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RECOMMENDATIONS AND GUIDELINES

Laboratory monitoring of $P2Y_{12}$ inhibitors: communication from the SSC of the ISTH

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Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ platelet adenosine diphosphate (ADP) receptor antagonist reduces ischemic events in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) but also increases bleeding [1–3]. Residual high on-treatment platelet reactivity (HPR) and low on-treatment platelet reactivity (LPR) in response to $P2Y_{12}$ receptor stimulation, as measured by different platelet function testing (PFT) methodologies, are associated with increased risk of ischemic and bleeding outcomes, respectively (see [4,5] and the references contained therein for descriptions of PFT assays and definitions of HPR and LPR), suggesting that altering antiplatelet therapy based on PFT would reduce adverse events. Small randomized and non-randomized studies demonstrated a reduction in ischemic events when $P2Y_{12}$ inhibitor therapy was modified if PFT indicated HPR (guided therapy) [6,7]. However, larger randomized controlled trials, using different PFT methods and different therapeutic strategies, demonstrated no improved outcome with vs. without guided therapy [8–11]. PFT has also been proposed as a means to determine when platelet function has recovered sufficiently to enable surgery with minimum risk of bleeding following $P2Y_{12}$ inhibitor withdrawal [12] and more recently to guide de-escalation therapy in ACS patients treated with PCI [13]. Goals of this position statement are to provide expert opinion on the utility of laboratory monitoring of $P2Y_{12}$ inhibitors to reduce ischemic and bleeding events in patients on DAPT and to guide timing of surgery if needed in $P2Y_{12}$ inhibitor-treated patients.

Clopidogrel is a second-generation (after ticlopidine) thienopyridine oral antiplatelet drug that inhibits ADP-induced platelet aggregation and decreases major adverse cardiovascular events (MACE) when combined with aspirin, compared to aspirin alone [1]. Clopidogrel requires conversion by cytochrome P450 (CYP) enzymes to an active metabolite (CAM), which irreversibly inhibits platelet $P2Y_{12}$ [14].

CYP gene variants influence production of CAM and the pharmacodynamic response to the drug [15]. Loss of function alleles leading to reduced generation of CAM (e.g. CYP2C19*2) have been associated with poor clinical outcomes [16,17], leading the Food and Drug Administration to issue a boxed warning advising that clopidogrel's effectiveness may be diminished in CYP2C19*2 carriers. Although CYP2C19 variants account for more than 10% of the variability in response to clopidogrel, other factors may contribute to most of the variation, including non-adherence, under-dosing, poor absorption, co-medications (atorvastatin, proton pump inhibitors and calcium antagonists), accelerated platelet turnover, inflammation and underlying platelet hyperreactivity. Thus, demonstration of HPR, the net effect of all of these factors, potentially offers a better predictive marker than these individual factors in clopidogrel-treated patients [18].

Newer $P2Y_{12}$ inhibitors (e.g. prasugrel and ticagrelor) produce greater inhibition of ADP-dependent platelet function and decrease MACE to a greater extent than

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clopidogrel [2,3]. Prasugrel, a third-generation thienopyridine compound, is, like clopidogrel, a prodrug. However, prasugrel's metabolism to active drug is independent of CYP2C19 and the possibility of mutations in this metabolic pathway that could influence platelet inhibition have been previously addressed [19]. In contrast to clopidogrel and prasugrel, ticagrelor, a direct $P2Y_{12}$ antagonist, is inherently active and thus is unaffected by CYP polymorphisms [20]. Clopidogrel-treated patients with HPR show significantly greater inhibition when switched to prasugrel or ticagrelor [21,22]. Nevertheless, even with these antiplatelet agents on-treatment platelet reactivity is variable, albeit less than with clopidogrel [21,22], thus their clinical benefit may be reduced in patients with HPR [5]. Moreover, unfortunately a significant fraction of the studies on the clinical efficacy of PFT-guided antiplatelet therapy have been performed by increasing clopidogrel dose and not by switching to prasugrel or ticagrelor [6–8,10]. Thus, there is a need for such studies to be undertaken. Arguments against $P2Y_{12}$ monitoring include cost, variability in individual on-treatment platelet responsiveness profile, the availability of $P2Y_{12}$ inhibitors with reduced variability, and the potential use of risk scores [23] to stratify patients.

