbosis de stents FArmacoactivos). J Am Coll Cardiol 2008;51:986–90.
7. Kuchulakanti, Chu WW, Torguson R, Ohlmann P, Rha SW, Clavijo LC, *et al.* Correlates and long-term outcomes of angiographically proven stent thrombosis with sirolimus- and paclitaxel-eluting stents. Circulation 2006;113:1108–13.
8. Park SH, Hong GR, Seo HS, Tahk SJ. Stent thrombosis after successful drug-eluting stent implantation. Korean Circ J 2005;35:163–71.
9. Gum PA, Kottke-Marchant K, Poggio ED, Gurm H, Welsh PA, Brooks L, *et al.* Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol 2001;88:230–5.
10. Gurbel PA, Blinden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
11. Wiviott SD, Antman EM. Clopidogrel resistance: A new chapter in a fast-moving story. Circulation 2004;109:3064-7.
12. Hulot J.-S, Bura A, Villard E, Azizi M, Remones V, Goyenvalle C, *et al.* Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. Blood 2006;108:2244–7.
13. Umemura K, Furuta T, Kondo K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. J Thrombosis Haemostasis 2008;6:1439–41.
14. Desta Z, Zhao X, Shin J.-G, Flockhart D. A. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmacokinet 2002;41:913–58.
15. rs4244285-SNPedia. SNPedia.com. 2021. Available from: https://www.snpedia.com/index.php/Rs4244285. [Last accessed on 2021 May 31].
16. Shetkar SS, Ramakrishnan S, Seth S, Chandna P, Verma SK, Bhargava B, *et al.* CYP 450 2C19 polymorphisms in Indian patients with coronary artery disease. Indian Heart J 2014;66:16-24.
17. George CA, Sreedharan ST, Satheesan SK, Surendranath SP. Frequency of CYP2C19*2 Allele in patients with acute coronary syndrome: A cross-sectional study from Central Kerala, India. J Clin Diagn Res 2021;15:BC17-21.
18. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, *et al.* Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. J Thromb Haemost 2007;5:2429–36.
19. Collet J.-P, Hulot J.-S, Anzaha G, Pena A, Chastre T, Caron C, *et al.* High doses of clopidogrel to overcome genetic resistance: The randomized crossover CLOVIS-2 (Clopidogrel and Response Variability Investigation Study 2). JACC Cardiovasc Interv 2011;4:392–402.
20. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, *et al.* Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007;50:1852–6.
21. 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;357:2001-15.
22. Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, *et al.* Standard vs high dose clopidogrel based on platelet function testing after percutaneous coronary intervention: The GRAVITAS randomized trial. JAMA 2011;305:1097-105.
23. Price MJ, Angiolillo DJ, Teirstein PS, Lillie E, Manoukian SV, Berger PB, *et al.* Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: A time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial. Circulation 2011;124:1132-7.
24. Trenk D, Stone GW, Gawaz M, Kastrati A, Angiolillo DJ, Müller U, *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: Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) study. J Am Coll Cardiol 2012;59:2159-64.
25. Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, *et al.* Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100-9.
26. Montalescot G, Rangé G, Silvain J, Bonnet JL, Boueri Z, Barthélémy O, *et al.* High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: A landmark analysis of the ARCTIC study. Circulation 2014;129:2136-43.
27. 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 end point, randomised controlled superiority trial. Lancet 2016;388:2015–22.
28. 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 2012;379:1705-11.
29. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ, *et al.* Pharmacogenomic approach

to selecting antiplatelet therapy in patients with acute coronary syndromes: The PHARMCLO trial. J Am Coll Cardiol 2018;71:1869–77.

30. 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;381:1621-31.
31. Janssen PWA, Bergmeijer TO, Vos GA, Kelder JC, Qaderdan K, Godschalk TC, *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.
32. Pereira NL, Farkouh ME, So D, Lennon R, Gellar 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 2020;324:761-71.
33. 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 Genom Precis Med 2020;13:e002640. doi: 10.1161/CIRCGEN.119.002640.
34. Aradi D, Storey RF, Komosci A, Trenk D, Gulba D, Kiss RG, *et al.* Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. Eur Heart J 2014;35:209-15.
35. Sibbing D, Aradi D, Alexopoulos D, Berg JT, 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 Interv 2019;12:1521-15.
36. Sofi F, Marcucci R, Gori AM, Giusti B, Abbate R, Gensini GF. Clopidogrel non responsiveness and risk of cardiovascular morbidity. An updated meta-analysis. Thromb Haemost 2010;103:841–8.
37. Brar SS, ten Berg J, Marcucci R, Price MJ, Valgimigli M, Kim HS, *et al.* Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention. A collaborative meta-analysis of individual participant data. J Am Coll Cardiol 2011;58:1945–54.
38. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, *et al.* Bleeding and stent thrombosis on P2Y12-inhibitors: Collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J 2015;36:1762–71.
39. Stone GW, Witzenbichler B, Weisz G, Rinaldi MJ, Neumann FJ, Metzger DC, *et al.* Platelet reactivity and clinical outcomes after coronary artery implantation of drug-eluting stents (ADAPT-DES): A prospective multicentre registry study. Lancet 2013;382:614-23.
