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STATE-OF-THE-ART REVIEW

Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary Intervention

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ABSTRACT

Dual-antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor is the standard treatment for patients undergoing percutaneous coronary intervention. The availability of different $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel, ticagrelor) with varying levels of potency has enabled physicians to contemplate individualized treatment regimens, which may include escalation or deescalation of $P2Y_{12}$-inhibiting therapy. Indeed, individualized and alternative DAPT strategies may be chosen according to the clinical setting (stable coronary artery disease vs. acute coronary syndrome), the stage of the disease (early vs. long-term treatment), and patient risk for ischemic and bleeding complications. A tailored DAPT approach may be potentially guided by platelet function testing (PFT) or genetic testing. Although the routine use of PFT or genetic testing in percutaneous coronary intervention–treated patients is not recommended, recent data have led to an update in guideline recommendations that allow considering selective use of PFT for DAPT deescalation. However, guidelines do not expand on when to implement the selective use of such assays into decision making for personalized treatment approaches. Therefore, an international expert consensus group of key leaders from North America, Asia, and Europe with expertise in the field of antiplatelet treatment was convened. This document updates 2 prior consensus papers on this topic and summarizes the contemporary updated expert consensus recommendations for the selective use of PFT or genotyping in patients undergoing percutaneous coronary intervention. (J Am Coll Cardiol Intv 2019;■:■–■) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CYP = cytochrome P450

DAPT = dual-antiplatelet therapy

HPR = high platelet reactivity

LoF = loss-of-function

LPR = low platelet reactivity

PCI = percutaneous coronary intervention

PFT = platelet function testing

Percutaneous coronary intervention (PCI) is among the most widely performed procedures worldwide, and the introduction of thienopyridine-type $P2Y_{12}$ receptor inhibitors, in addition to aspirin, termed dual-antiplatelet therapy (DAPT) (1), led to a substantial reduction in post-procedural thrombotic events (2). Because of rare but serious side effects of the first-generation thienopyridine ticlopidine (3), the second-generation thienopyridine clopidogrel became the first broadly administered $P2Y_{12}$ inhibitor that enabled reduction of the risk for thrombotic complications after PCI with an acceptable safety profile. However, clopidogrel's active metabolite generation is unpredictable, leading to significant interpatient variability in levels of on-treatment platelet reactivity (4) (**Figure 1**). Genetic polymorphisms have been identified to contribute, at least in part, to the observed variability in clopidogrel response (5–8). Subsequently, a multitude of studies have consistently shown that PCI-treated patients with impaired clopidogrel-induced platelet inhibition to be at increased risk for ischemic events, in particular stent thrombosis (9–12). These observations led to contemplate strategies of tailored antiplatelet

HIGHLIGHTS

- Different $P2Y_{12}$ inhibitors have enabled physicians to contemplate individualized treatment regimens.
- In selective scenarios, PFT and genotyping may be used as optional tools for guiding treatment.
- Further studies on DAPT deescalation and escalation are needed to refine existing treatment options.

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treatment regimens that included the use of more potent $P2Y_{12}$-inhibiting therapies in these patients. Along with this development and the expansion of DAPT options, including the newer generation $P2Y_{12}$ inhibitors prasugrel and ticagrelor (13,14), dedicated clinical trials were conducted that aimed at escalating $P2Y_{12}$ inhibiting therapy on the basis of the results of platelet function testing (PFT) (15–17). However, this series of trials failed to meet the endpoint of improving patient outcomes. A number of factors have been attributed to these disappointing findings, including definitions for impaired clopidogrel response, choice of $P2Y_{12}$-inhibiting agents to tailor therapy, and patient selection (i.e., confined mostly to low- to intermediate-risk patients). These studies, however, were paralleled by advances in stent technology, with the latest generation drug-eluting stents exhibiting a much lower risk for stent thrombosis compared with their first-generation counterparts (18). Such evolution in stent technology also has had important implications for the choice and duration of DAPT (19).

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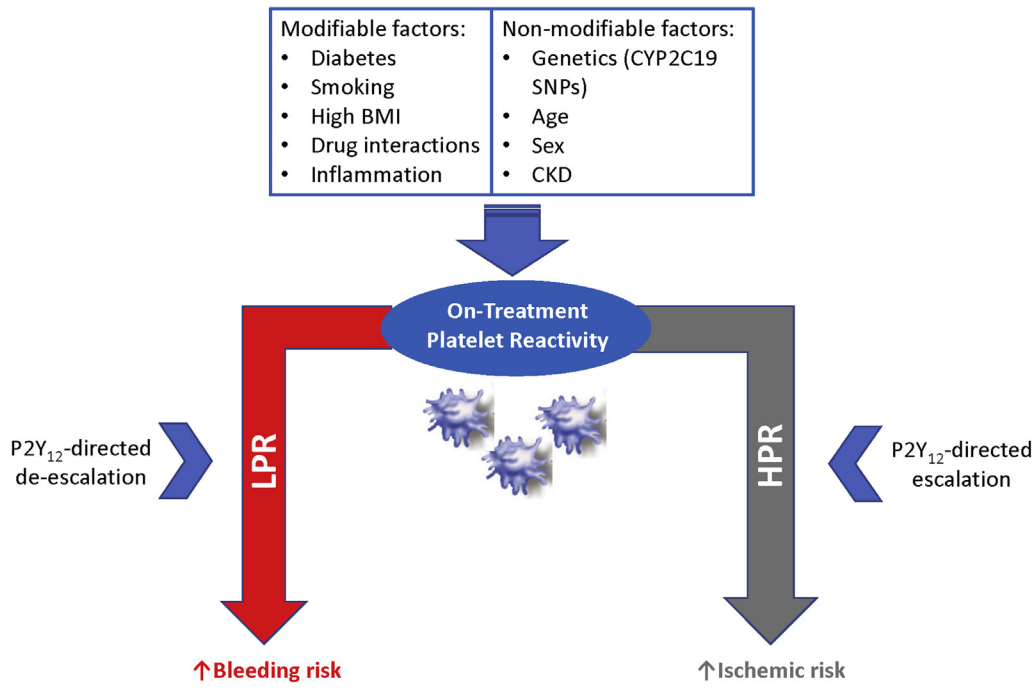
FIGURE 1 Modifiable and Nonmodifiable Factors That Affect the Level of on-Treatment Platelet Reactivity



Patients exhibiting low platelet reactivity (LPR) show an increased risk for bleeding events, and a $P2Y_{12}$-directed deescalation strategy may be an alternative dual-antiplatelet therapy (DAPT) approach in these patients. Patients exhibiting high platelet reactivity (HPR) show an increased risk for ischemic events, and a $P2Y_{12}$-directed escalation strategy may be an alternative DAPT approach in these patients.
BMI = body mass index; CKD = chronic kidney disease; SNP = single-nucleotide polymorphism.

