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EXPERT OPINION

Antiplatelet drugs and platelet reactivity: is it time to halt clinical research on tailored strategies?

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Personalized medicine of antiplatelet drugs in cardiovascular patients has led to a significant enthusiasm. Indeed, numerous longitudinal studies showed an association between high platelet reactivity and the recurrence of ischemic events. The first small randomized trials of $P2Y_{12}$ blockers tailored to each patient's platelet reactivity yielded encouraging reductions of coronary stent thrombosis in high-risk populations. The discovery of genetic variants contributing to the pharmacodynamic effect of clopidogrel has then paved the way toward a personalized antiplatelet therapy based on reliable and stable genetic tests. This enthusiasm was soon tempered by large interventional trials demonstrating that a platelet function testing-based strategy did not improve clinical outcome and that genetic variants discovered up to now only explained a small part of the pharmacodynamic effect of clopidogrel, thus limiting its clinical use. Looking back to the most recent trials, their target populations and the type of clinical setting, it seems that the one-size-fits all policy regarding antiplatelet drugs may be well acceptable for low-risk patients. On the contrary, integration of the clinical setting as well as other risk factors may help to identify subgroups of patients who could derive a benefit from a truly personalized management of antiplatelet therapy.

Keywords: antiplatelet drugs, personnalized treatments, platelet reactivity

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Aspirin and $P2Y_{12}$ receptor blockers are of paramount importance in the management of patients with a variety of atherothrombosis-related clinical conditions such as coronary heart disease, ischemic cerebro-vascular disease and peripheral arterial disease. $P2Y_{12}$ receptor blockers are particularly important during an acute thrombotic setting and clopidogrel may also be indicated for secondary long-term prevention [1]. For both aspirin and clopidogrel, there is an inter-individual variability in the pharmacodynamic effect [2-4] that led to the biological concept of high on-treatment platelet reactivity (HPR). Numerous observational studies have shown that HPR was predictive of ischemic events [5-7], notably in patients treated with clopidogrel. However, this HPR phenotype may be quite heterogeneous, depending on the type of assay used to assess platelet reactivity (PR) with inherent limitations related to the influence of external factors or the choice of the cut-off to define HPR, all of which may impair its prognostic value. A large enthusiasm regarding personalized medicine of antiplatelet drug therapy has grown following the discovery of genetic determinants of clopidogrel responsiveness [8,9] potentially allowing a stable evaluation of the risk compared to the more variable and heterogeneous platelet function [10].

The first randomized intervention trials of tailored treatment according to HPR in high-risk patients undergoing percutaneous coronary stenting showed quite impressive results [11,12] toward reducing the rate of stent thrombosis. However,

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Table 1. Selected past and ongoing randomized trials on platelet reactivity-based tailored antiplatelet therapy.

Study	Patients	Intervention	Event reduction	Strengths	Limitations
Bonello *et al*. (2009) [11]	429 PCI patients with NSTEMI and several risk factors	Up to four clopidogrel loading doses of 600 mg	Yes	Strong intervention prior to PCI; high-risk patients	Small size, delayed PCI
GRAVITAS (2011) [15]	2214 patients with PCI	600 mg re-loading post PCI and 150 mg/d for 6 months	No	Large sample	Low risk patients, limited impact of intervention on PR, low MACE rate
ARCTIC (2012) [16]	2440 patients with scheduled PCI and HPR	Various adjustments of antiplatelet drug dosing	No	Large sample, tailoring according to both aspirin and clopidogrel response	Low risk patients, <30% with ACS, low MACE rate
ANTARCTIC (2013) [25]	ACS patients aged 75 or more	Various adjustments of $P2Y_{12}$ blocker therapy	Ongoing	High-risk patients (ACS, age>75y)	Actual vascular risk level and MACE incidence yet unknown
TROPICAL-ACS (2013)	ACS patients	Various adjustments of $P2Y_{12}$ blocker therapy	Ongoing	ACS patients, combined incidence of bleeding and thrombotic events	Actual vascular risk level and MACE incidence yet unknown

ACS: Acute coronary syndrome; HPR: High platelet reactivity; MACE: Major adverse cardiovascular event; NSTEMI: Non-ST elevation myocardial infarction; PCI: Percutaneous coronary intervention.