40. Rinaldi MJ, Gohs FX, Kirtane AJ, Brodie BR, Stuckey TD, Redfors B, *et al.* Impact of point-of-care platelet function testing among patients with and without acute coronary syndromes undergoing percutaneous coronary intervention with drug-eluting stents (from the ADAPT-DES Study). Am J Cardiol 2019;123:549-57.
41. Alexopoulos D, Xanthopoulou I, Davlouros P, Plakomyti TE, Panagiotou A, Mavronasiou E, *et al.* Prasugrel overcomes high on-clopidogrel platelet reactivity in chronic coronary artery disease patients more effectively than high dose (150 mg) clopidogrel. Am Heart J 2011;162:733-9.
42. Saucedo JF, Angiolillo DJ, DeRaad R, Frelinger AL 3rd, Gurbel PA, Costigan TM, *et al.* Decrease in high on-treatment platelet reactivity (HTPR) prevalence on switching from clopidogrel to prasugrel: Insights from the switching antiplatelet (SWAP) study. Thromb Haemost 2013;109:347-55.
43. Bliden KP, Tantry US, Storey RF, Jeong YH, Gesheff M, Wei C, *et al.* The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: Combined analysis of the ONSET/OFFSET and RESPOND studies. Am Heart J. 2011;162:160-5.
44. Li P, Yang Y, Chen T, Liu Y, Cao A, Liu J, *et al.* Ticagrelor overcomes high platelet reactivity in patients with acute myocardial infarction or coronary artery in-stent restenosis: A randomized controlled trial. Sci Rep 2015;5:13789.
45. Alexopoulos D, Galati A, Xanthopoulou I, Mavronasiou E, Kassimis G, Theodoropoulos KC, *et al.* Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: A pharmacodynamic study. J Am Coll Cardiol 2012;60:193–9.
46. Alexopoulos D, Stavrou K, Koniari I, Gkizas V, Perperis A, Kontoprias K, *et al.* Ticagrelor vs prasugrel one-month maintenance therapy: Impact on platelet reactivity and bleeding events. Thromb Haemost 2014;112:551-7.
47. Perl L, Zemer-Wassercug N, Rechavia E, Vaduganathan M, Orvin K, Weissler-Snir A, *et al.* Comparison of platelet inhibition by prasugrel versus ticagrelor over time in patients with acute myocardial infarction. J Thromb Thrombolysis 2015;39:1-7.
48. Laine M, Gaubert M, Frère C, Peyrol M, Thuny F, Yvorra S, *et al.* Comparison of platelet reactivity following prasugrel and ticagrelor loading dose in ST-segment elevation myocardial infarction patients: The COMPASSION study. Platelets 2015;26:570-2.
49. Lhermusier T, Voisin S, Murat G, Mejean S, Garcia C, Bataille V, *et al.* Switching patients from clopidogrel to novel P2Y12 receptor inhibitors in acute coronary syndrome: Comparative effects of prasugrel and ticagrelor on platelet reactivity. Int J Cardiol 2014;174:874-6.
50. Alexopoulos D, Xanthopoulou I, Mavronasiou E, Stavrou K, Siapika A, Tsoni E, *et al.* Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with diabetes. Diabetes Care 2013;36:2211-6.
51. Laine M, Frère C, Toesca R, Berbis J, Barnay P, Pansieri M, *et al.* Ticagrelor versus prasugrel in diabetic patients with an acute coronary syndrome. A pharmacodynamic randomised study. Thromb Haemost 2014;111:273-8.
52. Alexopoulos D, Vogiatzi C, Stavrou K, Vlassopoulou N, Perperis A, Pentara I, *et al.* Diabetes mellitus and platelet reactivity in patients under prasugrel or ticagrelor treatment: An observational study. Cardiovasc Diabetol 2015;14:68.
53. Lemesle G, Schurtz G, Bauters C, Hamon M. High on-treatment platelet reactivity with ticagrelor versus prasugrel: A systematic review and meta-analysis. J Thromb Haemost 2015;13:931-42.
54. Zhang H, Zhang P, Dong P, Yang X, Wang Y, Zhang H, *et al.* Effect of ticagrelor versus prasugrel on platelet reactivity: A meta-analysis. Coron Artery Dis 2017;28:597-604.
55. Lemesle G, Schurtz G, Bauters C, Hamon M. High on-treatment platelet reactivity with ticagrelor versus prasugrel: A systematic review and meta-analysis. J Thromb Haemost 2015;13:931-42.
56. Dai L, Xu J, Jiang Y, Chen K. Impact of prasugrel and

ticagrelor on platelet reactivity in patients with acute coronary syndrome: A meta-analysis. Front Cardiovasc Med 2022;9:905607.

57. Kerneis M, Silvain J, Abtan J, Hauguel M, Barthélémy O, Payot L, *et al.* Platelet effect of prasugrel and ticagrelor in patients with ST-segment elevation myocardial infarction. Arch Cardiovasc Dis 2015;108:502-10.