Notably, PFT results and the presence of certain genetic markers were found to predict not only thrombotic but also bleeding events (9,10,20,21). In the era of latest generation drug-eluting stents and broader use of potent $P2Y_{12}$ inhibitors, thrombotic events dramatically decreased and prevention of bleeding complications became a major goal (22). Emphasis on bleeding reduction also arose given the ever growing awareness of its prognostic implications, including on mortality (23). These observations have led to the concept of tailoring DAPT by "deescalation" of $P2Y_{12}$ inhibitor treatment. In particular, this strategy has emerged as a bleeding reduction strategy in patients remote from the coronary intervention, when thrombotic risk decreases while bleeding risk persists, as well as for patients deemed unsuitable for long-term potent DAPT (e.g., those with high bleeding risk, socioeconomic factors) (24-27). Indeed, although a series of randomized trials incorporating PFT results to "escalate" DAPT have consistently failed, trials of "deescalation" have shown more promising results (24,26,28). These observations have also been reflected in recent guideline recommendations updates (29) and were incorporated in an update on the product label of clopidogrel (30).

Expert consensus statements on the role of PFT and genetic testing have been previously reported (11,31). In light of the new advances in the field, which include changes in guideline recommendations and drug labels, as well as the launching and conduct of randomized controlled trials in this field of research, an update to these prior documents is warranted. Accordingly, key opinion leaders from Europe, North America, and Asia with expertise in basic, translational, and clinical sciences in the field of antiplatelet therapy and/or who have contributed to the scientific research on platelet function or genetic testing were identified by the document chairs (D.S. and D.J.A.). Experts were also selected with the aim of achieving a balanced composition for the group of authors with varying point of views on the matter under discussion. All invited experts agreed to partake in the development of this document and endorse the advice provided. This was an academic collaboration among the identified experts. The compilation of this updated consensus was not directly or financially supported by

TABLE 1 Consensus Advice for Platelet Function Testing in Patients Undergoing Percutaneous Coronary Intervention

General advice on using PFT in clinical practice

- Point-of-care assays are preferred over laboratory-based PFT assays.
- Selection of assays should depend on the local site experience and availability.
- Clinically validated and standardized assays should be used, and physicians should apply standardized definitions and cutoff values to determine a status of HPR or LPR.
- Consensus (11,34) cutoff values to determine HPR and LPR exist for the following assays:

VerifyNow $P2Y_{12}$	HPR = 208 PRU	LPR = 85 PRU
Multiplate Analyzer	HPR = 46 U	LPR = 18 U
VASP	HPR = 50% PRI	LPR = 16% PRI
TEG platelet mapping	HPR = 47 mm	LPR = 31 mm

- PFT may be considered to guide decisions on timing of cardiac or noncardiac surgery and to reduce waiting time to surgery.

Patients with stable CAD (elective PCI)

- PFT results for patients on $P2Y_{12}$ inhibitor treatment may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after elective PCI in stable CAD.
- PFT to escalate treatment (switch to potent antiplatelet drugs) in patients with HPR on clopidogrel is not recommended on a routine basis but may be considered in specific clinical scenarios in patients with increased thrombotic risk.
- PFT to screen for HPR to determine the drug that would remain when DAPT cessation is desired (e.g., triple treatment in which one antiplatelet agent is planned to be omitted) is not recommended on a routine basis but may be considered in specific clinical scenarios.

Patients with acute coronary syndrome (NSTEMI/STEMI)

- PFT results for patients on $P2Y_{12}$ inhibitor treatment may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after PCI for ACS.
- PFT to escalate treatment in patients with HPR on clopidogrel is not recommended on a routine basis but may be considered in specific clinical scenarios.
- PFT to screen for HPR (on clopidogrel) when DAPT deescalation is contemplated (guided DAPT deescalation) may be considered in specific clinical scenarios (bleeding events, high bleeding risk, socioeconomic indications) as an alternative to DAPT with potent $P2Y_{12}$ receptor inhibitors.

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual-antiplatelet therapy; HPR = high-platelet reactivity; LPR = low platelet reactivity; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PFT = platelet function testing; PRI = platelet reactivity index; PRU = platelet reactivity units; STEMI = ST-segment elevation myocardial infarction; TEG = thromboelastography; VASP = vasodilator-stimulated phosphoprotein.

industry. Given that guidelines do not expand on when or when not to implement the selective use of such PFT or genetic testing into decision making for personalized treatment approaches, consensus for the various scenarios under discussion was reached within the group by surveys (poll with questions) addressing all relevant topics and subtopics and subsequent discussions of the available evidence by group members. This document summarizes the updated expert consensus recommendations for the selective use of PFT or genotyping in patients undergoing PCI. Although this document expands on the recent findings from trials of deescalation, its intent is not to advocate for deescalation of $P2Y_{12}$-inhibiting therapy routinely in clinical practice, where practitioners should abide, whenever possible, with guideline recommendations (29,32) on the choice of DAPT with highest level of evidence substantiated by the large-scale pivotal trials (13,14).

GENERAL ASPECTS OF PFT AND PCI

Different assays are available for the ex vivo assessment of on-treatment platelet reactivity to adenosine diphosphate (33). Available assays can be classified as point-of-care or near-patient-based assays (e.g., VerifyNow, Multiplate, thromboelastography) versus laboratory-based methods (light transmission aggregometry, vasodilator-stimulated phosphoprotein). Details of the relevant assays are beyond the scope of this review and have been summarized elsewhere (11,33). For practical reasons, the point-of-care assays should be preferred, but any selection of assays also depends on the availability and local site experience. There is also a consensus that, depending on site experience, clinically validated and standardized assays (VerifyNow, Multiplate, vasodilator-stimulated phosphoprotein, thromboelastography with platelet mapping) (9,10) should be used whenever possible. Moreover, there is consensus to continue to refer to standardized definitions and cutoff values of high platelet reactivity (HPR) or low platelet reactivity (LPR) (**Table 1**) (9,11,34). Similar to the international normalized ratio to detect levels of oral anticoagulation, it could be assumed that patients within the therapeutic window of $P2Y_{12}$ inhibition, defined as the level between LPR and HPR, might develop the lowest risk for adverse events. In aggregate, although nonrandomized observational data (9,10,21,35) generated during the past decade are supportive, it should be emphasized that further confirmative studies are needed to strengthen the concept of a "therapeutic window." More important, how adjusting treatment in patients out of the therapeutic window may affect the risk for bleeding or thrombotic complications also remains to be established. Moreover, single on-treatment measurements were included in most of the prior studies using PFT

TABLE 2 Major Randomized Clinical Trials of Platelet Function Testing for Guidance of $P2Y_{12}$ Receptor Inhibitor Treatment

