

# Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention

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## Preface

Optimizing outcomes after percutaneous coronary intervention (PCI) requires balancing between the risks of thrombotic and bleeding events in individual patients.<sup>1–3</sup> However, finding the optimal balance is not always straightforward since the risks of thrombotic and bleeding complications may differ extremely between individuals. In addition, the individual effects of anticoagulant and antiplatelet drugs are not uniform in patients.<sup>4</sup>

Recent European guidelines<sup>1,3</sup> recommend the use of prasugrel or ticagrelor instead of clopidogrel in all PCI-treated acute coronary syndrome (ACS) patients without contraindication, acknowledging that laboratory assessment of P2Y<sub>12</sub>-receptor inhibition may be considered only in selected cases when clopidogrel is used.<sup>1</sup> However, there is no guidance with respect to the appropriate methodology and the suggested interpretation of results.

The Working Group on Thrombosis of the European Society of Cardiology aimed to review the available evidence and the clinical relevance of platelet function testing in order to reach a consensus regarding the methodology, evaluation, and clinical interpretation of platelet function in patients undergoing PCI.

## Clinical guideline recommendations

Regarding the choice between available P2Y<sub>12</sub>-inhibitors, the 2011 ESC guidelines on non-ST segment elevation acute coronary

syndromes (NSTEMI-ACS)<sup>1</sup> and the 2012 guidelines on ST-segment elevation myocardial infarction<sup>3</sup> recommend prasugrel and ticagrelor for all ACS patients without contraindication, and clopidogrel is only recommended if these agents are not available. Despite the restrictive recommendations for clopidogrel, it still holds a class I indication in ACS due to the large differences in the availability of the new-generation P2Y<sub>12</sub>-inhibitors among European countries. According to the 2011 ACCF/AHA/SCAI guidelines for PCI,<sup>5</sup> a P2Y<sub>12</sub>-inhibitor should be given for ACS patients without preferring novel P2Y<sub>12</sub>-inhibitors over clopidogrel. Similarly, the 2012 ACCF/AHA unstable angina/non-ST-segment elevation myocardial infarction guidelines<sup>6</sup> and the 2013 ACCF/AHA ST-elevation myocardial infarction guidelines<sup>7</sup> do not explicitly endorse one of the P2Y<sub>12</sub>-inhibitors over the other, acknowledging that large-scale, randomized clinical data on the use of prasugrel and ticagrelor are still limited.

The 2011 ESC guidelines on NSTEMI-ACS<sup>1</sup> issued a class IIb indication for platelet function testing stating that it may be considered in selected cases when clopidogrel is used. However, routine use of platelet function testing is not recommended because dose adaptation of clopidogrel according to residual platelet reactivity failed to show any clinical benefit.<sup>8–10</sup> According to the 2011 ACCF/AHA/SCAI guidelines for PCI,<sup>5</sup> platelet function testing may be considered in patients at high risk for poor clinical outcomes after PCI. If results reveal high on-treatment platelet reactivity (HPR), alternative agents, such as prasugrel or ticagrelor, may be considered. (Supplementary material online, Table S1)

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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## Monitoring on-treatment platelet reactivity

There are a wide variety of methods for monitoring platelet reactivity (Supplementary material online, *Table S2*). The global aggregation measure approach (platelet aggregation) is usually less specific to the drug action while analysis of the drug effect with high specificity at subcellular levels [such as vasodilator-stimulated phosphoprotein (VASP) phosphorylation] gives less information regarding the overall state of the activation-aggregation cascade.

