

Platelet Function Testing and Genotyping for Tailoring Treatment in Complex PCI Patients

Athanasios Moulias, MD, PhD, ¹, Angeliki Papageorgiou, MD, ¹, and Dimitrios Alexopoulos, MD, PhD, FESC, FACC, ²

1. Department of Cardiology, General University Hospital of Patras, Patras, Greece; 2. Second Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens Medical School, Athens, Greece

Abstract

Dual antiplatelet therapy (DAPT), comprising aspirin and a P2Y₁₂ receptor inhibitor, is considered the cornerstone of treatment in patients who have undergone percutaneous coronary intervention (PCI). Patients with complex PCI (C-PCI) constitute a special PCI subpopulation, characterized by increased ischemic risk. Identifying the optimal DAPT strategy is often challenging and remains controversial in this setting. In an attempt to balance ischemic and bleeding risks in C-PCI patients receiving DAPT, treatment individualization regarding potency and duration has evolved as a feasible approach. Platelet function testing and genotyping have been evaluated in several trials with conflicting and mostly neutral results. The aim of this review is to critically appreciate the role of these tools for antiplatelet treatment tailoring specifically in C-PCI patients. Because existing evidence is limited, dedicated future studies are warranted to elucidate the utility of platelet function testing and genotyping in C-PCI.

Keywords

Percutaneous coronary intervention, complex percutaneous coronary intervention, platelet function testing, genotyping, dual antiplatelet therapy, P2Y₁₂ receptor inhibitors

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Correspondence: Athanasios Moulias, MD, PhD, Consultant Cardiologist, Department of Cardiology, General University Hospital of Patras, 26504 Patras, Greece. E: dramoulias@live.com

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Dual antiplatelet therapy (DAPT), comprising aspirin and a P2Y₁₂ receptor inhibitor, is the cornerstone of treatment in patients who have undergone percutaneous coronary intervention (PCI).^{1,2} Clopidogrel was the first broadly used P2Y₁₂ receptor inhibitor and conferred a significant reduction in ischemic events after PCI.^{3,4} However, clopidogrel's metabolic activation is unpredictable, leading to variability in response among patients. Genetic polymorphisms, among other factors, have been implicated in 'clopidogrel resistance'.⁵

Several studies have found an association between impaired response to clopidogrel (often termed high on-treatment platelet reactivity [HPR]) and adverse ischemic events.⁶⁻⁸ On the other hand, low platelet reactivity (LPR) has been recognized as a risk factor for bleeding events, which significantly influence the clinical outcome of patients with coronary artery disease (CAD) during and after myocardial revascularization.^{6,9}

These observations, along with the advent of more potent P2Y₁₂ inhibitors (prasugrel and ticagrelor), gave birth to the concept of antiplatelet treatment tailoring; this concerns the adaptation and individualization of antiplatelet therapy type and duration based on various factors, including clinical presentation, the patient's clinical profile, ischemic/bleeding scores, and laboratory/point-of-care tests. More specifically, potential strategies involve upfront selection of a more potent P2Y₁₂ inhibitor (such as prasugrel or ticagrelor) instead of clopidogrel based on genotyping,

and escalation (switching from clopidogrel to prasugrel or ticagrelor) or de-escalation (switching from prasugrel/ticagrelor to clopidogrel) of the initial antiplatelet treatment according to platelet function testing (PFT) results.¹⁰

Moreover, various scores – including the Predicting Bleeding Complications In Patients Undergoing Stent Implantation and Subsequent Dual Anti Platelet Therapy (PRECISE-DAPT) score, the DAPT score, ARC-HBR trade-off risk model and PARIS – have been proposed for uncoupling bleeding and ischemic risks in patients undergoing PCI and, thus, guiding DAPT duration in this context.¹¹⁻¹⁴

Patients with C-PCI constitute a special PCI subpopulation where antiplatelet treatment is challenging. Although no universal definition exists, C-PCI according to the European Society of Cardiology (ESC) involves at least one of the following procedural aspects: implantation of three or more stents; treatment of three or more lesions; bifurcation PCI with two stents; total stent length >60 mm; or chronic total occlusion (CTO) PCI.¹⁵ Additionally, left main (LM) or proximal left anterior descending (LAD) coronary artery PCI, saphenous vein graft PCI, bifurcation lesion with a side branch ≥2.5 mm, use of rotational atherectomy, lesion length ≥30 mm or the presence of thrombus in the coronary lesion have also been considered as procedural characteristics defining a coronary intervention as C-PCI.¹⁶

Table 1: High Platelet Reactivity and Low Platelet Reactivity Cutoff Values for Available Platelet Function Testing Assays

PFT assay	HPR	LPR
VerifyNow P2Y ₁₂	208 PRU	85 PRU
Multiplate Analyzer	46 U	19 U
VASP	50% PRI	16% PRI
TEG platelet mapping	47 mm	31 mm

HPR: high platelet reactivity, LPR: low platelet reactivity, PFT: platelet function testing, PRI: platelet reactivity index, PRU: platelet reactivity units, VASP: vasodilator-stimulated phosphoprotein. Adapted from: Tantry et al. 2013.²⁶ Used with permission from Elsevier.

In addition to procedural complexity, patient complexity because of multiple comorbidities and high-risk clinical features (such as smoking, diabetes, chronic kidney disease, peripheral arterial disease, hypertension and/or poor left ventricular function) is increasing over time in patients presenting for PCI.¹⁷ C-PCI patients are at increased risk for ischemic events and this risk is greater as procedural complexity increases.^{18–19} It is noteworthy that C-PCI patients seem to be at a higher risk for major bleeding as well.²⁰ DAPT of increased potency and duration might reduce adverse ischemic events but increase the risk of bleeding as well, which can compromise the clinical outcome.

The optimal antiplatelet treatment strategy in C-PCI remains a controversial and moving field. PFT and genotyping have been considered as potentially useful tools in individualizing antiplatelet treatment in attempts to balance ischemic and bleeding risks. The aim of this review is to summarize the existing evidence and critically appreciate the role of PFT and genotyping for antiplatelet treatment tailoring in C-PCI patients.