Study Characteristics	GRAVITAS (16) (2011)	TRIGGER-PCI (17) (2012)	ARCTIC (15) (2012)	ANTARCTIC (60) (2016)	TROPICAL-ACS (28) (2017)
Study population	n = 2,214	n = 423	n = 2,440	n = 877 (all >75 yrs)	n = 2,610
Proportion of patients with ACS	40%	0%	27%	100% (35% STEMI)	100% (55% STEMI)
PFT assay used	VerifyNow	VerifyNow	VerifyNow	VerifyNow	Multiplate analyzer
HPR cutoff value	≥230 PRU	>208 PRU	≥235 PRU or 15% IPA	≥208 PRU	ADPTest ≥46 U
LPR cutoff value	NA	NA	90% IPA	≤85 PRU	NA
Timing of PFT	12–24 h after PCI (to define HPR status), 30 days, and 6 mo	Morning after PCI (to define HPR status), 30 days, and 6 mo	In the catheterization laboratory before stent implantation and 2–4 weeks after PCI (monitoring group)	14 days after randomization and repeated 14 days after treatment adjustment (monitoring group)	14 days after hospital discharge for ACS PCI
Guidance approach	Escalation	Escalation	Escalation	Escalation and deescalation	Deescalation
Study design	Randomized, double-blind, superiority trial of high-dose vs. standard-dose clopidogrel in patients with HPR	Randomized, double-blind, superiority trial of prasugrel vs. clopidogrel in patients with HPR	Randomized, open-label, superiority trial of PFT monitoring vs. conventional strategy	Randomized, open-label, superiority study of PFT monitoring vs. conventional strategy	Randomized, open-label, noninferiority study of PFT-guided deescalation vs. conventional strategy
Control arm	No additional loading dose, 75 mg/day	No additional loading dose, 75 mg/day	Conventional strategy at physician's discretion (without monitoring and drug adjustment)	Prasugrel 5 mg (without monitoring and drug adjustment)	Conventional treatment with prasugrel (without drug or dose adjustment)
Experimental arm	Clopidogrel 600 mg initial dose, 150 mg/day	Prasugrel 60 mg initial dose, 10 mg/day	Strategy of platelet function monitoring, with drug adjustment in patients who had poor response to antiplatelet therapy	Strategy of platelet function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy	Strategy of PFT-guided deescalation with 1 week prasugrel followed by 1 week clopidogrel, then clopidogrel or prasugrel from day 14
Primary endpoint	6-mo incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis	6-mo incidence of cardiac death or myocardial infarction	1-yr incidence of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization	1-yr incidence of cardiovascular death, myocardial infarction, stroke, stent thrombosis, urgent revascularization, or BARC ≥2 bleeding	1-yr incidence of cardiovascular death, myocardial infarction, stroke or BARC ≥2 bleeding
Key safety endpoint (bleeding events)	Severe or moderate GUSTO bleeding	Non-CABG TIMI major bleeding	Major STEEPLE bleeding	BARC ≥2 bleeding	BARC ≥2 bleeding
Key clinical findings (ischemic and bleeding endpoints)	No differences in the primary ischemic endpoint (2.3% vs 2.3%; HR: 1.01; 95% CI: 0.58–1.76; p = 0.97) Bleeding was not increased with the high-dose regimen (1.4% vs 2.3%; HR: 0.59; 95% CI: 0.31–1.11; p = 0.10)	Inconclusive (study terminated prematurely for futility after enrollment of 423 patients of the 2,150 planned)	No differences in the primary ischemic endpoint (34.6% monitoring group vs. 31.1% conventional group; HR: 1.13; 95% CI: 0.98–1.29; p = 0.10) Bleeding was not increased in the monitoring vs. conventional group (2.3% vs. 3.3%; HR: 0.70; 95% CI: 0.43–1.14; p = 0.15)	No differences in the primary net benefit endpoint (28%, monitoring group vs. 28% conventional group; HR: 1.00; 95% CI: 0.78–1.29; p = 0.98) Ischemic event rates of 10% vs. 9% in monitoring vs. control group (HR: 1.06; 95% CI: 0.69–1.62; p = 0.80) Bleeding event rates of 21% vs. 20% in monitoring vs. control group (HR: 1.04; 95% CI: 0.78–1.40; p = 0.77)	Noninferiority for the primary net benefit endpoint (7.3% in guided vs. 9.0% in control group; p_{noninf} = 0.0004; HR: 0.81; 95% CI: 0.62–1.06) Ischemic event rates of 2.5% vs. 3.2% in guided vs. control group (HR: 0.77; 95% CI: 0.48–1.21; p_{noninf} = 0.01) Bleeding event rates of 4.9% vs. 6.1% in guided vs. control group (HR: 0.82; 95% CI: 0.59–1.13; p = 0.23)

Adapted and modified with permission from Angiolillo (95).

ANTARCTIC = Platelet Function Monitoring to Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome; ARCTIC = Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting; BARC = Bleeding Academic Research Consortium; CABG = coronary artery bypass grafting; CI = confidence interval; GRAVITAS = Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; HR = hazard ratio; IPA = inhibition of platelet aggregation; NA = not applicable; STEEPLE = Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; TIMI = Thrombolysis In Myocardial Infarction; TRIGGER-PCI = Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel; TROPICAL-ACS = Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes; other abbreviations as in Table 1.

TABLE 3 Observational and Other Randomized Studies of Platelet Function Testing for Guidance of $P2Y_{12}$ Inhibitor Treatment

Study	Patients (Indication)	Study Design (PFT Assay)	Key Results
Nonrandomized PFT guidance studies			
MADONNA (Siller-Matula et al.) (54) (2013)	798 (elective + ACS PCI)	Prospective nonrandomized nonblinded study comparing 2 cohorts (guided vs. nonguided treatment) (Multiplate Analyzer)	Risk for ST lower in guided vs. nonguided group (0.2% vs. 1.9%; p = 0.027)
ISAR-HPR registry (Mayer et al.) (53) (2014)	999 (elective + ACS PCI)	Nonrandomized nonblinded study comparing 2 cohorts (guided vs. nonguided treatment) (Multiplate Analyzer)	Risk for death and ST significantly lower in guided vs. nonguided cohort (1.2% vs. 3.7%; p = 0.009)
PECS registry (Aradi et al.) (59) (2014)	741 (ACS PCI)	Single-center nonrandomized nonblinded prospective registry comparing 2 cohorts (high-dose clopidogrel vs. prasugrel for patients with HPR) (Multiplate Analyzer)	Risk for death, MI, ST, and stroke significantly lower in HPR + prasugrel vs. HPR + high-dose clopidogrel group (9.9% vs. 22.7%; p < 0.03)
Randomized PFT guidance trials			
Bonello et al. (48) (2008)	162 (elective + ACS PCI)	Prospective multicenter RCT comparing 2 study groups (guided vs. nonguided treatment) (VASP)	Risk for CV death, definite ST, recurrent ACS, and revascularization significantly lower in guided vs. nonguided group (0% vs. 10%; p = 0.007)
Bonello et al. (47) (2009)	429 (elective + ACS PCI)	Prospective multicenter RCT comparing 2 study groups (guided vs. nonguided treatment) (VASP)	Risk for early definite ST significantly lower in guided vs. nonguided group (0.5% vs. 4.2%; p < 0.01)
Valgimigli et al. (50) (2009)	263 (elective PCI)	Prospective multicenter RCT comparing 2 study groups (guided vs. nonguided treatment) (VerifyNow)	Risk for periprocedural MI (<48 h) significantly lower in guided vs. nonguided group (20.4% vs. 35.1%; p = 0.009)
Cuisset et al. (49) (2008)	149 (elective PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment) (LTA)	Risk for death, definite/probable ST, and recurrent ACS significantly lower in guided vs. nonguided group (19% vs. 40%; p = 0.006)
Wang et al. (51) (2011)	306 (elective + ACS PCI)	Single-center RCT comparing 2 study group (guided vs. nonguided treatment) (VASP)	Risk for CV death, definite ST, recurrent ACS, and revascularization significantly lower in guided vs. nonguided group (9.3% vs. 20.4%; p = 0.008)
Aradi et al. (45) (2012)	200 (elective PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment) (LTA + VASP)	Risk for CV death, MI, and TVR significantly lower in guided vs. nonguided group (3.1% vs. 24.6%; p = 0.01)
Ari et al. (46) (2012)	94 (elective + ACS PCI)	Double-center RCT comparing 2 study groups (guided vs. nonguided treatment) (VerifyNow)	Risk for CV death, MI, ST, TVR, and recurrent ACS significantly lower in guided vs. nonguided group (4.3% vs. 17%; p = 0.045)
Hazarbasanov et al. (57) (2012)	192 (PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment) (Multiplate Analyzer)	Risk for CV death, MI, ST, and ischemic stroke significantly lower in guided vs. nonguided group (0% vs. 5.3%; p = 0.03)
CREATIVE trial (58) (Tang et al.) (2018)	1,078 (PCI)	Single-center RCT comparing 3 study groups including high-dose clopidogrel and cilostazol (TEG)	Adjunctive use of cilostazol in clopidogrel HPR patients significantly improved the clinical outcomes without increasing the risk for major bleeding (8.5% vs. 14.4%; p < 0.05)