$P2Y_{12}$ monitoring can be potentially useful in three situations: (i) to assess risk of thrombosis or bleeding in patients treated with $P2Y_{12}$ inhibitors, (ii) to guide antiplatelet therapy, and (iii) to determine the optimum timing of surgery following $P2Y_{12}$ inhibitor discontinuation.

There is general consensus that HPR has a negative prognostic value for MACE in $P2Y_{12}$ inhibitor-treated patients [5] and, although less certain, a predictive value for bleeding [4,5].

Before 2018, several large randomized clinical trials failed to demonstrate improved clinical outcomes with PFT-guided antiplatelet therapy [8–11]. However, the recent CREATIVE trial [24], another large randomized study, showed that intensification of antiplatelet therapy (addition of cilostazol) in clopidogrel plus aspirin-treated PCI patients with HPR, as measured by thromboelastography, significantly improved clinical outcomes (hazard ratio, 0.55; 95% CI, 0.35–0.87) without increasing bleeding. Thus, given these conflicting results, until this recent finding is replicated, consistent with previous guidelines [25], we believe that this strategy cannot be recommended at this time (Table 1). Given that the newer $P2Y_{12}$ inhibitors provide greater platelet inhibition and reduce ischemic outcomes compared with clopidogrel, using these agents in patients at high risk of ischemic events without $P2Y_{12}$ monitoring is reasonable and potentially more cost-effective than repeated testing. However, improved efficacy is associated with enhanced

Table 1 Position statement of the Platelet Physiology Scientific and Standardization Committee on the laboratory monitoring of P2Y12 inhibitors

Topic and Recommendation	Class†	Level‡	References
P2Y12 inhibitor monitoring to assess risk of bleeding or thrombosis during prolonged DAPT			
HPR and LPR determined by P2Y12-monitoring as described in [4,5] are associated with risk of ischemic and hemorrhagic events (respectively) and therefore may be considered in the overall management of patients. Optimal timing and frequency of this monitoring are unclear.	IIa	A	[4,5]
P2Y12 inhibitor monitoring to adjust P2Y12 inhibitor dose or adjust P2Y12 inhibitor selection			
Monitoring P2Y12 inhibition for the purpose of guiding the intensity of antiplatelet therapy is not recommended.	IIb	B	[8–10,24]
Monitoring P2Y12 inhibition for the purpose of guiding the duration of DAPT is not recommended.	IIb	B	[8–10,24]
P2Y12 inhibitor monitoring for early de-escalation from prasugrel to clopidogrel in patients considered not suitable for prolonged prasugrel therapy			
Monitoring $P2Y_{12}$ inhibition may be considered for early de-escalation from prasugrel to clopidogrel in patients considered not suitable for prolonged prasugrel therapy.	IIb	B	[13]
P2Y12 inhibitor monitoring to shorten the time window to surgery following P2Y12 inhibitor discontinuation			
It is reasonable, in balancing the risk of thrombosis during a delay to surgery with the risk of surgical bleeding, to consider the results of P2Y12 inhibitor monitoring to determine the timing of surgery • A cut-off of TEG MAADP > 50 is recommended if this test is available • A cut-off of PFA-100_P2Y CT <106 s is recommended if this test is available	IIa	B	[33,34]
• For other P2Y12 inhibitor monitoring tests, cut-offs with respect to CABG bleeding have not been established. However, it may be reasonable to consider proceeding to surgery if platelet reactivity is >80% that seen in P2Y12 inhibitor-free patients	IIb	C	[33,34]

CABG, coronary artery bypass graft; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; HPR, high on-treatment platelet reactivity; LPR, low on-treatment platelet reactivity; PFA, platelet function analyzer; TEG, thromboelastograph. †Class of recommendation: IIa, weight of evidence/opinion is in favor of usefulness/efficacy; IIb, usefulness/efficacy is less well established by evidence/opinion; III, evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. ‡Level of evidence: A, data derived from multiple randomized clinical trials or meta-analyses; B, data derived from a single randomized clinical trial or large non-randomized studies; C, consensus of opinion of the experts and/or small studies, retrospective studies and registries.