PFT and Genotyping in PCI

DAPT, comprising aspirin and a P2Y₁₂ receptor inhibitor, has improved PCI clinical outcomes by reducing ischemic complications.³ The second-generation thienopyridine clopidogrel was the first broadly used P2Y₁₂ receptor inhibitor, as it exhibited a better safety profile than the first-generation thienopyridine ticlopidine. However, platelet function measurements showed that the response to this regimen varied, with some patients exhibiting poor response, a condition often termed HPR or clopidogrel resistance, as mentioned above.²¹ Several factors have been implicated in the variation in response to clopidogrel, including diabetes, acute coronary syndrome, a high BMI, renal failure, older age, heart failure, inflammation, smoking, drug–drug interactions and genetic polymorphisms (mainly of *CYP2C19*).^{21–23}

The results of multiple studies indicating a clear association between HPR and adverse ischemic events after PCI paved the way for research efforts investigating the role of treatment tailoring.^{6,21} This approach initially involved increasing clopidogrel dose but this failed to reduce the incidence of death from cardiovascular causes, nonfatal MI, or stent thrombosis in HPR patients after PCI, perhaps because of a modest pharmacodynamic effect.²⁴

With the advent of the more potent P2Y₁₂ inhibitors prasugrel and ticagrelor, escalation of antiplatelet treatment by switching clopidogrel to a novel agent became an additional option. On the other hand, an increased response to P2Y₁₂ receptor inhibitor, leading to LPR, has been recognized as a risk factor for bleeding events, which compromise clinical outcomes after PCI.⁹ As a result, treatment de-escalation has also

been proposed as a potentially beneficial strategy for patients at a high risk of bleeding.²⁵

Several methods of PFT are available for the *ex vivo* measurement of platelet reactivity to adenosine diphosphate, including point-of-care assays (e.g. the VerifyNow P2Y₁₂ system [Werfen], the Multiplate analyzer [Roche], and thromboelastography [TEG] platelet mapping) and laboratory-based techniques (e.g. light transmission aggregometry [LTA] and vasodilator-stimulated phosphoprotein [VASP]).

There is a consensus that point-of-care assays should be preferred, and specific cut-off points for HPR and LPR have been defined for each assay (Table 1).^{8,26} Platelet reactivity assessed by a PFT assay in a P2Y₁₂-treated patient should ideally be within the therapeutic window between LPR and HPR, which is associated with the lowest risk of ischemic and bleeding events according to observational data.²⁷ Major randomized studies testing PFT-guided escalation of antiplatelet treatment in PCI patients failed to show clinical benefit, which calls its role in clinical practice into question.^{24,28–30} However, a PFT-guided de-escalation approach was found to be non-inferior for the primary endpoint of net clinical benefit (cardiovascular death, MI, stroke or bleeding grade ≥ 2 according to Bleeding Academic Research Consortium [BARC] criteria) compared with potent platelet inhibition for 12 months after PCI for acute coronary syndrome (ACS) in the TROPICAL-ACS randomized study (7% in the guided de-escalation group versus 9% in the control group; *p* for non-inferiority=0.0004; HR 0.81; 95% CI [0.62–1.06]). It is noteworthy that there was no increase in the combined risk of cardiovascular death, MI, or stroke in the early de-escalation group.³¹

As already mentioned, HPR in clopidogrel-treated patients may be related to polymorphisms of genes that encode cytochromes responsible for clopidogrel's metabolic activation. Research on genotyping has focused on polymorphisms of the *CYP2C19* gene, the most common and relevant being *CYP2C19**2 loss of function (LoF) polymorphism, causing *CYP2C19* activity to be lost. The *CYP2C19**3 allele is another LoF polymorphism, which has a low prevalence in white people.³² However, only 6–12% of the variability on clopidogrel response can be attributed to differences in genotype.^{5,33} It is reasonable to use genotyping only for clopidogrel-treated patients and point-of-care assays are recommended over laboratory-based methods.⁸

Some randomized studies have shown efficacy of *CYP2C19* genotyping in antiplatelet treatment tailoring for both elective and ACS PCI patients.^{34–37} However, the recently announced TAILOR-PCI study reported – though marginally – a non-significant (4% versus 5.9%; HR:0.66; *p*=0.056) reduction in major adverse cardiovascular events (MACE) (non-fatal myocardial infarction or stroke, cardiovascular death, severe recurrent ischemia or stent thrombosis) at 1 year in the genotyping compared with the non-genotyping group.³⁸

Beyond the *CYP2C19**2 LoF polymorphism, clinical factors are believed to have contributing roles in HPR and thrombotic complications. In this context, the ABCD-GENE (Age, Body mass index, Chronic kidney disease, Diabetes mellitus, and Genotyping) score was developed, which incorporates four clinical (age >75 years, BMI >30 kg/m², chronic kidney disease [estimated glomerular filtration rate <60 ml/min/1.73m²], and diabetes) and one genetic (*CYP2C19**2 LoF alleles) independent predictors of HPR. The ABCD-GENE score has been shown to independently correlate with all-cause death, as well as with the composite of all-cause death, stroke, or MI, both as a continuous variable and by using a cut-off point of ≥ 10 .³⁹

Table 2: Studies Investigating Platelet Function Testing for Treatment Tailoring in Complex Percutaneous Coronary Intervention Patients