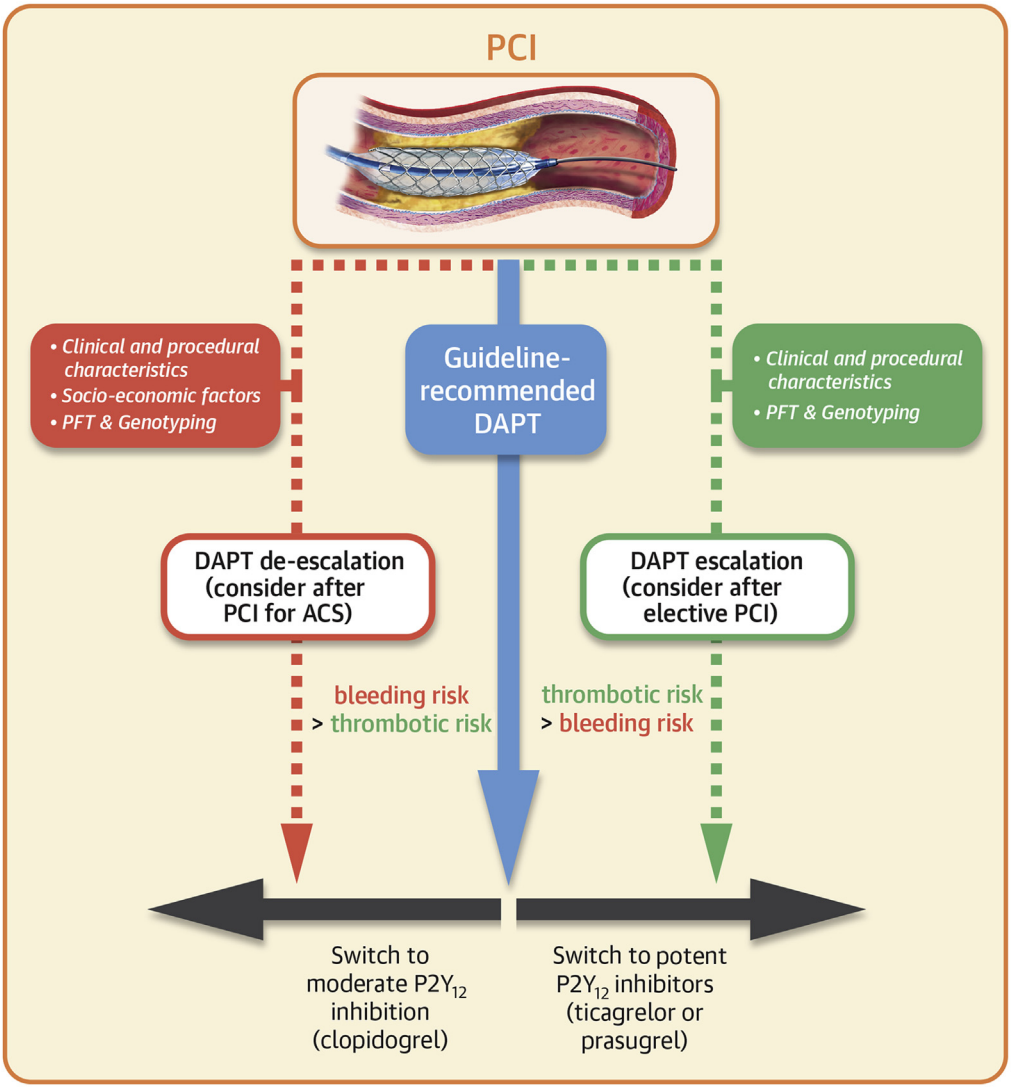
CV = cardiovascular; LTA = light transmission aggregometry; MI = myocardial infarction; RCT = randomized controlled trial; ST = stent thrombosis; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

for risk prediction or guidance. The optimal timing of testing with relationship to the PCI procedure remains a topic of debate. As for other biomarkers in cardiovascular medicine such as troponins and pro-brain natriuretic peptide, a single test is a representative snapshot of the status quo for the time point when it is determined. Testing results depend on a number of extrinsic and intrinsic variables and may change over time as influencing variables are subject to change over time.

Specific considerations may be warranted for East Asian patients, who carry a different risk profile for both ischemia and bleeding events compared with the Caucasian population (36). In this respect, a different genetic profile (higher prevalence for the cytochrome P450 (CYP) 2C19*2 and *3 loss-of-function [LoF] alleles) is associated with a significantly higher rate of HPR. Despite this difference, East Asians do not show an elevated risk for thrombotic complications. In contrast, a lower risk for ischemic events was described, leading to a phenomenon referred to as the "East Asian paradox" (36). Therefore, on the basis of these clinical observations, a right-shifted therapeutic window of on-treatment $P2Y_{12}$-directed platelet reactivity with higher cutoffs for HPR may apply to East Asian patients in contrast to Caucasians (36). It cannot be excluded, however, that this may be partly offset by other compensatory mechanisms, and further studies are needed here.

With respect to specific scenarios, PFT can also be used to test for patient adherence to antiplatelet treatment (37). However, it must be emphasized that the higher the expected prevalence of HPR on a specific antiplatelet drug, the greater the uncertainty with respect to defining (non)adherence. Specifically, when assessing this in clopidogrel-treated patients,

CENTRAL ILLUSTRATION **Dual-Antiplatelet Therapy Strategies After Percutaneous Coronary Intervention**



Sibbing, D. et al. J Am Coll Cardiol Intv. 2019;■(■):■–■.