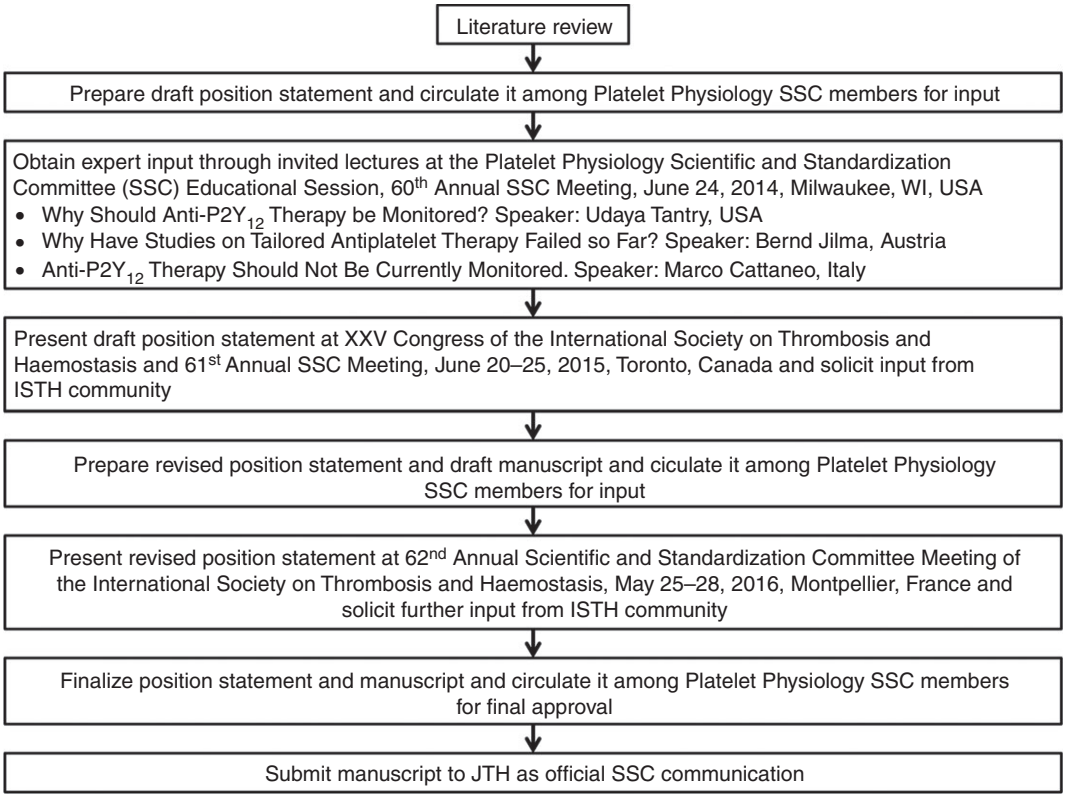

Fig. 1. Process for obtaining expert consensus recommendations on the laboratory monitoring of P2Y$_{12}$ inhibitors.

bleeding and limitations exist to the use of prasugrel [2,3]; moreover, HPR is still observed and is associated with increased risk of ischemic outcomes [5]. Recently, monitoring prasugrel-treated elderly patients undergoing PCI for ACS was not found to be superior to conventional treatment with respect to both ischemic and bleeding outcomes [11].

Several explanations have been put forth for the failure of large randomized controlled trials to demonstrate improved clinical outcomes with PFT-guided antiplatelet therapy. HPR might be a non-modifiable risk factor and/or PFT may not affect prognostic factors, such as adherence to treatment, procedure-related technical factors or coexisting conditions influencing platelet reactivity [10]. Nevertheless, given that platelets contribute to arterial thrombosis, greater inhibition of platelet function is predicted to result in reduction of MACE. Thus, it has been alternatively proposed [26] that some previous studies may have been flawed with respect to one or more of the following: (i) study design (e.g. sample size or definition of clinical endpoints), (ii) patient selection (low vs. high risk), (iii) PFT issues (poor predictive value, incorrect cut-off or improper timing), and (iv) inability of alternative therapy to overcome HPR. The CREATIVE trial may be an example of an appropriate combination of PFT and choice of intensified antiplatelet therapy leading to improved outcomes [24]. Whether optimizing additional parameters would result in improved clinical outcomes with P2Y$_{12}$ monitoring is unknown, but the results of the CREATIVE trial, registry studies [27] and model-based analyses [28] suggest this approach deserves additional testing.