Study	Population	Study Design	Main Endpoints	Main Results
Xu et al. 2014 ⁵⁵	384 ACS patients who received high-risk C-PCI	Randomized, single-center study Comparison of standard DAPT (conventional group) versus DAPT guided by modified TEG platelet mapping (PFT-guided group) • IPA _{AA} < 50% → ↑ASA to 200 mg daily; • IPA _{ADP} < 30% → ↑clopidogrel to 150 mg daily	MI, emergency TVR, ST, and death at 6 months	No significant differences in the primary efficacy endpoint (4.7% in the conventional versus 5.2% in the PFT-guided group; HR 1.13; p=0.79)
Chen et al. 2019 ⁵⁶	334 Taiwanese patients with stable CAD and scheduled stent implantation for intermediate-to-highly complex coronary lesions (SYNTAX score >22)	Prospective, single-blind, randomized study ASA + clopidogrel (group standard) versus ASA + ticagrelor (group ticagrelor) versus ASA + clopidogrel + cilostazol (group cilostazol) for 6 months of treatment then switching to ASA only	PRU levels 24 h, 7 days, and 1 month after PCI MACE (death, MI, revascularization of the original lesion) at 2 years	PRU levels decrease: in group ticagrelor > in group cilostazol > in group standard No significant difference in MACE between the three groups (group standard 12.1%, group cilostazol 8.7%, group ticagrelor 7.8%; p=NS)
De Gregorio et al. 2020 ⁵⁷	1,101 patients from the Florence CTO-PCI registry with available PFT (LTA)	Retrospective Patients stratified according to LTA results: optimal platelet reactivity (82%) and HPR (ADP test ≥70%) (18%) From 2011, escalation strategy applied: • HPR on clopidogrel → escalation to prasugrel or ticagrelor • HPR on new P2Y ₁₂ receptor antagonist → change between prasugrel and ticagrelor	Long-term cardiac survival (3 years)	Three-year survival was significantly higher in the optimal platelet reactivity group compared with HPR patients (95.3 ± 0.8% versus 86.2 ± 2.8%; p<0.001) HPR on clopidogrel 'not switched' associated with cardiac mortality (HR 2.37; p=0.003) after multivariable adjustment

ACS = acute coronary syndrome; ADP = adenosine diphosphate; ASA = acetylsalicylic acid; CAD = coronary artery disease; C-PCI = complex percutaneous coronary intervention; CTO = chronic total occlusion; DAPT = dual antiplatelet therapy; HPR = high on-treatment platelet reactivity; IPA_{AA} = inhibition of platelet aggregation by arachidonic acid; IPA_{ADP} = inhibition of platelet aggregation by adenosine diphosphate; LTA = light transmission aggregometry; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; PFT = platelet function testing; PRU = platelet reactivity unit; ST = stent thrombosis; TEG = thromboelastography; TVR = target vessel revascularization.

Current guidelines on DAPT recommend against (class III) the routine use of PFT and genotyping as antiplatelet treatment modification guidance in the context of PCI.^{2,15} However, according to the recently published ESC guidelines on non-ST-segment elevation ACS: "De-escalation of P2Y₁₂ receptor inhibitor treatment... may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. De-escalation may be done unguided based on clinical judgment, or guided by platelet function testing, or *CYP2C19* genotyping, depending on the patient's risk profile and availability of respective assays." (Class IIb, level of evidence A.)⁴⁰ Moreover, experts agree that use of PFT/genotyping may be reasonable in specific high-risk clinical scenarios, including C-PCI.⁸

Rationale for Use of PFT and/or Genotyping in C-PCI

During the last decade, C-PCI procedures have been increasingly performed. Moreover, as mentioned before, a rise in the high-risk clinical features (smoking, diabetes, chronic kidney disease, peripheral arterial disease, hypertension, and poor left ventricular function) of treated patients has also been observed.⁴¹ C-PCI patients are at a higher risk of ischemic events, and this risk becomes greater as procedural complexity increases.^{18,19,42} DAPT of increased potency (with prasugrel or ticagrelor) might reduce adverse ischemic events.

On these grounds, ESC guidelines for myocardial revascularization offer the option of administering prasugrel or ticagrelor in specific high-risk situations of elective PCI; however, the level of evidence for this is weak (IIb, C).¹ Moreover, prolonged DAPT has also been proposed as a potentially beneficial strategy for this high-risk group.¹⁹ Nevertheless, C-PCI patients seem to be at increased risk for major bleeding as well.²⁰ Consequently, more potent and/or prolonged DAPT might compromise clinical outcome by increasing bleeding events.

As C-PCI procedures are performed more often and in sicker patients, optimization of DAPT strategies is imperative to optimize clinical outcomes. Here, antiplatelet treatment tailoring according to each patient's ischemic and bleeding risk is a reasonable approach. PFT and genotyping may serve as tools to escalate or de-escalate DAPT to achieve the desired level of antiplatelet effect. Moreover, PFT could also be used to check compliance with treatment, which is crucial in this context.

Evidence Regarding Platelet Function Testing in Complex PCI

Numerous randomized and observational studies have investigated the potential role of PFT-guided antiplatelet treatment for the optimization of clinical outcomes of patients subjected to PCI.^{24,29–31,43–54} *Supplementary Table 1* provides an overview of the relevant studies in this field. Smaller randomized and non-randomized studies suggest PFT-guided treatment tailoring improves clinical outcomes.^{51–54} Nonetheless, major randomized trials have failed to confirm a benefit from a PFT-guided treatment escalation approach whereas a PFT-guided de-escalation approach was found to be non-inferior regarding the primary endpoint of net clinical benefit (cardiovascular death, MI, stroke or BARC bleeding grade ≥2) compared with potent platelet inhibition for 12 months after PCI for ACS.^{24,28–31}