The majority of percutaneous coronary intervention (PCI)-treated patients should be treated with guideline recommended dual-antiplatelet therapy (DAPT) **(blue arrow)**, which is clopidogrel in stable patients and ticagrelor or prasugrel in patients with ACS (acute coronary syndrome). Alternative strategies may occasionally be considered (see Table 7 for variables that contribute to clinical decision making), including a DAPT escalation strategy **(green arrow)** after elective PCI in stable coronary artery disease and a DAPT deescalation strategy **(red arrow)** after PCI for ACS. Escalation strategies may be reasonable when thrombotic risk outweighs bleeding risk, and deescalation strategies may be reasonable when bleeding risk outweighs thrombotic risk. Decision making is guided by clinical and procedural characteristics as well as socioeconomic considerations. Platelet function testing (PFT) and genotyping may be useful to inform guidance of treatment when DAPT escalation or deescalation is desired.

results must be interpreted with caution, as high levels of platelet reactivity could also be due to the presence of HPR. Thus, poor adherence to clopidogrel cannot be established on a single post-treatment PFT value, and the PFT assessment is only 1 aspect among others during the process of clinical decision making. Consequently, PFT results in clopidogrel-treated patients with witnessed drug intake may be useful to prevent uncertainties in patients with suspected nonadherence.

Although the overall risk for stent thrombosis has significantly declined (18), this event remains life

TABLE 4 Published and Ongoing Studies on Genotyping (CYP2C19) for Guidance of $P2Y_{12}$ Inhibitor Treatment

Study	Patients (Indication)	Study Design	Key Results
Observational studies on genotyping			
Deiman et al. (85) (2016)	73 (elective PCI)	Single-center observational study comparing 2 study groups (guided vs. nonguided treatment)	Risk for CV death, MI, ST, TVR, and stroke significantly lower in guided vs. control group (2.5% vs. 31%; $p = 0.003$)
Sanchez-Ramos et al. (86) (2016)	719 (elective + ACS PCI)	Single-center observational study comparing 2 cohorts (guided vs. nonguided treatment)	Risk for CV death, ACS, and stroke significantly lower in guided vs. control group (10.1% vs. 14.1%; $p = 0.037$)
Cavallari et al. (91) (IGNITE) (2018)	1,815 (elective + ACS PCI)	Multicenter observational study comparing 2 cohorts (intensified treatment vs. clopidogrel in LoF carriers)	Risk for death, MI, and stroke significantly lower in intensified treatment vs. clopidogrel group (8.7 vs. 23.4 per 100 patient-yrs; $p = 0.013$), non-LoF patients on clopidogrel had similar event rate as patients treated with prasugrel/ticagrelor
Randomized studies on genotyping			
Roberts et al. (74) (2012)	200 (elective + ACS PCI)	Single-center RCT with point-of-care genetic screening with subsequent prasugrel administration to CYP2C19*2 carriers	Point-of-care genetic testing after PCI is feasible, and treatment of identified CYP2C19*2 carriers with prasugrel reduced HPR rates
Xie et al. (87) (2013)	600 (elective + ACS PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment)	Risk for death, MI, stroke, and TVR significantly lower in guided vs. control group (2.66% vs. 9.03%; $p < 0.01$)
Shen et al. (88) (2016)	628 (elective + ACS PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment)	Risk for death, MI, and TVR significantly lower in guided vs. control group (4.2% vs. 9.4%; $p = 0.01$)
Notarangelo et al. (92) (2018)	888 (ACS PCI)	Single-center RCT comparing 2 study groups (guided vs. nonguided treatment)	Risk for CV death, MI, stroke, and BARC 3-5 bleeding significantly lower in guided vs. control group (15.9% vs. 25.9%; $p < 0.001$)
ADAPT-PCI (NCT02508116) (2018)	504 (elective + ACS PCI)	Double-center randomized study comparing 2 study groups (guided vs. nonguided group)	Prescription of prasugrel or ticagrelor significantly higher in guided vs. nonguided group (21% vs. 30%; $p = 0.03$)
Ongoing randomized trials on genotyping			
			Primary endpoint
POPular Genetics (78)	2,700 (STEMI PCI)	CYP2C19*2 and *3: ticagrelor or prasugrel vs. wild-type CYP2C19 allele: clopidogrel 75 mg	Composite of CV death, MI, definite ST, stroke, and PLATO major bleeding at 12 mo
TAILOR-PCI (NCT01742117)	5,270 (elective + ACS PCI)	CYP2C19*2 and *3: ticagrelor 90 mg vs. wild-type CYP2C19 allele: clopidogrel 75 mg	Composite of CV death, MI, stroke, ST, and severe recurrent ischemia at 12 mo

CYP = cytochrome P450; LoF, loss-of-function; PLATO = Platelet Inhibition and Patient Outcomes; other abbreviations as in Tables 1 to 3.

threatening, and PFT is a reasonable approach to seek for causative factors, including HPR (9,38). In fact, keeping in mind the aforementioned consideration related to the high variability of clopidogrel response and the fact that platelet reactivity may be increased in the acute setting of an acute coronary syndrome [ACS], PFT can be considered in patients on $P2Y_{12}$ inhibitor treatment who experienced recent stent thrombosis to better understand the mechanism of the event and to track adherence.

Another specific field of interest in which PFT may be useful is in patients with prior PCI on DAPT requiring cardiac or noncardiac surgery (39,40). In fact, in patients in whom DAPT needs to be interrupted, the use of PFT may be considered to guide decisions on timing of cardiac or noncardiac surgery, and its use may have the potential to reduce waiting times for patients who have a faster offset of antiplatelet effects or reduce the risk for surgical bleeding complications among those in whom it is slower (41). This advice is in line with recent guideline recommendations (Class IIb, Level of Evidence: B) (29).

PFT FOR RISK PREDICTION AND TREATMENT GUIDANCE IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

For more than a decade after the first description of clopidogrel's wide response variability in 2003 (4), numerous observational studies have provided data in support of $P2Y_{12}$-directed PFT for cardiovascular risk prediction after elective PCI (10,11,21,38,42). Evidence from these studies has established PFT measurements as a cardiovascular biomarker in patients with coronary artery disease (CAD). A large collaborative meta-analysis (9) in >20,000 patients has provided evidence for the existence of a therapeutic window of $P2Y_{12}$ receptor inhibition by showing

TABLE 5 Consensus Advice for Genotyping in Patients Undergoing Percutaneous Coronary Intervention

General advice on using genotyping in clinical practice • Point-of-care genotyping assays are preferred over laboratory-based assays. • Selection of assay should depend on the local site experience and availability. • Because of in vivo bioactivation properties of the available $P2Y_{12}$ receptor inhibitors, a rationale for genotyping exists for clopidogrel-treated patients but not prasugrel- or ticagrelor-treated patients.
Patients with stable CAD (elective PCI) • CYP2C19 genotyping in patients on clopidogrel treatment may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after elective PCI in stable CAD. • CYP2C19 genotyping to escalate treatment in LoF allele carriers (especially *2 and *3) during clopidogrel treatment is not recommended as a routine but may be considered in specific clinical scenarios (heterozygous and homozygous allele carriage should be taken into account). • CYP2C19 genotyping to screen for LoF alleles to determine the drug that would remain when DAPT deescalation (e.g., triple treatment in which one antiplatelet agent is planned to be omitted) is being considered is not recommended.
Patients with acute coronary syndrome (NSTEMI/STEMI) • CYP2C19 genotyping in patients on clopidogrel may provide useful prognostic data for cardiovascular risk prediction (for both bleeding and ischemic events) after PCI for ACS. • Genotyping to escalate treatment in LoF allele carriers is not recommended, because of lack of data from dedicated studies. • Genotyping to screen for LoF alleles when DAPT deescalation is being considered in an individual patient is not recommended, because of lack of data from dedicated studies.