58. Dillinger JG, Manzo Silberman S, Bal dit Sollier C, Amsallem M, Sideris G, Voicu S, *et al.* Ticagrelor effectiveness overestimated by VASP index: Platelet inhibition by ticagrelor versus prasugrel in acute coronary syndrome patients according to platelet function tests. Int J Cardiol 2014;176:557-9.
59. Franchi F, Faz GT, Rollini F, Park Y, Cho JR, Thano E, *et al*. Pharmacodynamic effects of switching from prasugrel to ticagrelor: Results of the prospective, randomized SWAP-3 study. JACC Cardiovasc Interv 2016;9:1089-98.
60. Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, *et al.* Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost 2010;8:250-6.
61. Cuisset T, Grosdidier C, Loundou AD, Quilici J, Loosveld M, Camoin L, *et al.* Clinical implications of very low on-treatment platelet reactivity in patients treated with thienopyridine: The POBA study (predictor of bleedings with antiplatelet drugs). JACC Cardiovasc Interv 2013;6:854-63.
62. Bonello L, Mancini J, Pansieri M, Maillard L, Rossi P, Collet F, *et al.* Relationship between post-treatment platelet reactivity and ischemic and bleeding events at 1-year follow-up in patients receiving prasugrel. J Thromb Haemost 2012;10:1999-2005.
63. Cuisset T, Gaborit B, Dubois N, Quilici J, Loosveld M, Beguin S, *et al.* Platelet reactivity in diabetic patients undergoing coronary stenting for acute coronary syndrome treated with clopidogrel loading dose followed by prasugrel maintenance therapy. Int J Cardiol 2013;168:523-8.
64. Costa TG, Katz M, Lemos Neto PA, Guerra JC, Franken M, Pesaro AE. Low platelet reactivity in patients with myocardial infarction treated with aspirin plus ticagrelor. Einstein (São Paulo) 2022;20:eAO7001.
65. Gragnano F, Capolongo A, Terraccino F, Gargiulo G, DeSio V, Cesaro A, *et al.* Escalation and de-escalation of antiplatelet therapy after acute coronary syndrome or PCI: Available evidence and implications for practice. J Clin Med 2022;11:6246.
66. Shahim B, Redfors B, Stuckey TD, Liu M, Zhou Z, Witzenbichler B, Duffy PL, *et al.* On-treatment platelet reactivity and ischemic outcomes in patients with diabetes mellitus: Two-year results from ADAPT-DES. J Am Heart Assoc 2023;12:e026482.
67. 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 2022;43:959-67.
68. 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;13:606-17.
69. Saito Y, Nishi T, Wakabayashi S, Ohno Y, Kitahara H, Ariyoshi N, *et al.* Validation of the ABCD-GENE score to identify high platelet reactivity in east Asian patients undergoing percutaneous coronary intervention. Int J Cardiol 2021;327:15-8.
70. Capodanno D, Angiolillo DJ, Lennon RJ, Goodman MG, Kim SK, O'Cochlain F, *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.
71. Legrand D, Barbato E, Chenu P, Magne J, Vrolix M, Wijns W, *et al.* The STIB score: A simple clinical test to predict clopidogrel resistance. Acta Cardiol 2015;70:516-21.
72. Antoniou S, Colicchia M, Guttmann OP, Rathod KS, Wright P, Fhadil S, *et al.* Risk scoring to guide antiplatelet therapy post-percutaneous coronary intervention for acute coronary syndrome results in improved clinical outcomes. Eur Heart J Qual Care Clin Outcomes 2018;4:283-9.
73. 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;390:1747-57.
74. 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 inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070–8.
75. Levine G, Bates E, Blankenship J, Bailey SR, Bittl JA, Cercek B, *et al.* 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. J Am Coll Cardiol 2011;58:e44–122.
76. Amsterdam E, Wenger N, Brindis R, Casey DE Jr, Ganiats TG, Holmes DR Jr, *et al.* 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes. J Am Coll Cardiol 2014;64:e139–228.
77. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS Guidelines on myocardial revascularization. EuroIntervention 2019;14:1435-534.
78. 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 2021;42:1289-367.
79. Verdoia M, Pergolini P, Nardin M, Rolla R, Barbieri L, Marino P, *et al.* Prevalence and predictors of high-on treatment platelet reactivity during prasugrel treatment in patients with acute coronary syndrome undergoing stent implantation. J Cardiol 2019;73:198-203.
80. He S, Lin Y, Tan Q, Mao F, Chen K, Hao J, *et al.* Ticagrelor resistance in cardiovascular disease and ischemic stroke. J Clin Med 2023;12:1149.
81. Adamski P, Buszko K, Sikora J, Niezgoda P, Fabiszak T, Ostrowska M, *et al.* Determinants of high platelet reactivity in patients with acute coronary syndromes treated with ticagrelor. Sci Rep 2019;9:3924.
82. Kubica J, Adamski P, Ostrowska M, Sikora J, Kubica JM, Sroka WD, *et al.* Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: The randomized, double-blind, placebo-controlled IMPRESSION trial. Eur Heart J 2016;37:245–25.