SCIENTIFIC EDITORIAL

Personalized antiplatelet therapy: The wrong approach?

Traitement antiplaquettaire personnalisé : fait-on fausse route ?

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The GRAVITAS (Gauging Responsiveness with A VerifyNow assay—Impact on Thrombosis And Safety) study has demonstrated the detrimental impact of high on-treatment platelet reactivity following stent implantation and the failure of a double clopidogrel maintenance dose to reduce cardiovascular events in patients deemed clopidogrel non-responders (Fig. 1) [1]. However, there was still evidence after the GRAVITAS study to support personalized medicine-based on platelet reactivity. The combination of a low-risk population together with platelet reactivity assessment after percutaneous coronary intervention (PCI) was recognized as a relevant limitation that may have accounted for the negative results of the GRAVITAS study.

The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel) study design was similar to that of the GRAVITAS study, but treatment intervention was more aggressive, using prasugrel instead of an increased clopidogrel maintenance dose (Fig. 1). The study was stopped prematurely due to a low event rate [2].

Platelet reactivity has been consistently reported as an independent predictor of ‘hard’ post-PCI endpoints, including stent thrombosis, myocardial infarction and cardiovascular mortality (Fig. 2) [3,4]. Notably, the hazard associated with high platelet reactivity is greater in patients with an acute coronary syndrome (ACS) than in patients undergoing PCI for stable angina; it accounts for approximately 60% of the definite/probable stent thrombosis events, demonstrating the dominant contribution that inadequate P2Y12 receptor inhibition makes to thrombotic events [5,6]. As a consequence, the bedside platelet function test has become an opportunity to guide antiplatelet therapy, particularly when there is an unexpected complication. This is also the case when new P2Y12 inhibitors are not available, in the absence, however, of a recommendation for this type of use [7,8].

KEYWORDS
Acute coronary syndrome; Antiplatelet therapy; Percutaneous coronary intervention

MOTS CLÉS
Syndrome coronaire aigu ; Traitement antiplaquettaire ; Angioplastie coronaire

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention.

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The ARCTIC (Assessment with a double Randomization of [1] a fixed dose versus a monitoring-guided dose of aspirin and Clopidogrel after drug-eluting stent implantation and [2] Treatment Interruption versus Continuation, 1 year after stenting) multicentre randomized study sought to determine whether a strategy based on systematic platelet function testing to tailor antiplatelet therapy is superior to standard care in 2440 patients with stable angina or non-ST-segment elevation ACS (NSTEMI) undergoing PCI [9]. In contrast to the GRAVITAS trial, this study randomized the use of platelet function testing with treatment intervention (monitoring arm) versus standard of care according to clinician’s preference without platelet function test (conventional arm) (Fig. 3). In the monitoring arm, serial platelet function tests (before stent implantation and during the maintenance phase) and treatment adjustments using a predefined treatment algorithm were performed. In addition to treatment intensification due to high on-treatment platelet reactivity, patients could be switched back from prasugrel to clopidogrel after PCI if low on-treatment platelet reactivity was measured. Despite halving the rate of high platelet reactivity to adenosine diphosphate (Fig. 4), the primary endpoint of death, myocardial infarction, stent thrombosis, stroke or urgent revascularization was similar after 1 year with the two strategies (hazard ratio [HR] 1.13, 95% confidence interval [CI] 0.98–1.29; p = 0.10).

The take-home message is that platelet reactivity is not only a measure of drug response, but also integrates the effect of response to P2Y₁₂ receptor antagonists and comorbidities, such as advanced age, diabetes and renal insufficiency. Platelet reactivity should also be considered as a surrogate marker for studies on antiplatelet treatments that may be helpful to explain the results of trials. This has been confirmed by the prespecified pharmacodynamic TRILOGY-ACS (A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction: Who Are Medically Managed) study, which demonstrated a real effect of treatment intensification but a lack of independent relationship between platelet reactivity and clinical outcome [10]. Such results further support the lack of benefit of intensification of antiplatelet therapy in medically managed patients [11] (Fig. 5).

What is the future of platelet function testing? The level of recommendation for routine platelet function testing in patients who undergo stent placement will remain low in accordance with the negative results of recent randomized studies (Table 1) [1,2,9]. Platelet activity rather appears as a reliable risk stratification approach but not as a modifiable

Figure 1. Design and results of the GRAVITAS and TRIGGER-PCI trials. CI: confidence interval; Clopi: clopidogrel; CV: cardiovascular; FU: follow-up; HR: hazard ratio; MI: myocardial infarction; PCI: percutaneous coronary intervention; PRU: P2Y₁₂ reaction units; ST: stent thrombosis.

Figure 2. Platelet reactivity as a marker of risk in patients who underwent percutaneous coronary intervention. HR: hazard ratio; HPR: high platelet reactivity; HRPR: high residual platelet reactivity; LRP: low residual platelet reactivity; LTA: light transmission aggregometry.

Figure 3. Platelet reactivity: a new way to tailor antiplatelet therapy? Platelet reactivity, measured by PRU, is a predictor of acute coronary syndrome events. The risk of acute coronary syndrome events increases from 0.9 to 1.2 PRUs, according to the number of PRUs (0–0.9 PRUs, 1.0–1.2 PRUs, >1.2 PRUs).