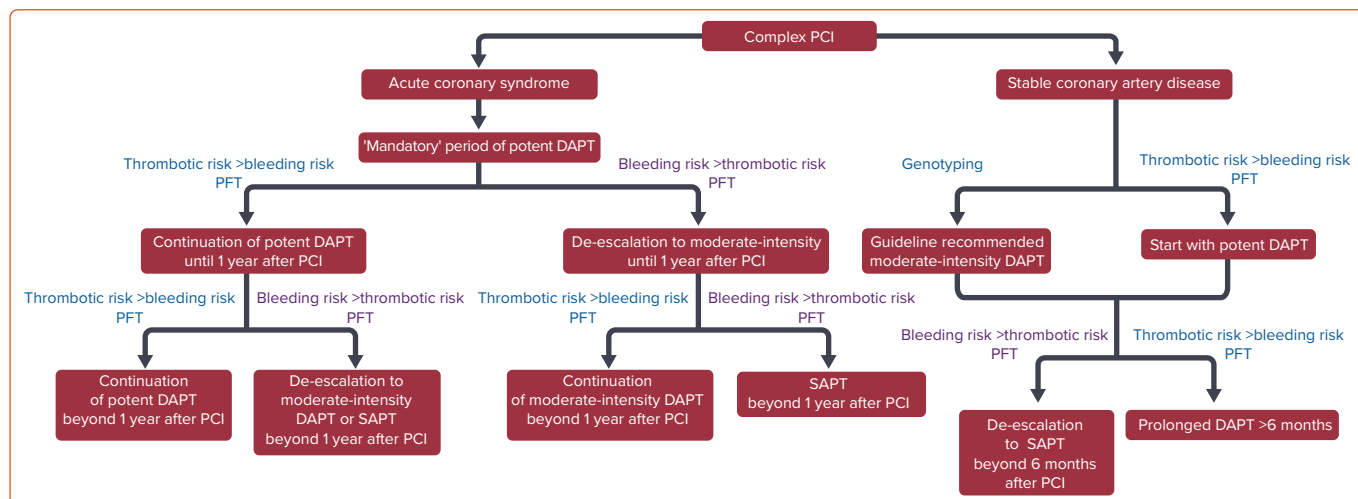
C-PCI patients (e.g. those with multivessel PCI, LM PCI, saphenous vein graft PCI, bifurcation PCI, lesion type B2/C or three or more stents) are represented in these studies to varying degrees (mostly poorly), and relevant data are not reported in some of them (*Supplementary Table 1*). Moreover, only a few studies have reported subgroup analyses of the primary endpoint for some procedural variables related to PCI complexity but not for the subgroup of C-PCI patients in total (*Supplementary Table 1*). Consequently, extrapolation of the results of these studies to C-PCI patients is questionable.

Table 3: Randomized Studies Investigating Genotyping for Antiplatelet Treatment Tailoring in Percutaneous Coronary Intervention Patients

Study	Population	Comparison	Main Endpoints	Main Results	C-PCI Patients	Conventional Group, n (%)	Genotyping Guided Group, n (%)
RAPID-GENE 2012 ⁵⁸	200 patients scheduled for PCI	Standard group (clopidogrel 75 mg daily) versus genotyping-guided group (prasugrel 10 mg daily for <i>CYP2C19</i> *2 carriers, clopidogrel 75 mg daily for non-carriers)	HPR (PRU>234) in <i>CYP2C19</i> *2 carriers after 7 days DAPT	Significant reduction of HPR in <i>CYP2C19</i> *2 carriers genotyping guided versus standard group (0 versus 30%, p=0.0092)	LM PCI Vein graft PCI	0 (0%) 2 (2%)	2 (2%) 4 (4%)
IAC-PCI 2013 ³⁷	600 ACS patients with successful PCI	Conventional group: 300 mg clopidogrel LD/75 mg MD versus personalized group (<i>CYP2C19</i> phenotype: EMs → standard dose of clopidogrel, IMs → double LD and MD of clopidogrel, PMs → double LD and MD of clopidogrel + cilostazol)	MACE (all-cause death, MI, stroke or TVR) at 180 days after intervention	MACE lower in the personalized than the conventional group (2.66% versus 9.03%; p=0.001)	LM PCI	17 (5.69%)	10 (3.32%)
Shen et al. 2016 ³⁶	628 CAD patients subjected to successful PCI	Routine group (75 mg clopidogrel daily) versus individual group (<i>CYP2C19</i> phenotype: EMs → clopidogrel 75 mg daily, IMs → clopidogrel 150 mg daily, PMs → ticagrelor 90 mg bid)	MACE (death from any cause, MI, TVR)	Lower MACE rate in individual group at 12 months after discharge compared with routine group (4.2% versus 9.4%; p=0.010)	LM lesion Multivessel disease	17 (5.3%) 62 (19.4%)	15 (4.9%) 69 (22.3%)
	ACS: rate not reported						
PHARMCLO 2018 ³⁵	888 ACS patients PCI: 532 (62.2%) Premature termination	Standard care versus pharmacogenomic (<i>ABCB1</i> , <i>CYP2C19</i> *2, and <i>CYP2C19</i> *17) guidance of P2Y ₁₂ receptor inhibitor administration	Composite of CV death, MI, stroke, or BARC 3/5 bleeding at 12 months	Significant reduction of the incidence of the primary endpoint in the pharmacogenomic compared with the standard-care arm (15.9% versus 25.9%; HR: 0.58; 95% CI: 0.43-0.78; p<0.001)	LM disease 3-vessel disease	45 (10.6%) 112 (26.5%)	60 (13.8%) 119 (27.4%)
POPular Genetics 2019 ³⁴	2,488 STEMI PCI patients	P2Y ₁₂ inhibitor on the basis of early <i>CYP2C19</i> genetic testing (genotype-guided group) versus standard treatment with ticagrelor or prasugrel for 12 months	Net adverse clinical events (death from any cause, MI, ST, stroke, or PLATO major bleeding at 12 months) PLATO major/minor bleeding at 12 months	Net adverse clinical events lower in genotype-guided group than standard group (5.1% versus 5.9%; p _{noninf} <0.001) Bleeding occurrence was lower in genotype-guided group (9.8% versus 12.5%; HR 0.78; 95% CI [0.61–0.98]; p=0.04)	LM PCI Bypass graft PCI Ostial lesion Bifurcation lesion	9 (0.73%) 6 (0.5%) 65 (5.5%) 239 (20.2%)	4 (0.3%) 5 (0.4%) 76 (6.4%) 214 (18.1%)
ADAPT-PCI trial 2020 ⁵⁹	504 PCI patients ACS: 49.9%	Genotyping of <i>CYP2C19</i> major alleles (*2, *3, *17) to guide antiplatelet drug selection (genotyped group) versus no genotyping (usual care)	Rate of prasugrel or ticagrelor prescribing in each arm MACE endpoint: CV death, nonfatal MI, nonfatal stroke, urgent revascularization, ST	Use of prasugrel or ticagrelor significantly higher in genotyped compared with usual care group (30% versus 21%; HR 1.60; 95% CI [1.07–2.42]; p=0.03) No significant differences in MACE in the genotyped compared with the usual care group (13.7% versus 10.2%; p=0.27)	Stented vessels≥2	25 (10%)	27 (11%)
TAILOR-PCI 2020 ³⁸	5,302 elective + ACS PCI patients	Non genotyping group (clopidogrel 75 mg MD) versus genotyping group (ticagrelor 90 mg twice a day for carriers, clopidogrel 75 mg daily for non-carriers)	Composite MACE (non-fatal MI or stroke, CV death, severe recurrent ischemia, ST) at 1 year TIMI major or minor bleeding	Non-significant reduction of MACE in the genotyping compared with the non-genotyping group (4% versus 5.9%; HR 0.66; p=0.056) No difference in bleeding (1.9% versus 1.6%)	LM PCI	21 (2%)	32 (4%)

