Editorial

Tailored antiplatelet therapy in high-risk ACS patients treated with PCI stenting: lessons from the ANTARCTIC trial

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The recently reported ANTARCTIC trial by Cayla and colleagues is the latest large-scale study of personalized antiplatelet therapy based on platelet function testing (1). In this open-label, blinded end-point, randomized, controlled trial, the authors ascertained the net clinical benefit of individualized antiplatelet therapy based on platelet function monitoring in elderly patients undergoing stenting (PCI) for an acute coronary syndrome (ACS). Eight hundred and seventy-seven ACS patients aged over 75 years were randomly assigned to receive either prasugrel 5 mg daily with no monitoring or treatment adjustment (conventional group, n=442) or the same starting agent, but with the possibility to tailor antiplatelet therapy either through dose titration or switching to an alternative $P2Y_{12}$ receptor inhibitor in case of inadequate platelet response (monitoring group, n=435). In the monitoring group, platelet function testing was assessed using the VerifyNow^{TM} assay 14 days post-PCI and repeated 14 days later in patients who required therapy adjustment. High platelet reactivity (HPR) and low platelet reactivity (LPR) to adenosine diphosphate (ADP) were defined as >208 and <85 PRU, respectively. The dose of prasugrel was escalated from 5 to 10 mg daily in patients with HPR, or therapy was switched to clopidogrel 75 mg per day in patients with LPR.

The findings from this well-designed trial in elderly patients with ACS (who represent a population at high risk for ischemic and bleeding events) too frequently excluded

from clinical studies, can be summarized as follows: (I) the platelet function testing guided-therapy approach resulted in treatment intensification for 4% of patients (16/435) and de-escalation of antiplatelet regimen for 39% (171/435) of patients in the monitoring group; (II) at 12 months, the primary composite end-point of cardiovascular death, myocardial infarction, stroke, definite stent thrombosis, urgent revascularization or bleeding, occurred in 120 (28%) patients in the monitoring group compared with 123 (28%) patients in conventional group (P=0.98); (III) the main safety endpoint of major bleeding (BARC type 2, 3 or 5) occurred in about a fifth of patients in each group (P=0.77); and (IV) this lack of statistical differences between groups was consistent across all the individual components of both ischemic and bleeding endpoints.

The ANTARCTIC trial is the latest in a string of trials reporting disappointing results for tailored antiplatelet therapy based on platelet function monitoring. Indeed, the rationale for personalized antiplatelet therapy stems naturally from numerous pharmacodynamic studies which demonstrated a wide variability of response to $P2Y_{12}$ receptor inhibition in particular in patients treated by clopidogrel (2-4). Moreover, several reports suggested an association between HPR and post stenting ischemic events such as stent thrombosis or cardiovascular death (5), and a possible link between LPR and bleeding events in stented patients (6-8). Altogether, these observations

Table 1 Randomized control trials assessing the utility of platelet function monitoring to reduce ischemic/bleeding outcomes in PCI patients

Studies	GRAVITAS	TRIGGER-PCI	ARCTIC	ANTARCTIC
Patients characteristics	~58% stable CAD ~27% UA without MI ~15% NSTE-ACS PCI with ≥ 1 DES	Stable CAD PCI with ≥1 DES	73% stable CAD 27% NSTE-ACS PCI with DES	ACS patients ≥75 years ~48% NSTEMI ~34% STEMI ~18% UA
Number of patients	n=2,800	n=423	n=2,440	n=877
Level of ischemic risk	Low risk	Low risk	Low risk	High risk
PFM method	VerifyNow™ assay	VerifyNow™ assay	VerifyNow™ assay	VerifyNow™ assay
PFM cutoff	HPR: ≥230 PRU	HPR: >208 PRU	HPR: ≥235 PRU or ≤15% inhibition	HPR: ≥208 PRU LPR: ≤85 PRU
Timing PFM	12 to 24 h after PCI	2 to 7 h after the first clopidogrel 75 mg maintenance dose the morning after PCI	Before PCI stenting Control PFM 2 to 4 weeks after PCI	Day 14 after PCI Control PFM 14 days after 1st test
Treatment in the PFM group	Clopidogrel 600 mg loading dose, followed by 150 mg maintenance dose	Clopidogrel 600 mg loading dose, followed by prasugrel 10 mg daily	Clopidogrel 600 mg loading dose, followed by clopidogrel 150 mg daily (~90%) or prasugrel 10 mg daily (~10%)	Prasugrel 5 mg daily (55%); prasugrel 10 mg (4%); clopidogrel 75 mg (39%)
Primary efficacy end-point	6-month cardiovascular death, nonfatal MI, or stent thrombosis: 2.3% *vs.* 2.3%; HR 1.01, P=0.97	6-month cardiovascular death or myocardial infarction: 0% *vs.* 0.5%; P=NE	1-year death, MI (including periprocedural increase in cardiac biomarkers), stent thrombosis, stroke, or urgent revascularization: 34.6% *vs.* 31.1%; HR 1.13, P=0.10	1-year cardiovascular death, MI, stroke, stent thrombosis, urgent revascularization, and BARC-defined bleeding (types 2, 3, or 5): 28% *vs.* 28%; HR 1.0, P=0.98
Bleeding outcomes	Severe or moderate GUSTO bleeding: 1.4% *vs.* 2.3%; HR, 0.59, P=0.10	Non-CABG major TIMI bleeding: 1.4% *vs.* 0.5%; P=NE	Major STEEPLE bleeding: 2.3% *vs.* 3.3%; HR 0.57, P=0.12	BARC-defined bleeding (types 2, 3, or 5): 21% *vs.* 20%; HR 1.04, P=0.77