Figure 4. Platelet reactivity during the maintenance phase. The platelet reactivity measured by PRU is significantly lower in the monitoring arm than in the standard arm. The decrease in platelet reactivity is associated with a decrease in the risk of acute coronary syndrome events. The risk of acute coronary syndrome events decreases from 5.9 to 1.2% for platelet reactivity measured by PRU.
risk factor that may help to guide therapy. However, the ARCTIC study has evaluated neither the accuracy of platelet function testing specific to the treatment effect of P2Y12 inhibitors, such as vasodilator-stimulated phosphoprotein (VASP), nor the combination of fast genotyping with platelet function testing in clopidogrel-treated patients. Fast genotyping is now available to identify clopidogrel metabolizer profile and guide P2Y12 inhibition strategy, especially in ACS patients [12, 13], with the possibility of having patients in a prespecified window of platelet inhibition to avoid both bleeding and ischaemic events. In the ARCTIC study, half of the patients were genotyped; whether there is a significant interaction between treatment monitoring and clopidogrel metabolizer profile may generate new research hypotheses.

Low platelet reactivity has been associated with major bleeding, a common complication of the more potent P2Y12 inhibitors and a strong determinant of cardiovascular mortality. In the ARCTIC study, treatment monitoring was associated with a non-significant reduction in major

![Figure 3](image3.png)

**Figure 3.** The ARCTIC trial design. ASA: acetylsalicylic acid (aspirin); FU: follow-up; GP: glycoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; Rd: randomization.

![Figure 4](image4.png)

**Figure 4.** The effect of treatment adjustment in the monitoring arm on the rate of clopidogrel and aspirin non-responders. MD: maintenance dose.

Table 1  Clinical guideline recommendations regarding platelet function testing.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Statement</th>
<th>CoR</th>
<th>LoE</th>
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<tbody>
<tr>
<td>ESC PCI guidelines 2005</td>
<td>The emerging question of possible clopidogrel resistance requires more investigations</td>
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<tr>
<td>ACC/AHA/SCAI PCI guideline 2005</td>
<td>In patients in whom subacute thrombosis may be catastrophic or lethal (unprotected left main, bifurcating left main or last patent coronary vessel), platelet aggregation studies may be considered</td>
<td>Iib</td>
<td>C</td>
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<tr>
<td>ESC guidelines on myocardial revascularization 2010</td>
<td>Monitoring of antiplatelet response by platelet function assays is currently used for clinical research, but not in daily clinical practice</td>
<td>III</td>
<td>C</td>
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<tr>
<td>ESC NSTE-ACS guidelines 2011</td>
<td>Platelet function testing may be considered in selected cases when clopidogrel is used. Several trials currently under way may clarify the impact of adapting therapy on the basis of the results of platelet reactivity assays, but, so far, the routine clinical use of platelet function tests in clopidogrel-treated patients with ACS cannot be recommended</td>
<td>Iib</td>
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<tr>
<td>ACC/AHA/SCAI PCI guidelines 2011</td>
<td>Platelet function testing may be considered in patients at high risk for poor clinical outcomes. In patients treated with clopidogrel with high platelet reactivity, alternative agents, such as prasugrel or ticagrelor, might be considered. The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended</td>
<td>Iib</td>
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<tr>
<td>ACCF/AHA UA/NSTEMI guidelines 2012</td>
<td>Platelet function testing to determine platelet inhibitory response in patients with UA/NSTEMI (or after ACS and PCI) on P2Y₁₂ receptor inhibitor therapy may be considered if results of testing may alter management</td>
<td>Iib</td>
<td>B</td>
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<tr>
<td>ESC STEMI guidelines 2012</td>
<td>No specific recommendation</td>
<td>—</td>
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<tr>
<td>ACCF/AHA STEMI guidelines 2013</td>
<td>The roles of platelet function testing and genetic screening for clopidogrel metabolism in the acute phase of STEMI care are uncertain</td>
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ACC: American College of Cardiology; ACCF: American College of Cardiology Foundation; ACS: acute coronary syndrome; AHA: American Heart Association; CoR: class of recommendation; ESC: European Society of Cardiology; LoE: level of evidence; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SCAI: Society for Cardiovascular Angiography and Interventions; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina.

and minor bleeding (3.1% versus 4.5%, HR: 0.69; 95% CI: 0.46–1.05; p = 0.08). We may therefore expect that bleeding in patients at low ischaemic risk may be the future of treatment monitoring. This is in line with a recent investigation of bleeding risk in patients undergoing coronary artery bypass graft (CABG) surgery. A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naive patients and a waiting time that was approximately 50% shorter than that recommended in current guidelines [14]. These results led to an upgrade in the guidelines, to base timing of surgery on platelet function monitoring rather than the arbitrary use of a specified period of delay [15].

Personalized antiplatelet therapy is looking at the patient with a different approach to the routine clinical approach. It is not a wrong approach per se. We are just at the beginning of the story and platelet function monitoring should be envisioned as an attractive approach to refining antiplatelet strategy in gravely ill and fragile patients. This is the specific objective of the ongoing ANTARCTIC (Assessment of a Normal versus Tailored dose of prasugrel After stenting in patients aged > 75 years to Reduce the Composite of bleeding, stent Thrombosis and Ischemic Complications; NCT01538446) trial, which is looking at the net clinical benefit of P2Y₁₂ inhibition in elderly ACS patients who undergo stent implantation (Fig. 6). What we need is the right test in the right population with the right antiplatelet dosing regimen.
Figure 6. The ANTARCTIC trial design. ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; CV: cardiovascular; MACE: major adverse cardiac events; MI: myocardial infarction; PCI: percutaneous coronary intervention; PRU: P2Y12 reaction units; yo: years old.

Disclosure of interest

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