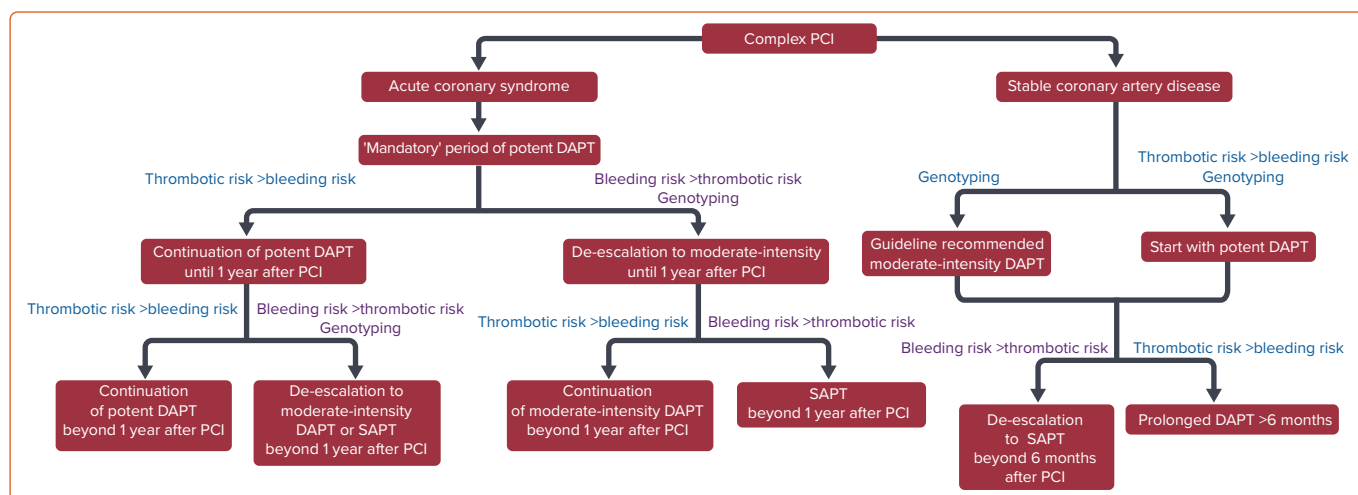
ACS = acute coronary syndrome; CAD = coronary artery disease; C-PCI = complex percutaneous coronary intervention; CV = cardiovascular; DAPT = dual antiplatelet treatment; EMs = extensive metabolizers; HPR = high on treatment platelet reactivity; IMs = intermediate metabolizers; LD = loading dose; LM = left main; MACE = major adverse cardiac events; MD = maintenance dose; PCI = percutaneous coronary intervention; PLATO = Platelet Inhibition and Patient Outcome; PMs = poor metabolizers; TVR = target vessel revascularization.

Figure 1: Treatment with Platelet Function Testing



Potent DAPT: aspirin + ticagrelor or prasugrel; moderate-intensity DAPT: aspirin + clopidogrel. DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PFT = platelet function testing; SAPT = single antiplatelet therapy.

Figure 2: Treatment with Genotyping



Potent DAPT is aspirin + ticagrelor or prasugrel; moderate-intensity DAPT is aspirin + clopidogrel. DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PFT: platelet function testing, DAPT: dual antiplatelet therapy; SAPT = single antiplatelet therapy

To have more robust evidence regarding the role of PFT in C-PCI, dedicated clinical trials enrolling exclusively patients subjected to high-risk interventions are required. However, relevant studies to date are scarce and suffer the limitations of small sample size or non-randomized design.⁵⁵⁻⁵⁷ The design and main results of these studies are presented in Table 2.

In a randomized, single-center study, Xu et al. failed to show any improvement in the primary ischemic endpoint by using a guided DAPT escalation strategy, using modified TEG platelet mapping in ACS patients who underwent C-PCI.⁵⁵ Similarly, no significant difference in MACE was reported by Chen et al. by the administration of more potent antiplatelet therapy (aspirin plus ticagrelor, or aspirin plus clopidogrel and cilostazol) compared with standard treatment (aspirin plus clopidogrel) in stable CAD patients scheduled for C-PCI, in spite of achieving a greater platelet reactivity unit decrease with the more intense antiplatelet treatment. This study did not investigate the guided strategy, but implies that more pronounced platelet inhibition does not confer additional benefit in stable CAD C-PCI patients.⁵⁶ Finally, in a retrospective study including 1,101 patients from the Florence CTO-PCI registry, HPR on clopidogrel 'not switched' was associated with increased cardiac mortality (HR 2.37;

p=0.003) after multivariable adjustment, compared with an LTA-based treatment escalation strategy in HPR patients who underwent CTO PCI.⁵⁷

Evidence Regarding Genotyping in Complex PCI

As with PFT, no studies regarding genotyping have been conducted exclusively for C-PCI. Table 3 contains a summary of the randomized studies investigating the role of genotyping (CYP2C19) for antiplatelet treatment tailoring in PCI patients.^{34-37,58,59}

Although some small randomized studies have shown clinical benefit, the recent large-scale, randomized TAILOR-PCI study questioned the benefit from point-of-care, genotype-guided, anti-platelet therapy (ticagrelor 90mg twice daily for carriers and clopidogrel 75 mg daily for non-carriers) compared with routine care (clopidogrel 75 mg as directed) in patients undergoing PCI (electively or for ACS).³⁴⁻³⁸ The reduction of MACE (non-fatal MI or stroke, cardiovascular death, severe recurrent ischemia or stent thrombosis) at 1 year in the genotyping compared with the non-genotyping group was marginally non-significant (4% versus 5.9%; HR 0.66; p=0.056). No significant difference in thrombolysis in MI (TIMI) major or minor bleeding classification was noted as well (1.9% versus 1.6%).