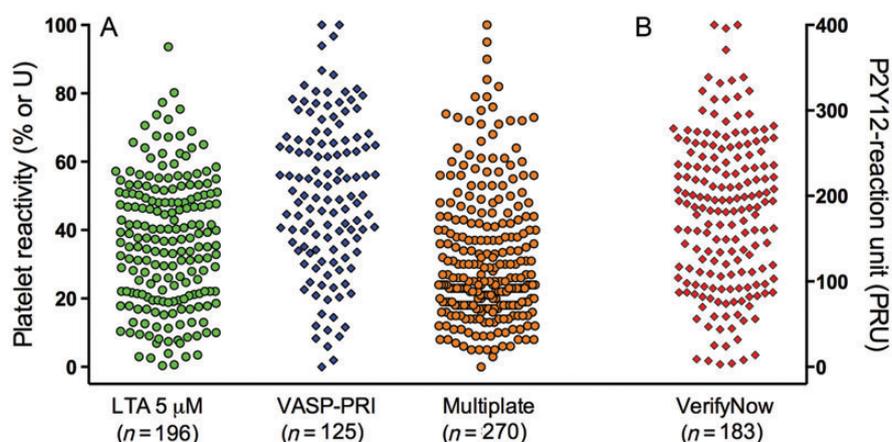
Testing the efficacy of aspirin is methodologically more complicated and less reliable than measuring the effects of P2Y<sub>12</sub>-receptor inhibitors.<sup>11,12</sup> Monitoring the serum levels of thromboxane B<sub>2</sub> (TxB<sub>2</sub>), the stable metabolite of TXA<sub>2</sub> after aspirin administration is complex.<sup>13</sup> As a surrogate, its urinary-excreted stable metabolite (11-dehydrothromboxane B<sub>2</sub>, dTXB<sub>2</sub>) can be determined.<sup>11</sup> However, these compounds can be generated via COX-1-independent, COX-2-dependent pathways, which may reflect the overall inflammatory status rather than platelet inhibition by aspirin 'per se'.<sup>13</sup> Therefore, the antiplatelet efficacy of aspirin is preferentially assessed via the indirect effect of TXA<sub>2</sub>-induced platelet aggregation by adding arachidonic acid to blood samples.<sup>11</sup> Many non-COX-specific agonists (ADP, epinephrine, and collagen) are also used to evaluate 'aspirin response' with a common drawback of overestimation of true aspirin resistance.<sup>12,14</sup> Therefore, most of the available methods are not specific for the effect of aspirin, but also reflect the overall inflammatory and hyper-reactive state of patients.<sup>13</sup>

Residual platelet reactivity during P2Y<sub>12</sub>-inhibitor treatment is evaluated via stimulating platelets with ADP.<sup>15</sup> Results can be assessed at the stage of intracellular signalling pathways (VASP) or at the level of the subsequent aggregation process.<sup>16</sup> Compared with the poor

inter-assay correlation in case of aspirin testing, ADP-stimulated assays have better agreement among themselves.<sup>17,18</sup> However, there are substantial methodological differences between ADP-stimulated assays that explain why this agreement is still far from perfect, resulting in heterogeneity in identification of subjects at risk for thrombotic events<sup>15</sup> (*Figure 1*). According to the available evidence, there are currently four ADP-stimulated assays [VASP, Multiplate, VerifyNow, and light transmission aggregometry (LTA)] that were shown to predict clinical outcomes in large numbers of patients after PCI.<sup>15,19–24</sup> Although the methodology of assessment in three of these tests is fairly standardized, LTA lacks standardization for sample collection, preparation, and processing.<sup>15</sup> Most important advantages and disadvantages of these assays are discussed in detail in the Supplementary material online (platelet function assays: advantages and limitations).

### Consensus summary

Monitoring platelet reactivity during clopidogrel treatment with ADP-stimulated platelet assays is more specific to the drug action and more predictive for thrombotic events than the assessment of aspirin responsiveness.<sup>23</sup> Based on the currently available evidence, the recommended assays for monitoring platelet inhibition during P2Y<sub>12</sub>-inhibitors are the VerifyNow P2Y<sub>12</sub> assay, the Multiplate device with the ADP kit and the VASP assay. Although the optimal thresholds to define a higher risk for thrombotic events may depend on the clinical situation and are still under investigation, available evidence suggests 208 PRU with the VerifyNow,<sup>23,25</sup> 46 U with the Multiplate assay<sup>22</sup> and 50% with the VASP assay.<sup>19,21</sup> (Supplementary material online, *Table S2*) LTA is only recommended when no standardized assays are available. Measurement of response to aspirin therapy is not recommended.



**Figure 1** Inter-individual variability in platelet reactivity after 600 mg clopidogrel loading dose. Inter-individual variation in platelet reactivity values in consecutive stable angina patients tested 6–24 h after a 600 mg clopidogrel loading dose with four different platelet function assays. Notably, each platelet function plot represents a unique stable angina patient population after a 600 mg clopidogrel loading dose. Patients in (A) were recruited for light transmission aggregometry, vasodilator-stimulated phosphoprotein phosphorylation (VASP-PRI) and Multiplate testing in the Heart Institute, University of Pécs, Hungary, while those in (B) represent a similar patient population enrolled in Institut de Cardiologie, Pitié-Salpêtrière Hospital, Paris, France. LTA, light transmission aggregometry; VASP-PRI, vasodilator-stimulated phosphoprotein phosphorylation index.