Abbreviations as in Tables 1 and 4.

highly significant associations of PFT results with both ischemic (HPR) and bleeding (LPR) events.

ESCALATION STRATEGIES. Evidence from randomized trials supporting routine PFT for guidance of treatment with the aim of escalating $P2Y_{12}$ inhibitor treatment (i.e., switch from clopidogrel to ticagrelor or prasugrel) in elective PCI patients who exhibit HPR on clopidogrel is limited. All major trials with the approach of guided DAPT consistently failed to meet their primary endpoints. Tables 2 and 3 provide an overview of important randomized and nonrandomized studies in this field of research. The GRAVITAS (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety) trial (16) (Table 2), being the first major trial in the field of PFT-guided treatment, used high-dose clopidogrel for DAPT escalation but failed to show a benefit of this specific strategy. In retrospect, this is not surprising, as high-dose clopidogrel does not meaningfully reduce levels of platelet reactivity among patients with HPR (43) or in patients predicted to be poor metabolizers on the basis of their genetic background (44). Of note, GRAVITAS enrolled mostly stable, low-risk patients, and prasugrel and ticagrelor were not available during the conduct of the trial. The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial (17) (Table 2), which tested prasugrel for PFT-guided treatment escalation in patients undergoing elective PCI, was stopped prematurely because of futility. With 423 patients enrolled in the study, the numbers of patients and outcome events were too small to draw conclusions. In the sequence of trials, ARCTIC (Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting) (15) (Table 2) also failed to show a benefit of PFT-guided DAPT escalation. However, ways to achieve escalation varied in ARCTIC (e.g., high-dose clopidogrel or use of glycoprotein IIb/IIIa inhibitors), and prasugrel was used in only <10% of patients in the experimental study arm. Despite some promising data from smaller randomized studies (45-51) (Table 3) and a respective meta-analysis (52) as well as nonrandomized PFT data (53,54) in patients with stable CAD, the available evidence is clearly against the routine use of PFT to escalate treatment in patients with HPR on clopidogrel. Nevertheless, this expert group agrees that a very selective and optional use of PFT to guide possible escalation of $P2Y_{12}$-inhibiting therapy is reasonable to consider in specific clinical scenarios in which adequate platelet inhibition is crucial (e.g., left main coronary artery stenting, last patent vessel PCI, complex lesions, 2-stent bifurcation treatment, prior stent thrombosis) in patients not at excessive risk for bleeding.

DEESCALATION STRATEGIES. In patients on DAPT, scenarios may arise in which physicians contemplate stopping one of the antiplatelet drugs (clopidogrel or aspirin). These may include patients developing bleeding complications or when there may be concerns for bleeding (e.g., patients also requiring oral anticoagulant treatment). Data on cutoff values for PFT in a setting of combined antiplatelet treatment and oral anticoagulation are limited, and it may well

be that cutoff values that best determine patients' risk for ischemia or bleeding may differ in this cohort compared with values obtained in patients with antiplatelet treatment and without concomitant oral anticoagulation. Moreover, data in patients in stable condition for using PFT in such a setting and with the aim of screening for drug responsiveness to determine the drug that would remain when the other is stopped are limited. However, this expert group agrees that it may be reasonable to consider the use of PFT in these very specific clinical settings. **Table 1** summarizes the consensus advice for the use of PFT in patients with stable CAD undergoing elective PCI.

PFT FOR RISK PREDICTION AND TREATMENT GUIDANCE IN PATIENTS WITH ACUTE CORONARY SYNDROME

Similar to patients with stable CAD, observational data lend some support to the use of $P2Y_{12}$-directed PFT for cardiovascular risk prediction after PCI for ACS (10,11,21,38,42,55). Current guidelines on PCI-treated patients with ACS strongly recommend that in the absence of contraindications, the use of ticagrelor or prasugrel should be preferred over clopidogrel (32) (**Central Illustration**). However, socioeconomic issues or a presumed high bleeding risk may favor the use of clopidogrel in selected cases. Of note, clopidogrel remains in use in patients with ACS even in the absence of contraindications (56).

ESCALATION STRATEGIES. In specific settings, PFT may be useful to identify especially high-risk patients with HPR on clopidogrel in whom treatment escalation should be strongly considered. Here, PFT may be used as an optional tool among other variables, including patient characteristics that may prompt use of ticagrelor or prasugrel. However, as mentioned earlier, the major randomized trials assessing guided escalation of $P2Y_{12}$-inhibiting therapy (**Table 2**) failed to show any clinical benefit (15,16), whereas only smaller (**Table 3**) randomized (46–48,51,57,58) and nonrandomized (53,54,59) studies provided some evidence in support for a selective use of PFT, as outlined earlier.

Elderly patients with ACS carry a specific risk profile for both ischemic and bleeding complications. The ANTARCTIC (Platelet Function Monitoring to Adjust Antiplatelet Therapy in Elderly Patients Stented for an Acute Coronary Syndrome) trial (**Table 2**) (60) addressed some limitations of prior studies such as ARCTIC (15), TRIGGER-PCI (17), and GRAVITAS (16) and focused on elderly (≥75 years of age) high-risk patients with ACS specifically. The study enrolled 877 patients and compared a reduced dose of prasugrel (5 mg/day, as recommended for elderly patients) with PFT-guided escalation (10 mg prasugrel) or deescalation (75 mg clopidogrel) in the intervention arm. Study results were neutral, with similar ischemic and bleeding rates in both groups. When interpreting the results of ANTARCTIC, it should be noted that superiority of low-dose prasugrel (being the recommended dose in elderly patients) over standard clopidogrel treatment has never been demonstrated, independent of whether PFT was included (61).

DEESCALATION STRATEGIES. Deescalation of $P2Y_{12}$-inhibiting therapy (i.e., from prasugrel or ticagrelor to clopidogrel) in patients with ACS is common clinical practice (24,25). Triggers for deescalation include

TABLE 6 Advantages and Disadvantages of Platelet Function Versus Genetic Testing

	PFT	Genotyping
Availability of different assays	✓	✓
Availability of rapid bedside assay	✓	✓
Absence of interassay variability	X	✓
No variability of results over time	X	✓
Association with ischemic events	✓	✓
Association with bleeding events	✓	✓
Availability of clinical trial data on guided therapy	✓	✓
Feasibility in clinical practice	✓	✓
Results not influenced by extrapatient factors	X	✓
Direct measure of response to therapy	✓	X
Assessment of influence of both genetic and nongenetic factors on platelet function	✓	X
No need to be performed while on treatment	X	✓

A check mark denotes that the method is positively linked to the respective characteristic, and an X denotes a negative link.
PFT = platelet function testing.