Nevertheless, the results of this study show signs of benefit from the genetically guided antiplatelet therapy, since approximately one-third fewer adverse events occurred in the genetically guided treatment group compared with the standard treatment group. Notably, a prespecified sensitivity analysis allowing for multiple events per patient favored the use of genotype-guided therapy over the conventional approach in *CYP2C19* LoF carriers (HR 0.60; 95% CI: 0.41–0.89; $p=0.01$).

Moreover, a post hoc analysis found a nearly 80% reduction in the rate of adverse events in the first 3 months of treatment among patients who received genetically guided therapy. This finding may be clinically relevant, considering that ischemic events are more frequent during the first 30 days after PCI in this population and potent P2Y₁₂ inhibitor therapy may be beneficial during this early period. Bleeding is more pronounced during later period with potent P2Y₁₂ inhibitors.

However, it should be noted that the representation of C-PCI in these studies was limited (Table 3). Therefore, it is not known to which extent their results are relevant to the C-PCI group of patients.

Conclusion

Taking into consideration the increasing performance of C-PCI procedures worldwide along with the associated high ischemic risk, refinement of antiplatelet treatment strategies is becoming imperative for this special group of patients.

Tailoring DAPT potency and duration is a reasonable approach and PFT/genotyping may serve as valuable tools in this attempt (Figures 1 and 2). To date, large-scale randomized clinical trials have failed to show any clinical benefit from routine monitoring of platelet function in PCI patients. However, since C-PCI patients are mostly under-represented in these studies and subgroup analyses are limited, it remains unclear whether C-PCI patients would benefit from a tailored strategy guided by PFT.

Similarly, results from randomized studies are not convincing so far regarding the utility of genotyping results for treatment escalation after

PCI. However, as with PFT studies, it is not known to which extent these results can be extrapolated to C-PCI patients. A patient-level meta-analysis, including C-PCI patients enrolled in PFT/genotyping studies, could potentially provide further insights into this field of research. Nonetheless, the heterogeneity in the design of conducted studies will definitely affect its reliability.

Dedicated randomized studies enrolling exclusively C-PCI patients in different clinical settings (such as stable CAD and ACS) are warranted and will elucidate the role of treatment tailoring based on PFT and genotyping in this group of patients. Notably, the establishment of a universal definition for C-PCI is required and will facilitate future research efforts.

Until more robust evidence becomes available in this controversial field, clinicians should follow the guidelines and adopt a PFT/genotyping-guided approach for treatment tailoring selectively, according to their clinical judgement, in specific C-PCI patients where balancing ischemic and bleeding risks is challenging (Figures 1 and 2). Noteworthy, the results of PFT and/or genotyping should always be evaluated in combination with the patient's clinical, procedural and socioeconomic parameters to optimize antiplatelet treatment planning. □

Clinical Perspective

- Patients with complex percutaneous coronary intervention (C-PCI) constitute a special PCI subpopulation at increased ischemic risk.
- Antiplatelet treatment in C-PCI patients remains controversial.
- Tailoring antiplatelet treatment in C-PCI patients is a reasonable approach and platelet function testing (PFT)/genotyping might serve as valuable tools in this.
- Existing evidence from clinical studies in this field is limited.
- Dedicated studies for C-PCI patients are warranted to elucidate the utility of antiplatelet treatment tailoring based on PFT and/or genotyping in this context.

1. Neumann FJ, M Sousa-Uva, Ahlsson A et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165. <https://doi.org/10.1093/eurheartj/ehy394>; PMID: 30165437.
2. Levine GN, ER Bates, JA Bittl, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; 68:1082–115. <https://doi.org/10.1016/j.jacc.2016.03.513>; PMID: 27036918.
3. Yusuf S, F Zhao, SR Mehta, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494–502. <https://doi.org/10.1056/NEJMo010746>; PMID: 11519503.
4. Steinhubl SR, PB Berger, JT Mann 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411–20. <https://doi.org/10.1001/jama.288.19.2411>; PMID: 12435254.
5. 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;302:849–57. <https://doi.org/10.1001/jama.2009.1232>; PMID: 19706858.
6. Aradi D, A Kirtane, L Bonello, 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. <https://doi.org/10.1093/eurheartj/ehv104>; PMID: 25896078.
7. Stone GW, Witzensichler B, Weisz G, 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. [https://doi.org/10.1016/S0140-6736\(13\)61170-8](https://doi.org/10.1016/S0140-6736(13)61170-8); PMID: 23890998.
8. Sibbing D, Aradi D, Alexopoulos D, et al. Updated expert consensus statement on platelet function and genetic testing for guiding P2Y₁₂ receptor inhibitor treatment in percutaneous coronary intervention. *JACC Cardiovasc Interv* 2019;12:1521–37. <https://doi.org/10.1016/j.jcin.2019.03.034>; PMID: 31202949.
9. Ndrepepa G, Berger PB, Mehili J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. *J Am Coll Cardiol* 2008;51(7):690–7. <https://doi.org/10.1016/j.jacc.2007.10.040>; PMID: 18279731.
10. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet P2Y₁₂ receptor-inhibiting therapies. *Circulation* 2017;136:1955–75. <https://doi.org/10.1161/CIRCULATIONAHA.117.031164>; PMID: 29084738.
11. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet* 2017;389:1025–34. [https://doi.org/10.1016/S0140-6736\(17\)30397-5](https://doi.org/10.1016/S0140-6736(17)30397-5); PMID: 28290994.
12. Yeh RW, Secemsky, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA* 2016;315:1735–49. <https://doi.org/10.1001/jama.2016.3775>; PMID: 27022822.
13. Urban P, Gregson J, Owen R, et al. Assessing the risks of bleeding vs thrombotic events in patients at high bleeding risk after coronary stent implantation: the ARC-high bleeding risk trade-off model. *JAMA Cardiol* 2021;6:410–9. <https://doi.org/10.1001/jamacardio.2020.6814>; PMID: 33404627.
14. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. *J Am Coll Cardiol* 2016;67:2224–34. <https://doi.org/10.1016/j.jacc.2016.02.064>; PMID: 27079334.
15. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J* 2018;39:213–60. <https://doi.org/10.1093/eurheartj/ehx419>; PMID: 28886622.
16. Benetou DR, Andreou I, Varlamos C, et al. Tailoring dual antiplatelet therapy for the complex PCI patient: current status and perspectives. *Cardiovasc Drugs Ther* 2020;34:697–706. <https://doi.org/10.1007/s10557-020-07009-6>; PMID: 32472238.
17. Bortnick AE, Epps KC, Selzer F, et al. Five-year follow-up of patients treated for coronary artery disease in the face of an increasing burden of co-morbidity and disease complexity (from the NHLBI Dynamic Registry). *Am J Cardiol* 2014;113:573–9. <https://doi.org/10.1016/j.amjcard.2013.10.039>; PMID: 24388624.
18. Wilensky RL, Selzer F, Johnston J, et al. Relation of percutaneous coronary intervention of complex lesions to clinical outcomes (from the NHLBI Dynamic Registry). *Am J Cardiol* 2002;90:216–21. [https://doi.org/10.1016/S0002-9149\(02\)02457-8](https://doi.org/10.1016/S0002-9149(02)02457-8); PMID: 12127606.
19. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after complex PCI. *J Am Coll Cardiol* 2016;68:1851–64. <https://doi.org/10.1016/j.jacc.2016.03.513>; PMID: 27036918.

