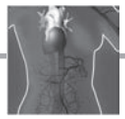
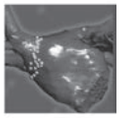
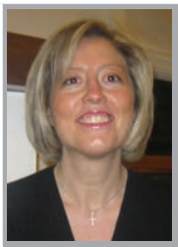




Personalized antiplatelet therapy in acute coronary syndromes: a dead-end street or a future scenario?

"...it was clearly demonstrated that the entity of platelet inhibition on clopidogrel is a determinant of ischemic ... events at follow-up of patients with acute coronary syndromes. Clopidogrel has been an excellent model to study personalized antiplatelet therapy."

KEYWORDS: acute coronary syndrome ■ antiplatelets ■ clopidogrel ■ monitoring ■ platelet ■ platelet hyper-reactivity ■ prasugrel ■ ticagrelor



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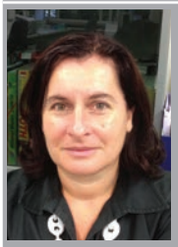

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Antiplatelet therapy with two drugs – aspirin and a P2Y12 inhibitor – is the cornerstone of treatment in the setting of acute coronary syndromes (ACS) [1]. While aspirin is crucial for the treatment of chronic atherosclerotic disease, a dual antiplatelet therapy is needed in the presence of acute platelet and clotting activation, conditions that underlie the clinical manifestation of unstable angina and myocardial infarction [2].

Clopidogrel, prasugrel and ticagrelor are the P2Y12 inhibitors available for this treatment. Current guidelines indicate prasugrel or ticagrelor as the first-line therapy, followed by clopidogrel [3]. These recommendations were derived from the results of the TRITON-TIMI 38 [4] and PLATO [5] trials, which have demonstrated a superiority of prasugrel and ticagrelor to clopidogrel in terms of efficacy in reducing ischemic events (for ticagrelor, a reduction was also was found in mortality, a nonprespecified end point) at the cost of a significantly higher proportion of bleeding events.

These results fit in the context of the high interindividual variability of clopidogrel. In recent years, based on studies of clopidogrel, it was clearly demonstrated that the entity of platelet inhibition on clopidogrel is a determinant of ischemic and, possibly, bleeding events at follow-up of patients with ACS [6–9]. Due to its intrinsic limitations linked to the type of molecule, clopidogrel has been an excellent model to study personalized antiplatelet therapy.

Only 15% of the administered clopidogrel is metabolized into the active drug, R-130964 [10]. The main reason associated with an inadequate platelet inhibition is the insufficient generation of active metabolite. Genetic and acquired determinants are responsible for this. Carriers of *CYP2C19*2* polymorphism synthesize an enzyme that works less efficiently and are at a greater risk of developing high platelet reactivity [10]. This genetic determinant is associated with clopidogrel metabolism. Therefore, platelet hyper-reactivity caused by this genetic variant is overcome by the newer antiplatelets, such as prasugrel and ticagrelor. However, acquired determinants are also associated with high platelet reactivity on clopidogrel [11], and these conditions may also affect the response also to the new antiplatelet drugs. Diabetes, advanced age, reduced ejection fraction, and the entity of platelet turnover and inflammation are conditions associated with a higher platelet reactivity and higher risk of developing an insufficient platelet inhibition on therapy [12]. These conditions may be persistent (i.e., diabetes and advanced age) or transient (i.e., platelet turnover and inflammation). Indeed, regarding the 'acute phase' of ACS, it was found that a proportion of patients with high platelet reactivity on clopidogrel in the acute phase has an adequate platelet inhibition at 6 months from the acute event [12]. This suggests, at least in part, that the reduction of inflammation activation after ACS is associated with a reduced platelet reactivity and, possibly, with a decreased percentage of patients with an inadequate platelet inhibition on the same drug.

We have observed that patients with an inadequate platelet inhibition on clopidogrel (measured by light transmission aggregometry, VerifyNow® [Accumetrics, CA, USA], Multiplate® [Roche, Mannheim, Germany] or VASP (Lancet Laboratories, Johannesburg, South Africa) and using ADP as an agonist) are at significantly higher risk of ischemic recurrences [6–9,13–15]. On the other hand, data are increasingly linking an excessive platelet inhibition

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with bleeding risk [16]. Therefore, the issue of personalized antiplatelet therapy is strictly associated with the issue of antiplatelet monitoring.