## Prognostic value of platelet reactivity testing

### High on-treatment platelet reactivity to ADP and thrombotic events

Numerous prospective, observational studies, including large patient populations, demonstrated that HPR to ADP is an independent and strong predictor of post-PCI ischaemic events.<sup>22–24,26–31</sup> High on-treatment platelet reactivity has been associated with a significant increase in non-fatal myocardial infarction, definite/probable stent thrombosis, or cardiovascular mortality by four independent meta-analyses.<sup>32–35</sup> The prospective, multicentre, large-scale ADAPT-DES registry involving 8583 patients demonstrated that HPR identified with the VerifyNow assay was an independent predictor of both early (HR: 3.00, 95% CI:1.39–6.49,  $P = 0.005$ ) and 1-year ST (HR: 2.49, 95% CI:1.43–4.31,  $P = 0.001$ ).<sup>23</sup> Notably, the hazard associated with HPR was greater in patients with ACS than in patients undergoing PCI for stable angina.<sup>36</sup> High on-treatment platelet reactivity to ADP explained almost 60% of the early ST events.<sup>23</sup> Owing to the very low incidence of ST observed with new-generation drug-eluting stents, the positive predictive value of HPR remains low (<10%), with a large proportion of patients who tolerate HPR without any adverse events.<sup>15,23</sup> However, HPR should not be viewed as a diagnostic marker for ST (such as troponin for myocardial infarction) but rather as a risk factor for the patient (such as diabetes or high cholesterol for myocardial infarction).<sup>37</sup> Therefore, diagnostic tests (such as ROC curve analysis, positive, and negative predictive value) are not appropriate to judge the utility of platelet function estimates; instead, the associated relative risk (hazard or odds ratio) should be used to determine the clinical usefulness of platelet function testing.<sup>37</sup>

It is also important to know that platelet reactivity values during clopidogrel treatment are not only a measure of drug response, but rather a global integrator of response to P2Y<sub>12</sub>-inhibitors and co-existing patient comorbidities that highly interfere with platelet activation (such as advanced age, diabetes, renal insufficiency).<sup>24,38,39</sup>

### Aspirin responsiveness and thrombotic events

In contrast to the independent predictive value of HPR to ADP for thrombotic events, clinical relevance of platelet function testing reflecting the response to aspirin remains unclear. Although the 'aspirin resistant' phenotype was associated with higher risk of ischaemic events in a few studies,<sup>40</sup> it is important to note that most of these results were gained from patients treated with aspirin monotherapy, not double anti-platelet therapy (DAPT). Moreover, many of these studies included non-specific platelet assays to determine 'aspirin resistance' that rather reflect the overall 'hyper-reactive platelet phenotype' than the specific effects of aspirin.<sup>13,14,41</sup> The ADAPT-DES registry found no difference in response to aspirin between patients with and without stent thrombosis.<sup>23</sup> Similar to this, another large study found that high platelet reactivity to arachidonic acid is not associated with adverse clinical events.<sup>42</sup> Therefore, current evidence does not support the prognostic utility of screening for aspirin response in patients after PCI.

## Value of platelet reactivity in patients managed without percutaneous coronary intervention

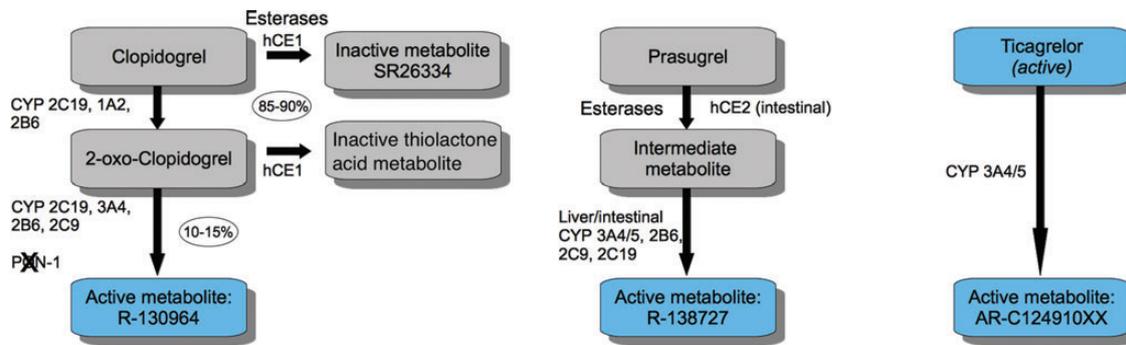
In the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) randomized controlled clinical trial,<sup>43</sup> stabilized ACS patients managed without revascularization were randomized to either prasugrel or clopidogrel treatment.<sup>44</sup> Although prasugrel demonstrated stronger and more consistent P2Y<sub>12</sub>-receptor inhibition with significantly lower rate of HPR compared with clopidogrel, the benefit achieved in platelet inhibition did not translate into a significant clinical improvement.<sup>43,44</sup> According to the platelet function substudy, HPR was a univariate predictor of adverse clinical events, but not an independent predictor of the composite of cardiovascular death, myocardial infarction, or stroke.<sup>44</sup> In addition to this trial, another prospective study investigated the link between platelet function results and clinical outcome in stable outpatients with coronary artery disease.<sup>45</sup> In the Antiplatelet Drug Resistances and Ischemic Events (ADRIE) study, platelet function estimates were not associated with major ischaemic events.<sup>45</sup>

Overall, in contrast to patients undergoing PCI, HPR seems to carry less prognostic information in patients managed without revascularization, decreasing the value of platelet function testing in this subset.