Whether P2Y$_{12}$ monitoring can be of assistance in deciding on DAPT duration has not been assessed. The treatment algorithm for duration of P2Y$_{12}$ inhibitor therapy suggests that in acute coronary syndromes without ST-segment elevation or non-ST-segment elevation myocardial infarction patients treated with medical therapy or PCI, P2Y$_{12}$ inhibitor should be maintained for up to 12 months, and thereafter it may be reasonable to continue it if the risk of bleeding is not high [29]. Likewise, in patients with stable ischemic heart disease treated with stenting it is reasonable to continue P2Y$_{12}$ inhibitor beyond 1 or 6 months (for bare metal stent or drug-eluting stent, respectively) if the risk of bleeding is not high. Long duration of ticagrelor 60 or 90 mg twice daily significantly reduced ischemic outcomes [30] and virtually eliminated HPR [31]. However, major bleeding was also increased in these patients, highlighting the need to consider the balance between increased risk of non-fatal bleeding associated with LPR and the reduced risk of fatal and non-fatal ischemic events. Although studies have shown a connection between risk of bleeding and LPR [4,5], prospective evaluation in clinical trials is required to establish whether PFT may guide duration of DAPT. Most recently, a large randomized trial has shown that a

strategy of early PFT-guided de-escalation to clopidogrel is non-inferior to standard treatment with prasugrel in patients with ACS managed with PCI [13], suggesting that PFT may be useful in patients not suitable for prolonged therapy with potent $P2Y_{12}$ inhibitors.

Worldwide over three million patients undergo PCI each year, > 90% with stenting, and it is estimated that ≥ 5% will need non-cardiac surgery within the first year. Current guidelines state that in patients who require non-emergency major non-cardiac surgery, postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, should be considered unless the patient is at high risk of ischemic events [32]. Nevertheless, shortening the delay before surgery is often highly desirable. PFT demonstrated variation between individuals in the time required to recover platelet function following $P2Y_{12}$ inhibitor discontinuation, and prospective studies showed that a strategy based on preoperative PFT reduced postoperative bleeding and blood consumption and/or shortened waiting time [33,34]. These results suggest it may be reasonable to decide on surgical timing based on PFT.

Conclusions and recommendations

Recommendations were based on a multistep consensus process (Fig. 1).

PFT cannot at present be recommended to guide $P2Y_{12}$ inhibitor choice or select patients most likely to benefit from prolonged antiplatelet treatment but may be considered in deciding an early de-escalation from prasugrel to clopidogrel in patients considered not suitable for prolonged prasugrel therapy (Table 1).

It is reasonable, in patients requiring surgery, to consider the results of $P2Y_{12}$ inhibitor monitoring to determine the timing of surgery (Table 1). New, larger, prospective studies are, however, warranted to confirm PFT usefulness.

Although present evidence does not support PFT-guided antiplatelet therapy, limitations of the studies performed, differences in cost between generic clopidogrel and newer $P2Y_{12}$ antagonists, and the enhanced bleeding risk of the latter, continue to motivate clinical research on this subject. Critical issues in future studies include study design (particularly sample size and control groups), choice of high-risk populations, appropriate selection of monitoring test and cut-off, appropriate timing of (and possibly repeated) testing and switching to alternative therapy (i.e. within days rather than weeks of stent placement), and clearly defined clinical efficacy outcomes.

A critical issue remains the most appropriate PFT method: limitations of currently used techniques urge further research on new methods.

Addendum

A. L. Frelinger, C. Gachet, P. Harrison and P. Gresele conceived the project; A. L. Frelinger wrote the manuscript; P. Gresele, C. Gachet, A. D. Mumford, P. Noris, D. Mezzano and P. Harrison provided critical comments and revisions; all authors have approved the final version.

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