TABLE 7 Clinical and Procedural Variables That Contribute to Dual-Antiplatelet Therapy Strategy Decisions After Percutaneous Coronary Intervention

Variables that could be considered for favoring DAPT escalation
Prior stent thrombosis on adequate antiplatelet therapy
Stenting of the last remaining patent coronary artery
Diffuse multivessel disease (especially in patients with diabetes) implanted ≥3 stents
Bifurcation with 2 stents implanted (especially left main coronary artery)
Total stent length >60 mm
Treatment of a chronic total occlusion
Variables that could be considered for favoring DAPT deescalation
Prior major bleeding/prior hemorrhagic stroke
anemia
clinically significant bleeding on dual-antithrombotic therapy

See **Central illustration** for DAPT strategies and decision making after PCI. Table content and variables adapted with permission from European Society of Cardiology 2017 DAPT guidelines (1).
Abbreviations as in **Table 1**.

bleeding (or concerns for bleeding) and nonbleeding side effects as well as socioeconomic factors (24,25). However, it is important to note that there is a potential for increased ischemic risk with a uniform deescalation of $P2Y_{12}$-inhibiting therapy after PCI, particularly if performed too soon after the index event. Indeed, dedicated large-scale trials are urgently needed because the available data on uniform deescalation are conflicting (26,62). However, landmark analysis from large-scale clinical trials is informative toward the decision-making process for deescalation. In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) trial, significant ischemic risk reductions for the primary study endpoint were seen both before and after 30 days, although the reduction was greatest during the first month after PCI. Further on, most excess bleeding events arose during the maintenance treatment phase (27). In the PLATO trial, the ischemic benefits (including a mortality reduction) of ticagrelor versus clopidogrel accrued over time, even beyond 30 days and up to 1 year of follow-up (13). However, similar to prasugrel, the risk for minor and major bleeding increased with the duration of ticagrelor therapy (63). These observations indeed argue against early deescalation but have led to consideration of a strategy of later deescalation of $P2Y_{12}$-inhibiting therapy following the high-thrombotic risk period early after PCI as a strategy to minimize bleeding while preserving efficacy.

To date, no large-scale trial has evaluated the safety and efficacy of a routine and unguided deescalation strategy in (high-risk) patients with ACS. Because clopidogrel is subject to large response variability (4) and because a significant proportion of patients exhibit HPR on clopidogrel (9), PFT may prove useful for guidance of (early) deescalation in patients with ACS in whom such practice is contemplated on clinical or socioeconomic grounds. The recent randomized TROPICAL-ACS (Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes) trial (**Table 2**) met its primary endpoint by demonstrating noninferiority for a net clinical benefit endpoint in patients scheduled for PFT-guided deescalation versus conventional prasugrel treatment (28). The rates of ischemic events (cardiovascular death, myocardial infarction, or stroke) were similar in the guided deescalation study group vs. control group (32 vs. 42 events; hazard ratio: 0.77; 95% confidence interval: 0.48 to 1.21), with a trend toward less bleeding during guided treatment. In a subsequent pre-specified subgroup analysis, treatment effects of guided deescalation depended on patient age, with younger patients deriving a significant net clinical benefit (64). A further pre-specified analysis of the trial provided evidence for considering HPR as a modifiable risk factor (65). In particular, selecting prasugrel or clopidogrel on the basis of PFT guidance resulted in similar ischemic outcomes compared with uniform prasugrel therapy in patients without HPR. Although infrequent, HPR on prasugrel was associated with increased risk for ischemic events, and LPR was a strong and independent predictor of bleeding both on prasugrel and clopidogrel. Reflecting the results of TROPICAL-ACS, recent practice guidelines have updated their recommendations by including a Class IIb (Level of Evidence: B) recommendation on a guided DAPT deescalation strategy, which may be considered as an alternative DAPT strategy, especially for patients with ACS deemed unsuitable for 12-month potent platelet inhibition (29). In line with this guideline update, the consensus advice of this group also supports that this strategy be considered not uniformly but in selected ACS patients (non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction) as an alternative to 12 months of potent platelet inhibition (per the physician's clinical judgment). It must be acknowledged that such a guided deescalation strategy results in clopidogrel treatment in most but not in all patients, as some patients would have to be escalated back to prasugrel. Limitations of the TROPICAL-ACS trial must be acknowledged, and although it was powered for demonstrating noninferiority for a net clinical benefit endpoint, it was not powered for ischemic events alone. Thus, further confirmative large-scale trials would help corroborate the safety of such a concept with respect to ischemic risk for patients with ACS after treatment deescalation. **Table 1** summarizes the consensus advice for the use of PFT in patients after PCI for ACS.

GENERAL ASPECTS OF GENOTYPING AND PCI

Common genetic variants of genes encoding cytochromes responsible for clopidogrel active metabolite generation influence the antiplatelet action of the drug (66). Given the in vivo bioactivation properties and results of pharmacokinetic and pharmacodynamic studies of the potent $P2Y_{12}$ receptor inhibitors (67-69), data supporting genotyping in prasugrel- or ticagrelor-treated patients are lacking. For clopidogrel, the utility of genotyping may be disease specific, as strong and consistent associations have been reported for patients with CAD (both ACS and non-ACS)

undergoing PCI but not for medically managed ACS patients or for patients with atrial fibrillation (5,70–73). Similar to PFT, a number of different assays and methods are available for genotyping of relevant genetic variants. We recommend using validated rapid assays that have been shown to be feasible to use in clinical practice, such as the Spartan RX CYP2C19 System, over laboratory-based assays (e.g., TaqMan) if timely results are needed to guide selection of $P2Y_{12}$ receptor inhibitors (74–76). With respect to targets of genotyping, research has focused on common and functionally relevant polymorphisms within the CYP2C19 gene. Most important is the CYP2C19*2 LoF polymorphism, which results in a loss of CYP2C19 enzyme activity (66). When both CYP2C19 wild-type (*1) alleles are replaced by *2, conversion of clopidogrel to its active metabolite is virtually absent. Second is CYP2C19*17 (a gain-of-function allelic variant), which results in increased enzyme function of CYP2C19 because of a mutation in the 5-flanking promoter region of the gene that confers higher CYP2C19 transcriptional activity (16). Beyond these common single-nucleotide polymorphism, the CYP2C19*3 allele is another LoF polymorphism within the CYP2C19 gene, occurring at a very low frequency (<1%) in Caucasians but with higher frequency (5% to 10%) in the Asian population. Taking the available evidence into consideration, strong and consistent associations were observed for CYP2C19 LoF (*2 and *3) alleles with ischemic events including stent thrombosis, while data on CYP2C19*17 and a possible association with bleeding or ischemic events are conflicting (20,67,77). This is also the reason why ongoing trials using genotyping for guidance of treatment mainly include LoF alleles within the panel of genetic variants that determine treatment (78,79). A summary of additional genetic variants within and beyond the CYP system, most of which have minor influence on clopidogrel metabolism, is beyond the scope of this review and is provided elsewhere (80). Finally, genetic variants are just 1 influential factor affecting clopidogrel activity; numerous epigenetic factors such as gastrointestinal absorption, drug interactions, and adherence are also involved. Thus, the information derived from genotyping cannot be taken as a surrogate for PFT to assess antiplatelet drug response (81).