## Role of genotyping to predict thrombotic events after percutaneous coronary intervention

Genetic variability related to the steps of clopidogrel metabolism is responsible for the variable efficiency of generation of the active metabolite of clopidogrel and consequential variable platelet inhibition<sup>15,16,46</sup> (Figure 2). The hepatic two-step oxidative process is of particular importance, as it is dependent on a highly polymorphic family of mono-oxygenases of the cytochrome P450 (CYP) enzymes.<sup>15,16</sup> Pharmacogenomic analyses have identified CYP2C19 as the predominant isoenzyme in catalysing both oxidative steps;<sup>47</sup> however, both loss-of-function (mainly \*2) and gain-of-function (\*17) variant alleles of CYP2C19 are common in the population resulting in variable active metabolite generation.<sup>48–51</sup> Carriers of the \*2 allele have been shown to have lower levels of active metabolite, less potent platelet inhibition and an elevated risk for thrombotic events in patients after PCI.<sup>47,52,53</sup> The genotype, however, accounts for only ~2–12%<sup>38,50,54</sup> of the inter-individual variability of response to clopidogrel and is only one of the many cellular and clinical factors involved in high platelet reactivity. Despite the large number of factors influencing platelet inhibition with clopidogrel, the rapid inactivation after absorption is likely to explain why genetic polymorphisms in hepatic enzymes deeply influence the active metabolite formation and associated platelet inhibition with clopidogrel,<sup>55</sup> but do not have substantial impact on platelet inhibition after prasugrel<sup>56</sup> or ticagrelor<sup>51</sup> treatment. (Figure 2).

Rapid and accurate point-of-care genetic tests have become available recently, and selecting P2Y<sub>12</sub>-inhibitor based on genotype was shown to reduce the prevalence of HPR.<sup>57</sup> However, clinical data



**Figure 2** Comparison between the metabolic transformations of clopidogrel, prasugrel and ticagrelor. Grey panels show inactive substances, while cyan panels show active molecules capable of inhibiting P2Y<sub>12</sub>-receptor. CYP, cytochrome P450 enzyme system; hCE, human cholinesterase; PON-1, paraoxonase-1 enzyme (despite prior suggestion, it does not play a role in the activation process of clopidogrel).

are still lacking whether treatment modification based on rapid genotyping is able to improve clinical outcomes.

### Consensus summary

High on-treatment platelet reactivity to ADP is a strong and independent predictor of adverse thrombotic events, especially early stent thrombosis in patients on clopidogrel after PCI.<sup>23,32–34</sup> The association is stronger in patients with ACS, while less established in patients with stable angina.<sup>36</sup> Although the genotype accounts for only a small portion of the inter-patient variability with clopidogrel, patients harbouring CYP2C19 LOF alleles are at higher risk for stent thrombosis.<sup>52,53</sup>

Inter-individual differences in response to aspirin are not associated with stent thrombosis in patients treated with DAPT following PCI;<sup>23,42</sup> therefore, testing the response to aspirin cannot be recommended.

In patients managed without revascularization, HPR is not an independent predictor of recurrent ischaemic events; therefore, platelet function testing to change antiplatelet strategy is not recommended in this subset.<sup>44</sup>

## Treatment intensification in patients with high on-treatment platelet reactivity

It is still debated whether HPR is a marker of higher risk or a modifiable risk factor that can be used to tailor treatment in patients after PCI.<sup>8,10,27,58</sup> Theoretically, there are several options to intensify platelet inhibition in patients with HPR: increasing the dose of aspirin or clopidogrel, switching from clopidogrel to a new-generation of P2Y<sub>12</sub>-receptor inhibitor or adding a third antiplatelet agent on top of standard therapy (Supplementary material online, Table S3).