The concept of using platelet function to alter antiplatelet therapy was tested in the GRAVITAS and ARCTIC trials [17,18]. Both trials did not demonstrate a reduced incidence of ischemic events in patients with platelet hyper-reactivity treated with a higher dose of clopidogrel and/or different drugs. Based on these results, many authors consider the issue of personalized antiplatelet therapy to be a dead-end street. Neither of these trials were correctly designed to respond to the question of whether laboratory monitoring may help clinicians to choose the right antiplatelet therapy in ACS patients. The patients enrolled significantly differ from those patients in which high platelet reactivity was found to be associated with ischemic risk. In fact, until now, we only found a significant association between the entity of platelet inhibition and ischemic risk in ACS patients, and not in stable coronary artery disease patients. In addition, both trials did not efficiently correct the high platelet reactivity. In GRAVITAS, a strategy based on the double dosage of clopidogrel was used (150 mg/day) and, in approximately 40% of patients, high platelet reactivity persisted after the introduction of increased dosage [17]. In ARCTIC, only 11% of patients were treated with an alternative antiplatelet drug, such as prasugrel, and again, the majority of patients were treated with an increased dosage of clopidogrel or with an additional use of anti-IIb/IIIa inhibitors [18]. Finally, it was calculated that the number of patients enrolled in ARCTIC may be insufficient to adequately answer the question of whether a strategy based on laboratory monitoring is better than a standard strategy [19].

> "*The issue of personalized antiplatelet therapy is strictly associated with the issue of antiplatelet monitoring.*"

The studies on the measurement of platelet reactivity on clopidogrel therapy have taught us that a group of ACS patients are characterized by the presence of an 'aggressive' platelet that is not related to the metabolism of clopidogrel, which confers a higher long-term risk. The benefit–risk ratio of the newer antiplatelets in these patients has to be investigated in order to evaluate the reduction of the prothrombotic burden associated with this phenotype. Indeed, it is not known whether prasugrel or ticagrelor are able to completely overcome high platelet reactivity. They will correct the inadequate metabolization of carriers of *CYP2C19*2*, but no data are available on the efficiency of these drugs in relation to high platelet reactivity linked to diabetes, advanced age and inflammation among others.

> "*...a group of acute coronary syndrome patients are characterized by the presence of an 'aggressive' platelet that is not related to the metabolism of clopidogrel, which confers a higher long-term risk.*"

Furthermore, we cannot forget that some patients may be treated efficiently with the 'old' clopidogrel and in some of these, the use of the newer drugs might be associated with an increased risk of bleeding events. This is a concept that goes against marketing: not one drug for all patients, but different drugs for different patients. In the studies on platelet reactivity, we have learned that the entity of inflammation in ACS is an important determinant of platelet reactivity, together with platelet turnover and reticulated platelets. These conditions are time-related – in that, it may be possible to imagine that a single patient might need a different entity of platelet inhibition according to different times. An issue to be investigated is the possible utility of a different entity of platelet inhibition according to the acute, subacute or chronic phase of the disease. For all these reasons, the issue of monitoring antiplatelet therapy is open. An algorithm taking into account clinical data, platelet-function profiles and genetic information, must be developed and evaluated. The aim of this approach will be to calculate personalized antiplatelet strategies to reduce ischemic events without increasing the risk of bleeding events. Recently published and ongoing clinical trials have been designed to evaluate whether the administration of antiplatelet treatments tailored to platelet inhibition is a safe and an effective strategy. However, antiplatelet treatments tailored not only to platelet function but also to procedural, environmental and genetic factors are warranted. The available data highlight an urgent need for prospective studies to clarify whether personalized therapeutic strategies will improve outcomes in high-risk patients with vascular disease. To choose a 'superior' drug based on the results of large clinical trials, in which patients with different risk profiles are all considered equal, may not be the best strategy. The approach should focus

on choosing the best drug by identifying the therapeutic strategy that, taking into account the individual characteristics of patients, warrants the higher benefit–risk ratio. Prospective studies evaluating different antiplatelet treatments tailored to the individual characteristics of patients (genetic profiles, residual platelet reactivity, drug–drug interactions, and traditional and procedural risk factors) are urgently needed. This will identify therapeutic strategies that will provide the greatest benefit for each individual patient in this high-risk clinical setting. In the near future, we can foresee the development of an algorithm that weighs genetic or acquired risk factors for cardiovascular complications, which will help clinicians to better predict the risk for individual patients and to administer the best therapeutic strategy in each case.

Personalized medicine could provide patients with different therapeutic solutions based on platelet-function testing, patients' clinical characteristics and genetic markers. Clopidogrel pharmacogenetics, as well as pharmacogenetics of other drugs, have represented important models to identify strategies and solutions to improve healthcare. Preliminary data are available on the possible utility of pharmacogenetic testing for clopidogrel.

The scientific knowledge deriving from genetics, pharmacogenetics, transcriptomics, metabolomics, the microbiome, proteomics and imaging is rapidly growing, and the major challenge will be to translate and integrate this mass of information to consolidate disease knowledge and procedures of management of patients.

In our opinion, for antiplatelet therapy in ACS, the definition of algorithms for the evaluation of antiplatelet treatments tailored to individual characteristics of patients it is urgently needed, in order to identify therapeutic strategies that will provide the best benefit for the single patient in this high-risk clinical setting.

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