GENOTYPING IN PATIENTS WITH STABLE CAD

On the basis of the available evidence, CYP2C19 genotypes can be used for outcome prediction in clopidogrel-treated patients after elective PCI (5,20,68,82,83). Although the CYP2C19*2 and *3 alleles are relevant for ischemic risk prediction in this respect (5,68,72,84), presence of the *17 allele was found to be associated with a higher bleeding risk (20). With respect to tailoring treatment by using genotyping results for escalation of $P2Y_{12}$-inhibiting therapy in CYP2C19*2 allele carriers (heterozygous or homozygous), data from larger randomized trials are lacking. As summarized in **Table 4**, some smaller randomized trials and nonrandomized studies have provided some evidence in support for genotyping (85–90). For example, nonrandomized data from the IGNITE network showed a higher risk for ischemic events in patients with a CYP2C19 LoF allele if clopidogrel versus potent $P2Y_{12}$ receptor inhibitors were prescribed (91). In 2010, the U.S. Food and Drug Administration issued a boxed warning that noted reduced effectiveness of clopidogrel in patients who are poor metabolizers of the drug and a statement that tests are available to identify genetic differences in CYP2C19 function. Although randomized evidence is currently lacking, the ongoing large-scale TAILOR-PCI (Tailored Antiplatelet Therapy Following PCI) trial (NCT01742117), with an estimated enrollment of >5,000 patients (stable CAD and ACS patients), aims at escalating treatment on the basis of genotyping results by switching patients with LoF alleles from clopidogrel to ticagrelor. On the basis of available evidence and the Food and Drug Administration boxed warning, the consensus advice is that CYP2C19 genotyping (for LoF alleles) should not be used routinely in patients with stable CAD but may reasonable to consider in specific high-risk clinical scenarios (e.g., left main coronary artery stenting, last patent vessel PCI, complex lesions, 2-stent bifurcation treatment, prior stent thrombosis). Another area of interest for CYP2C19 genotyping is in patients scheduled for PCI who are $P2Y_{12}$ receptor inhibitor naive. Here, genotyping may be used selectively and as an optional tool to help decide whether these patients should be treated with clopidogrel or potent $P2Y_{12}$ receptor inhibitors. This recommendation is not based on randomized data but derives from expert consensus opinion. Genotyping with the aim of screening for LoF alleles for possible $P2Y_{12}$ inhibitor deescalation is not recommended.

GENOTYPING IN PATIENTS WITH ACUTE CORONARY SYNDROMES

Similar to patients with stable CAD, CYP2C19 genotypes (especially LoF alleles) can be used for risk prediction in clopidogrel-treated patients after PCI for ACS. Of note, data for patients with ACS from the

randomized TRITON-TIMI 38 trial showed that there was a significant interaction between CYP2C19 genotype and the benefit of prasugrel versus clopidogrel (which was greater in patients who carried CYP2C19 LoF alleles) (69).

To date, however, there is no evidence from randomized trials of genotyping for guidance (escalation or deescalation) of $P2Y_{12}$ inhibitor treatment in patients with ACS. The recent PHARMCLO trial (92) evaluated whether selecting $P2Y_{12}$ inhibitor treatment on the basis of consideration of genetic and clinical characteristics leads to better outcomes versus standard of care, which is based on clinical parameters only. In that study, the primary study endpoint (net clinical benefit) was improved in the genotyping arm. However, results of this study need to be interpreted with caution, as the study was stopped prematurely and only 25% of the targeted enrollment was achieved (93). Indeed, a dedicated randomized clinical trial is ongoing that focuses on patients with ACS (ST-segment elevation myocardial infarction): the POPular (Patient Outcome After Primary PCI) Genetics trial (NCT01761786) (79) is randomizing 2,700 patients with ST-segment elevation myocardial infarction to a CYP2C19 genotype-guided deescalation strategy in which patients without CYP2C19 LoF alleles are kept on clopidogrel treatment versus conventional therapy. The trial aims to demonstrate noninferiority for a net clinical benefit endpoint. **Table 5** summarizes the expert consensus for the use of genotyping in patients after PCI.

SUMMARY AND PERSPECTIVES

DAPT is the standard of care in patients undergoing PCI. Clopidogrel is the recommended $P2Y_{12}$ inhibitor in stable CAD, while prasugrel and ticagrelor are recommended, in the absence of contraindications, in patients with ACS. Indeed, practitioners should abide, whenever possible, by guideline recommendations (29,32) on the choice of DAPT, as they have the highest level of evidence and are substantiated by the large-scale pivotal trials. However, for individual patients, multiple factors, including thrombotic and bleeding risk as well as socioeconomic considerations, may play a role in the choice of $P2Y_{12}$ inhibitor therapy (24,25) (**Central Illustration**). In these selective scenarios, the use of PFT and genetic testing has been proposed as optional tools to aid clinical decision making on the choice of $P2Y_{12}$-inhibiting therapy. It is important to note that although results of proof-of-concept studies may make a guided approach on drug selection attractive, the robustness of the evidence, particularly when considering adequately powered randomized trials, still does not allow recommending the use of PFT or genetic testing routinely in clinical practice. Nevertheless, in selected cases, escalation strategies may be desired when thrombotic risk outweighs bleeding risk, and deescalation strategies may be desired when bleeding risk outweighs thrombotic risk. In this context, PFT and genetic testing may be considered as optional tools for guidance of treatment when DAPT escalation or deescalation is required. Each of these guided approaches has advantages and disadvantages (**Table 6**), and certain variables may favor escalation or deescalation of treatment (**Table 7**). Indeed, the results of these tests should never be used alone but must be integrated with numerous other clinical, angiographic, procedural, and socioeconomic variables, which together should guide optimal DAPT decisions. Ultimately, it needs to be acknowledged that different health care systems across the globe may have an impact on the uptake and adherence to different $P2Y_{12}$ inhibitors as well as reimbursement for PFT or genetic testing (94). The experience accumulated over the past decade on studies of PFT and genetic testing to guide the choice of antiplatelet therapy has enabled fine-tuning of the design of ongoing clinical trials (95). Past and ongoing trials in this field are mainly investigator-initiated strategy trials (phase IV), which by definition differ in many ways from the pivotal phase III drug trials (96). Indeed, the results of these ongoing strategy trials that should focus on various areas of clinical use (DAPT escalation, DAPT deescalation, timing of surgery) will further refine the field of personalizing $P2Y_{12}$ receptor inhibitor treatment in patients undergoing PCI.

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