### Dose increase in case of aspirin

Although there is no dedicated RCT that has evaluated the clinical relevance of increased dose of aspirin based on platelet reactivity testing, findings from a large RCT comparing low-dose and high-dose aspirin in patients with ACS without platelet function testing suggest

no benefit for using high doses (> 100 mg) of aspirin.<sup>59,60</sup> The Randomized Trial of Optimal Clopidogrel and Aspirin Dosing in Patients with ACS Undergoing an Early Invasive Strategy with Intent For PCI (CURRENT OASIS-7 trial) compared low-dose (75–100 mg) and high-dose (300–325 mg) aspirin in 25 087 patients with ACS and found no difference in the 30-day risk of cardiovascular death, myocardial infarction, or stroke in both the overall ACS population<sup>59</sup> (HR: 0.96, 95% CI: 0.85–1.08,  $P = 0.47$ ) and in the subgroup of patients who underwent PCI<sup>60</sup> (HR: 0.98, 95% CI: 0.84–1.13,  $P = 0.76$ ). There was a higher rate of gastrointestinal bleeding in the high-dose aspirin group (0.24 vs. 0.38%,  $P = 0.051$ ).<sup>59</sup> Similarly, higher risk of bleeding with high-dose aspirin was observed in the *post hoc* analysis of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial.<sup>61</sup> *Post hoc* analysis of the PLATElet inhibition and patient Outcomes (PLATO) trial, prompted by regional differences between North America and other countries in the primary endpoint of the trial, suggested a possible interaction between ticagrelor and high-dose aspirin.<sup>62,63</sup> After extensive statistical modelling, investigators suggested that the use of high-dose aspirin might explain the trend for an increased risk of cardiovascular death, myocardial infarction, or stroke in patients randomized to ticagrelor, whereas others treated with low-dose aspirin and ticagrelor had a significant benefit over clopidogrel.<sup>62,63</sup> However, since this interaction lacks—so far—any biological explanation and comes from a *post hoc*, non-pre-specified analysis, it should be interpreted cautiously.

### Consensus summary

Although some markers of platelet activation reflecting response to aspirin might be influenced by a dose escalation, measuring aspirin responsiveness is not recommended since these platelet activation markers are not associated with thrombotic events after PCI.<sup>23,42</sup> In general, high-dose (> 100 mg) aspirin treatment does not improve clinical efficacy, but might expose patients to higher risk of (gastrointestinal) bleeding.<sup>59,61</sup> Therefore, a low maintenance dose ( $\leq 100$  mg) of aspirin is recommended with P2Y<sub>12</sub>-inhibitors and dose increase is discouraged, even when based on platelet function results.

## Dose adjustment of clopidogrel

Many pharmacodynamic studies have shown that increasing the loading or maintenance dose of clopidogrel significantly enhances platelet inhibition;<sup>64,65</sup> however, this impact is rather modest and highly dependent on the patient's genotype.<sup>65</sup> The first large-scale, randomized study to investigate the clinical impact of giving high-dose (additional 600 mg loading dose and 150 mg maintenance dose) vs. standard-dose clopidogrel for patients with HPR identified by the VerifyNow P2Y<sub>12</sub> assay was the Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety (GRAVITAS) trial.<sup>8</sup> In the study, 41% of the 5479 patients were found to have HPR 12–24 h after PCI for stable angina or due to NSTEMI-ACS. No ST-elevation patients were enrolled, and only 10% of patients had AMI on recruitment.<sup>8</sup> The primary endpoint of cardiovascular death, myocardial infarction, or stent thrombosis at 6 months was identical between high-dose and standard-dose groups (HR: 1.01, 95% CI: 0.58–1.76, *P* = 0.98). GUSTO moderate/severe bleeding events were also not significantly different; even numerically lower in the 150-mg group.<sup>8</sup> A time-dependent *post hoc* analysis of the trial suggested that patients having PRU values <208 at 30 days or 6 months had a significant clinical benefit in the primary endpoint,<sup>25</sup> suggesting that the modest and variable effect of high-dose clopidogrel might be one reason for the negative findings, and the achieved level of platelet reactivity might be clinically important when high-dose clopidogrel is given.

The Responsiveness to Clopidogrel and Stent Thrombosis 2—ACS (RE-CLOSE-2 ACS) single-centre observational registry evaluated the clinical impact of increasing the dose of clopidogrel or switching to ticlopidine in 1789 ACS patients with HPR after PCI.<sup>27</sup> According to the results, patients with HPR persisted at significantly higher risk for adverse ischaemic events despite the treatment adjustment with high-dose clopidogrel or ticlopidine, when compared with patients without HPR, including a higher risk for mortality.<sup>27</sup>