- jacc.2016.07.760; PMID: 27595509.
20. Genereux P, Giustino G, Redfors B, et al. Impact of percutaneous coronary intervention extent, complexity and platelet reactivity on outcomes after drug-eluting stent implantation. *Int J Cardiol* 2018;268:61–7. <https://doi.org/10.1016/j.ijcard.2018.03.103>; PMID: 30041804.
 21. 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;107:2908–13. <https://doi.org/10.1161/01.CIR.0000072771.11429.83>; PMID: 12796140.
 22. Campo G, Valgimigli M, Gemmati D, et al. Poor responsiveness to clopidogrel: drug-specific or class-effect mechanism? Evidence from a clopidogrel-to-ticlopidine crossover study. *J Am Coll Cardiol* 2007;50:1132–7. <https://doi.org/10.1016/j.jacc.2007.04.092>; PMID: 17868803.
 23. Siller-Matula JM, Trenk D, Schror K, et al. Response variability to P2Y12 receptor inhibitors: expectations and reality. *JACC Cardiovasc Interv* 2013;6:1111–28. <https://doi.org/10.1016/j.jcin.2013.06.011>; PMID: 24262612.
 24. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. *JAMA* 2011;305:1097–105. <https://doi.org/10.1001/jama.2011.290>; PMID: 21406646.
 25. Alexopoulos D, Lianos I, Vlachakis P, et al. De-escalation of treatment with oral P2Y12 receptor inhibitors: current status and perspectives. *J Cardiovasc Pharmacol Ther* 2019;24:304–14. <https://doi.org/10.1177/1074248418823724>; PMID: 30722685.
 26. Tantry US, Bonello L, Aradi D, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. *J Am Coll Cardiol* 2013;62:2261–73. <https://doi.org/10.1016/j.jacc.2013.07.101>; PMID: 24076493.
 27. Sibbing D, Steinhubl SR, Schulz S, et al. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. *J Am Coll Cardiol* 2010;56:317–8. <https://doi.org/10.1016/j.jacc.2010.03.048>; PMID: 20633826.
 28. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med* 2012;367:2100–9. <https://doi.org/10.1056/NEJMoa1209979>; PMID: 23121439.
 29. Trenk D, Stone GW, Gawaz M, et al. A randomized trial of prasugrel versus clopidogrel in patients with high platelet reactivity on clopidogrel after elective percutaneous coronary intervention with implantation of drug-eluting stents: 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. <https://doi.org/10.1016/j.jacc.2012.02.026>; PMID: 22520250.
 30. Cayla G, T Cuisset, J Silvain, et al. Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. *Lancet* 2016;388:2015–22. [https://doi.org/10.1016/S0140-6736\(16\)31323-X](https://doi.org/10.1016/S0140-6736(16)31323-X); PMID: 27581531.
 31. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. *Lancet* 2017;390:1747–57. [https://doi.org/10.1016/S0140-6736\(17\)32155-4](https://doi.org/10.1016/S0140-6736(17)32155-4); PMID: 28855078.
 32. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* 2009;360:354–62. <https://doi.org/10.1056/NEJMoa0809171>; PMID: 19106084.
 33. Hochholzer W, Trenk D, Fromm MF, et al. Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. *J Am Coll Cardiol* 2010;55:2427–34. <https://doi.org/10.1016/j.jacc.2010.02.031>; PMID: 20510210.
 34. Claessens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. *N Engl J Med* 2019;381:1621–31. <https://doi.org/10.1056/NEJMoa1907096>; PMID: 31479209.
 35. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCO Trial. *J Am Coll Cardiol* 2018;71:1869–77. <https://doi.org/10.1016/j.jacc.2018.02.029>; PMID: 29540324.
 36. Shen DL, Wang B, Bai J, et al. Clinical value of CYP2C19 genetic testing for guiding the antiplatelet therapy in a Chinese population. *J Cardiovasc Pharmacol* 2016;67:232–6. <https://doi.org/10.1097/FJC.0000000000000337>; PMID: 26727381.
 37. Xie X, Ma YT, Yang YN, et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: a randomized control trial. *Int J Cardiol* 2013;168:3736–40. <https://doi.org/10.1016/j.ijcard.2013.06.014>; PMID: 23850318.
 38. Pereira NL, ME Farkouh, D So, 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. <https://doi.org/10.1001/jama.2020.12443>; PMID: 32840598.
 39. Angiolillo DJ, Capodanno D, Danchin N, et al. Derivation, validation, and prognostic utility of a prediction rule for nonresponse to clopidogrel: the ABCD-GENE score. *JACC Cardiovasc Interv* 2020;13:606–17. <https://doi.org/10.1016/j.jcin.2020.01.226>; PMID: 32139218.
 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;42:1289–367. <https://doi.org/10.1093/eurheartj/ehaa575>; PMID: 32860058.
 41. Landes U, Bental T, Levi A, et al. Temporal trends in percutaneous coronary interventions thru the drug eluting stent era: insights from 18,641 procedures performed over 12-year period. *Catheter Cardiovasc Interv* 2018;92: E262–70. <https://doi.org/10.1002/ccd.27375>; PMID: 29027735.
 42. Stefanini GG, Serruys PW, Silber S, et al. The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: a substudy of the RESOLUTE All Comers Trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). *J Am Coll Cardiol* 2011;57:2221–32. <https://doi.org/10.1016/j.jacc.2011.01.036>; PMID: 21616282.