these results were soon tempered by the heterogeneous predictive ability of HPR due, at least in part, to differences across biological assays used in the different studies but also to the different clinical settings and patient populations. Indeed, HPR is not predictive of ischemic events in a wide array of stable cardiovascular outpatients treated with clopidogrel [13] or in medically managed acute coronary syndrome (ACS) patients [14]. Similarly, the results of the early intervention randomized trials [11,12] were not replicated in larger trials [15,16], potentially because of very low clinical event rates undermining study power but also because of a too modest intervention with a limited effect on PR. Other limitations included the cut-off chosen to define HPR, the type of test and the type of outcomes that may not be related to HPR. A few selected major randomized trials are detailed in **Table 1**. In parallel, significant attention was drawn to the genetic determinants of the HPR phenotype and more particularly the CYP2C19*2 loss-of-function variant, which is responsible for a lower bio-activation of clopidogrel and subsequent platelet inhibition activity. Though the statistical and biological relevance of the association between CYP2C19*2 and HPR is significant, the size of the effect and its clinical relevance are questionable [17,18]. Indeed, the CYP2C19*2 variant has a poor sensitivity (38%) for the prediction of HPR [18]. Consistently, the initial 2009 FDA boxed warning was updated in 2010 and no longer advise to avoid clopidogrel in carriers of the CYP2C19*2 variant and strong recommendations to genotype patients have been removed [19]. More deceiving yet is the absence of other significant genetic contributors despite a known heritability of the PR phenotype [20]. These controversial and somehow disappointing observations, together with the release of more potent P2Y12 receptor blockers logically lead to question the future of a tailored treatment in antiplatelet therapy. Is it time to halt clinical research on tailored strategies? The question may sound somewhat provocative but this issue deserves to be discussed in keeping with recent data in the field.

In this issue of *Expert Opinion On Pharmacotherapy*, Tantry *et al*. provides a well-documented review on the topic [21] with updated information from a vast array of studies and a critical view to better understand limitations and drawbacks of the different trials. They also describe differences between two concepts: i) antiplatelet resistance, related to highly specific biological tests and a true failure of the drug to hit its target receptor/enzyme; and ii) HPR, related to a preserved ability of platelet to aggregate despite drug activity on its target. The authors also emphasize on the concept of a therapeutic window to reach a balance between reducing ischemic and avoiding bleeding events and address future perspectives. Indeed, looking back to Phase III trials on antiplatelet drugs, it appears to be difficult to further improve the annual rate of recurrence of ischemic events in ACS patients < 10% without significantly increasing the risk of major bleedings, further supporting the therapeutic window concept of $P2Y_{12}$ receptor blocker therapy [22]. Although new $P2Y_{12}$ inhibitors such as prasugrel and ticagrelor are more potent than clopidogrel, there is still a biological variability [23] that may be of concern regarding both ischemic and bleeding risks.

Taking together and as suggested by Tantry *et al*., it seems that assessing for PR may be more relevant in percutaneous coronary intervention patients with ACS. As pointed out by the authors, this is suggested by data from the ADAPT-DES registry showing that HPR was predictive of recurrent ischemic event only in patients with ACS whereas it was not in patients without ACS. However the interaction between HPR and the ACS status was not significant and it is likely

that other factors are also involved. Indeed, the initial overall level of cardiovascular risk may thus be of utmost importance [24]. Consequently, the one-size-fits-all strategy based on clopidogrel may be the right choice in low-risk patients such as those included in GRAVITAS or ARCTIC whereas higher risk patients could benefit from truly personalized management including their PR. Efforts should thus concentrate on the identification of higher ischemic or bleeding risk patients who may benefit of such a personalized antiplatelet therapy. This evaluation of the level of risk should now be implemented in future interventional trials of tailored antiplatelet strategy. Although ongoing trials on tailored $P2Y_{12}$ strategies, including TROPICAL-ACS (ClinicalTrials.gov identifier: NCT01959451) and ANTARCTIC [25], partly include this concept of risk levels, additional efforts in this direction are still needed.

In parallel, more fundamental approaches such as those related to high throughput technologies [26] may help to delineate the mechanisms modulating PR and to unveil the set of genes that determine the known heritability of clopidogrel responsiveness.

In conclusion, research on antiplatelet drug reactivity and tailored treatment strategy based on PR should not be halted on the basis of contrasted data. New approaches are needed and should encompass clinical factors in addition to platelet function or genetic test results, for the sake of a truly personalized medicine.

Declaration of interest

J-L Reny has received payment for lectures by Merck Sharp and Dohme. P Fontana has received consultancy for Evolva; grants from Evolva and Astra Zeneca, and honoraria from Bayer, AstraZeneca and Siemens. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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