More recently, the Assessment by a Double Randomization of a Conventional Antiplatelet Strategy vs. a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption vs. Continuation One Year after Stenting (ARCTIC) multicentre, randomized study sought to determine whether a strategy based on VerifyNow testing to tailor antiplatelet therapy is superior to standard care in 2440 patients with stable angina or NSTEMI-ACS undergoing PCI.<sup>10</sup> In contrast to the GRAVITAS trial,<sup>8</sup> this study randomized the use of platelet function testing with treatment intervention (monitoring arm) vs. standard of care according to clinician's preference without platelet function test (conventional arm). In the monitoring arm, serial platelet function tests (before stent implantation and during the maintenance phase) and treatment adjustments using a predefined treatment algorithm [including high-dose clopidogrel, high-dose aspirin, and glycoprotein IIb/IIIa inhibitors (GPI)] were performed. Since prasugrel became available late after study initiation, it was rarely used in the study in both arms. In addition to treatment intensification, patients were also switched back from prasugrel to clopidogrel after PCI if low on-treatment platelet reactivity (LPR) was observed on testing. The primary endpoint of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization was similar after 1 year between treatment arms (HR: 1.13, 95% CI: 0.98–1.29, *P* = 0.10).<sup>10</sup> Interestingly, there was a trend for more

stent thrombosis but less major bleeding in the monitoring arm, a finding that needs further investigation and clarification.<sup>10</sup>

A meta-analysis is also available to compare standard-dose clopidogrel with intensified antiplatelet therapy in patients with HPR.<sup>58</sup> Although the analysis included many small-sized studies and treatment intensification was highly heterogeneous in the included cohorts (repeated loading doses of clopidogrel, 150 mg maintenance dose of clopidogrel, GPI) or prasugrel], the pooled results showed a significantly reduced risk in definite/probable ST and in cardiovascular mortality without a significant increase in bleeding complications favouring intensified antiplatelet therapy in patients with HPR.<sup>58</sup> Notably, the meta-regression analysis showed a significant association between the risk of stent thrombosis and the net clinical benefit achieved after intensified antiplatelet therapy, supporting the concept that not only the platelet function results, but also the patients' baseline clinical and procedural risk for stent thrombosis must be taken into account when the optimal antiplatelet strategy is selected: patients at high risk for stent thrombosis might profit more from treatment intensification than others at low risk for stent thrombosis.<sup>58</sup>

## Switch to potent P2Y<sub>12</sub>-inhibitor in patients with high on-treatment platelet reactivity

The only randomized trial that aimed to investigate the clinical impact of giving a new-generation P2Y<sub>12</sub>-inhibitor for patients with HPR was prematurely terminated due to futility.<sup>9</sup> In the Testing platelet Reactivity In patients underGoing elective stent placement on clopidogrel to Guide alternative thErapy with pRasugrel (TRIGGER-PCI) study, stable angina patients with HPR (>208 PRU) screened by the VerifyNow P2Y<sub>12</sub> assay after uncomplicated, successful PCI with DES implantation were randomized to receive standard-dose clopidogrel or 10 mg of prasugrel.<sup>9</sup> Although the primary hypothesis was to achieve a significant reduction in cardiovascular death and myocardial infarction with prasugrel during 6 months, an interim analysis performed after 236 patients completing 6-month follow-up demonstrated that only one primary endpoint event had occurred, corresponding to an incidence of 0.4%. On the contrary, there were three TIMI major bleeding events in the prasugrel arm and one in the clopidogrel group within the total cohort of 423 randomized patients. The unanticipated low rate of ischaemic events led the study steering committee to discontinue the trial for futility.

Just recently, results of a prospective, single-centre registry were presented on the clinical effects of selecting P2Y<sub>12</sub>-inhibitors based on platelet function testing in consecutive, high-risk ACS patients undergoing PCI.<sup>66</sup> Platelet reactivity to ADP was measured with the Multiplate device after 600 mg loading dose of clopidogrel in 563 patients. Among 141 subjects with HPR the choice of prasugrel or high-dose clopidogrel was compared in a non-randomized manner, while others having sufficient platelet inhibition continued low-dose clopidogrel. After 200 days of follow-up, prasugrel was significantly more effective than high-dose clopidogrel in reducing the risk of vascular mortality or definite/probable stent thrombosis in patients with HPR, while good responders on clopidogrel had similarly low risk to thrombotic events as those treated with prasugrel.<sup>66</sup>

## Adding a third antiplatelet agent on top of DAPT in patients with high on-treatment platelet reactivity

Two randomized, controlled clinical trials demonstrated that adding either tirofiban or abciximab to standard DAPT during PCI of elective patients with HPR might reduce the risk of peri-procedural myonecrosis.<sup>67,68</sup> However, the impact of this strategy on hard clinical outcomes, including major bleeding is unclear, as these studies were not powered to these endpoints. Although the ARCTIC study also used GPI-*s* for PCI to intensify antiplatelet therapy in patients with HPR, there was no sign of any benefit in the primary endpoint in the monitored compared with the standard-care arm.<sup>10</sup>