CAD, coronary artery disease; UA, unstable angina; NSTE-ACS, non–ST-segment elevation-acute coronary syndrome; MI, myocardial infarction; DES, drug-eluting stent; NE, not evaluated due to insufficient data; PCI, percutaneous coronary intervention; PFM, platelet function monitoring; HPR, high platelet reactivity; LPR, low platelet reactivity.

led to the concept of a therapeutic window for DAPT (i.e., an "optimal" range of platelet reactivity) to improve outcomes, with the added complexity of defining standardized threshold values for HPR and LPR according to the type of platelet function assay used (9). However, so far studies on the potential of platelet function testing to improve outcomes in HPR patients undergoing PCI have yielded conflicting results in cohort studies and in randomized trials. Although promising results from smaller studies were reported (10), large-scale randomized, controlled trials consistently failed to establish any difference in cardiovascular outcomes between a conventional strategy and a platelet function monitoring-guided approach (*Table 1*). Some considerations help to position the ANTARCTIC trial results in the current landscape of platelet function-

based tailoring of antiplatelet therapy.

Previous studies have been criticized for enrolling low-risk patients whose rates of outcomes did not allow much differentiation between the standard-of-care and the adjusted treatment arms, as were the case in the GRAVITAS and the TRIGGER-PCI studies (11,12). In contrast, the ANTARCTIC trial targeted a higher risk population of patients, who indeed went on to have a higher rate of adverse events, but who nonetheless did not seem to benefit from tailored therapy. It has also been suggested that the therapeutic adjustments attempted provided only marginally altered platelet inhibition (11). While the intensification arm of ANTARCTIC did use an effective increase in prasugrel dose, it only occurred in 4% of patients receiving 5 mg of prasugrel daily. This rate is significantly lower than would have been expected,

given that the GENERATIONS trial that assessed platelet function on prasugrel 5 *vs.* 10 mg in very elderly stable CAD patients, found 14% of patients presenting with HPR, with a more stringent HPR definition (13). It is therefore not clear why the ANTARCTIC study population, which should have presented with higher platelet reactivity due to their ACS presentation (14), had such an important underrepresentation of HPR leading to intensification of treatment. Other criticisms of prior trials included the fact that newer $P2Y_{12}$ receptor inhibitors provide a significantly more predictable and profound inhibition of platelet function at the time of PCI than clopidogrel, advocating that these agents should be used at presentation to cover the HPR associated with ACS and PCI (11,12,15). The ANTARCTIC trial addressed this issue through homogeneous administration of prasugrel 5 mg to all participants, with possible de-escalation to clopidogrel 75 mg daily in patients with LPR. However, recent studies in elderly patients have shown similar rates of bleeding complications between patients treated with prasugrel 5 mg and clopidogrel 75 mg (13,16), and therefore the failure to improve the prognosis of patients in the monitoring group in the ANTRACTIC study might reflect the similar bleeding risks associated with these drug regimens rather than the actual predictive value of platelet function monitoring. The ongoing TROPICAL-ACS trial also includes a de-escalation arm based on platelet function monitoring, and should help shed light on this important issue (17). Finally, an important consideration that still plagues the field of personalized antiplatelet therapy, is the fact that all previous studies, including ANTARCTIC, investigated the question of a tailored antiplatelet therapy based on a single platelet function assay, the VerifyNow™ system (1,11,12,14). While the VerifyNow™ assay remains the most widely used and studied test for the link between HPR and clinical outcomes after PCI, other assays capture different aspects of platelet function and identify different patients as requiring antiplatelet therapy adjustment (18). Whether strategies based on alternative platelet function testing modalities would yield the same results remains an open debate, which the ongoing TROPICAL-ACS trial using the Multiplate™ technology may help to answer (17).

In summary, while the findings from the ANTARCTIC study are in line with previous trials of platelet function testing-driven personalization of antiplatelet therapy, there are still a number of open questions that require elucidation before recommendations for or against platelet function monitoring may be made. Moreover, it may be that a combination of clinical, genomic and pharmacodynamic variables will be necessary to provide the optimal patient profile to target personalized antiplatelet therapy. Ongoing research with alternative approaches to personalization is eagerly awaited.

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