 43. Bonello L, Camoin-Jau L, Arques S, et al. Adjusted clopidogrel loading doses according to vasodilator-stimulated phosphoprotein phosphorylation index decrease rate of major adverse cardiovascular events in patients with clopidogrel resistance: a multicenter randomized prospective study. *J Am Coll Cardiol* 2008;51:1404–11. <https://doi.org/10.1016/j.jacc.2007.12.044>; PMID: 18387444.
 44. Bonello L, Camoin-Jau L, Armero S, et al. Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *Am J Cardiol* 2009;103:5–10. <https://doi.org/10.1016/j.amjcard.2008.08.048>; PMID: 19101221.
 45. Valgimigli M, Campo G, de Cesare N, et al. Intensifying platelet inhibition with tirofiban in poor responders to aspirin, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind, prospective, randomized Tailoring Treatment with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. *Circulation* 2009. 119:3215–22. <https://doi.org/10.1161/CIRCULATIONAHA.108.833236>; PMID: 19528337.
 46. Cuisset T, Frere C, Quilici J, et al. Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel nonresponders: a prospective, randomized study. *JACC Cardiovasc Interv* 2008;1:649–53. <https://doi.org/10.1016/j.jcin.2008.08.018>; PMID: 19463379.
 47. Wang XD, Zhang DF, Zhuang SW, et al. Modifying clopidogrel maintenance doses according to vasodilator-stimulated phosphoprotein phosphorylation index improves clinical outcome in patients with clopidogrel resistance. *Clin Cardiol* 2011;34:332–8. <https://doi.org/10.1002/clc.20884>; PMID: 21538388.
 48. Aradi D, Rideg O, Vorobcsuk A, et al. Justification of 150 mg clopidogrel in patients with high on-clopidogrel platelet reactivity. *Eur J Clin Invest* 2012;42:384–92. <https://doi.org/10.1111/j.1365-2362.2011.02594.x>; PMID: 21902692.
 49. Hazarbasanov D, Velchev V, Finkov B, et al. Tailoring clopidogrel dose according to multiple electrode aggregometry decreases the rate of ischemic complications after percutaneous coronary intervention. *J Thromb Thrombolysis* 2012;34:85–90. <https://doi.org/10.1007/s11239-012-0684-z>; PMID: 22249353.
 50. Tang YD, Wang W, Yang M, et al. Randomized comparisons of double-dose clopidogrel or adjunctive cilostazol versus standard dual antiplatelet in patients with high posttreatment platelet reactivity: results of the CREATIVE trial. *Circulation* 2018;137:2231–45. <https://doi.org/10.1161/CIRCULATIONAHA.117.030190>; PMID: 29420189.
 51. Siller-Matula JM, Francesconi M, Dechant C, et al. Personalized antiplatelet treatment after percutaneous coronary intervention: the MADONNA study. *Int J Cardiol* 2013;167:2018–23. <https://doi.org/10.1016/j.ijcard.2012.05.040>; PMID: 22656044.
 52. Mayer K, Schulz S, Bernlochner I, et al. A comparative cohort study on personalised antiplatelet therapy in PCI-treated patients with high on-clopidogrel platelet reactivity. Results of the ISAR-HPR registry. *Thromb Haemost* 2014;112:342–51. <https://doi.org/10.1160/TH13-10-0874>; PMID: 24718389.
 53. Aradi D, Tornyo A, Pinter T, et al. Optimizing P2Y12 receptor inhibition in patients with acute coronary syndrome on the basis of platelet function testing: impact of prasugrel and high-dose clopidogrel. *J Am Coll Cardiol* 2014. 63:1061–70. <https://doi.org/10.1016/j.jacc.2013.12.023>; PMID: 24486281.
 54. Valentini R, Marcucci R, Comito V, et al. Prasugrel in clopidogrel nonresponders undergoing percutaneous coronary intervention: the RECLOSE-3 study (REsponsiveness to CLOpidogrel and StEnt Thrombosis). *JACC Cardiovasc Interv* 2015;8:1563–70. <https://doi.org/10.1016/j.jcin.2015.07.010>; PMID: 26386764.
 55. Xu L, Wang L, Yang X, et al. Platelet function monitoring guided antiplatelet therapy in patients receiving high-risk coronary interventions. *Chin Med J (Engl)* 2014;127:3364–70. PMID: 25269896.
 56. Chen YC, Lin FY, Lin YW, et al. DAPT plus cilostazol is better than traditional DAPT or aspirin plus ticagrelor as elective PCI for intermediate-to-highly complex cases: prospective, randomized, PRU-based study in Taiwan. *Am J Cardiovasc Drugs* 2019;19:75–86. <https://doi.org/10.1007/s40256-018-0302-3>; PMID: 30467686.
 57. De Gregorio MG, Marcucci R, Migliorini A, et al. Clinical implications of ‘tailored’ antiplatelet therapy in patients with chronic total occlusion. *J Am Heart Assoc* 2020;9:e014676. <https://doi.org/10.1161/JAHA.119.014676>; PMID: 32067582.
 58. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* 2012;379:1705–11. [https://doi.org/10.1016/S0140-6736\(12\)60161-5](https://doi.org/10.1016/S0140-6736(12)60161-5); PMID: 22464343.
 59. Tuteja S, Glick H, Matthai W, et al. Prospective CYP2C19 genotyping to guide antiplatelet therapy following percutaneous coronary intervention: a pragmatic randomized clinical trial. *Circ Genom Precis Med* 2020;13:e002640. <https://doi.org/10.1161/CIRCGEN.119.002640>; PMID: 31928229.