### Consensus summary

In patients with acute coronary syndrome undergoing PCI, prasugrel and ticagrelor should be the preferred choices over clopidogrel unless contraindications exist (Supplementary material online, Table S4).<sup>1,3,63,69,70</sup>

Although clinical data are presently scarce, platelet function testing may be considered in selected clopidogrel-pretreated ACS patients with a history of major spontaneous bleeding event or at low risk for thrombotic events (such as troponin negative patients without high-risk clinical features) to guide the choice between available P2Y<sub>12</sub>-inhibitors.<sup>1</sup> Since the availability of prasugrel and ticagrelor is restricted or limited to certain indications in a significant number of countries, platelet function testing may be considered in these countries to identify patients with HPR, who are at heightened risk for thrombotic complications on clopidogrel and require a potent P2Y<sub>12</sub>-inhibitor (prasugrel or ticagrelor).<sup>23,66</sup> Administration of high-dose clopidogrel in ACS patients with HPR is not recommended.<sup>8,10,27,66</sup>

In stable angina patients after uncomplicated PCI, standard-dose clopidogrel should be preferred and routine platelet function testing is not recommended.<sup>9</sup>

Platelet function testing may be considered if results may change the P2Y<sub>12</sub>-inhibitor strategy due to (i) unexpected definite stent thrombosis despite being adherent to clopidogrel; (ii) markedly elevated risk for stent thrombosis (prior stent thrombosis or complex stenting procedure in high-risk patients), and (iii) last remaining vessel or unprotected left main stem PCI involving the bifurcation. The final decision-making on the preferred P2Y<sub>12</sub>-inhibitor should incorporate both the platelet function result and the bleeding risk of the patient.

In patients with absolute indications for sustained oral anticoagulation after PCI (atrial fibrillation, intraventricular thrombus or prosthetic heart valves), triple therapy consisting of DAPT and an oral anticoagulant (either vitamin K-antagonist or Factor IIa or Xa antagonist) should include standard-dose clopidogrel. Platelet function testing to guide dose modification of clopidogrel or switch to prasugrel/ticagrelor is not recommended in these patients.<sup>71–73</sup>

## Role of platelet function testing in predicting the risk of bleeding events

The risk of bleeding is dependent on the clinical characteristics of the patient and on the combination and dosage of various antiplatelet and

anticoagulant agents used in the specific setting.<sup>2</sup> In addition to the clinical and pharmacological determinants, the large inter-patient variability in response to P2Y<sub>12</sub>-inhibitors is also an important contributor to bleeding events. In a single-centre study including 2533 patients undergoing PCI, the authors found that LPR on clopidogrel were associated with a three-fold higher risk for in-hospital major bleeding events.<sup>74</sup> More recently, the 1-year results of the large-scale, multicentre ADAPT-DES registry showed in >8500 patients that platelet reactivity after PCI is an independent predictor of bleeding events: clopidogrel-treated patients with a PRU less than 208 had a significantly elevated risk for TIMI major non-CABG-related bleeding.<sup>74</sup> Compared with clopidogrel, excessive P2Y<sub>12</sub>-receptor inhibition is even more common with prasugrel and ticagrelor. Two recent studies showed that prasugrel-treated patients with LPR had a higher risk for bleeding events.<sup>75,76</sup> According to a small study, switching these subjects from prasugrel to clopidogrel might reduce the risk of minor bleeding complications; however, a group of patients with HPR is unmasked during clopidogrel treatment with unknown clinical consequences.<sup>77</sup>

Together with the predictive value of HPR in predicting thrombotic complications, the higher risk for bleeding in patients with LPR suggests the relevance of a therapeutic window for P2Y<sub>12</sub>-receptor inhibitors, in that both thrombotic and bleeding complications might be the lowest.<sup>75,78,79</sup> Therefore, the approach of using platelet function assays to titrate the inhibitory effect of P2Y<sub>12</sub>-inhibitors into a therapeutic window is both mechanistically and scientifically appealing, but further randomized studies should validate the benefit of such a strategy (NCT01538446).

### Consensus summary

Although evidence is culminating<sup>74,75,79,80</sup> (Supplementary material online, Table S5), the link between LPR and bleeding events in PCI patients exposed to P2Y<sub>12</sub>-inhibitors is not as clearly established as for HPR and stent thrombosis. In addition, outcome studies are lacking in patients with LPR. Therefore, despite the growing lines of evidence on the relevance of therapeutic window with P2Y<sub>12</sub>-inhibition, reducing the dose of prasugrel/ticagrelor or switching back to clopidogrel based solely on platelet function results cannot be recommended.<sup>1,3</sup>

However, in selected patients who experience a major bleeding event during P2Y<sub>12</sub>-inhibitor treatment and remain at increased risk for recurrent bleeding, platelet function testing might be considered to determine the potency of platelet inhibition and to facilitate the optimal P2Y<sub>12</sub>-inhibitor strategy during/after the bleeding episode.

## Conclusions and future directions

Combined platelet inhibition with double antiplatelet therapy provides the greatest clinical benefit in preventing PCI-related complications.<sup>1,3</sup> DAPT should consist of aspirin and a P2Y<sub>12</sub>-inhibitor.<sup>1,3</sup> Aspirin given at low doses ( $\leq 100$  mg) results in effective suppression of thromboxane generation in the vast majority of patients; higher doses might increase gastrointestinal bleeding complications without decreasing thrombotic events.<sup>59,61</sup> Therefore, aspirin should be given at low doses and platelet function testing to adjust dosing is not recommended (Supplementary material online, Table S4).

On the contrary, there are large differences in the achieved level of platelet inhibition during treatment with clopidogrel<sup>4</sup> and HPR is associated with higher risk for stent thrombosis.<sup>23,32</sup> In routine practice, clinical presentation and patient characteristics should guide the choice between available P2Y<sub>12</sub>-inhibitors during and after PCI: prasugrel or ticagrelor is preferred for ACS while clopidogrel is recommended in PCI for stable angina.<sup>1,3,69</sup> In selected patients who have high suspected clinical and/or procedural risk for adverse outcomes (thrombosis or bleeding) with recommended P2Y<sub>12</sub>-inhibitors, platelet function testing may help the decision-making by providing information on the level of platelet reactivity (Supplementary material online, Table S4).

Clinicians should be aware that platelet function devices measure different aspects of platelet physiology; some are also hampered by poor standardization (LTA) and cumbersome testing process (VASP); therefore, the authors of the present paper recommend the more standardized, user-friendly assays (VerifyNow and Multiplate) to prevent methodical errors during testing and allow easier generalization of test results. This is particularly important with respect to the sharp cutoffs (Supplementary material online, Table S2) recommended to predict thrombotic and bleeding events. However, it needs to be emphasized that platelet function results should only be interpreted in the clinical and angiographic context of each individual: platelet reactivity to ADP might be one important piece of information that can help the decision-making, but cannot be the only criterion on which a clinical decision is based.

The main reason why platelet function testing has a low-level of recommendation (class IIb)<sup>1</sup> and a restrictive indication in current guidelines is the lack of adequately sized, positive, randomized, controlled studies to show an improvement in clinical outcomes by using these assays in patients undergoing PCI. We believe the failure of previous studies<sup>8–10</sup> demonstrated that possible future trials should (i) be large multi-centre studies that are realistically powered for ischaemic endpoints; (ii) include patients at high risk for stent thrombosis (preferably AMI); (iii) use potent P2Y<sub>12</sub>-inhibitors such as prasugrel or ticagrelor instead of high-dose clopidogrel to intensify platelet inhibition; and (iv) test the clinical value of other platelet function assays that were not used in previous studies. Based on current guidelines,<sup>1,3</sup> ACS patients are recommended to be treated with prasugrel or ticagrelor; therefore, a superiority trial among ACS patients with a conventional standard-dose clopidogrel group is unethical and contradicts guidelines. Therefore, future trials comparing platelet function-guided and conventional approach might be designed according to non-inferiority principles for thrombotic events, and if non-inferiority is met, possible benefits in preventing bleeding and cost-effectiveness should be further analysed (similar to trials comparing warfarin and novel oral anticoagulants). The cost-effectiveness perspectives are highly important, because the balance of the drug-related costs, event-related costs, and the cost of platelet testing should be clearly analysed in an era when clopidogrel is widely available in generic forms.

Another important area for future research is the role of platelet function assays to prevent bleeding complications. This is particularly important with novel P2Y<sub>12</sub>-inhibitors in (i) low-risk ACS patients; (ii) in the elderly population (NCT01538446); and (iii) in patients in whom both antiplatelet drugs and chronic oral anticoagulants are indicated.

Just recently, a new class of antiplatelet agents (PAR-1 thrombin receptor inhibitors) has been tested in clinical trials. Although the results of the two trials<sup>81,82</sup> are somewhat controversial regarding the clinical benefits of vorapaxar, future research might also focus on the possible association between PAR-1 inhibition and unwanted clinical events, as thrombin-mediated platelet activation is a key process in arterial thrombus formation.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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