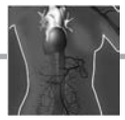
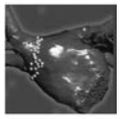
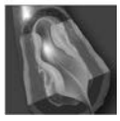
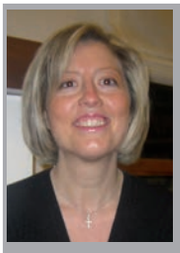




High on-clopidogrel platelet reactivity and risk of MACE after PCI with stent implantation

"Large clinical trials have demonstrated that dual antiplatelet therapy (aspirin plus clopidogrel) reduces the risk of recurrent cardiovascular events in patients with coronary artery disease."

KEYWORDS: acute coronary syndrome ■ clopidogrel ■ genetic ■ platelet



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Large clinical trials have demonstrated that dual antiplatelet therapy (aspirin plus clopidogrel) reduces the risk of recurrent cardiovascular events in patients with coronary artery disease. Dual antiplatelet therapy is the standard of care in patients with acute coronary syndromes undergoing stent implantation [1].

Aspirin irreversibly acetylates the serine residue (ser529) in COX-1 preventing the binding of arachidonic acid to the catalytic site. Controversy exists regarding the clinical relevance of non-COX-1-mediated antiplatelet effects of aspirin. Clopidogrel is a second-generation thienopyridine that is converted to an active metabolite by the hepatic cytochrome P450 pathway. The active thiol metabolite of clopidogrel forms a covalent disulfide bond with cys17 and cys270 residues present in the extracellular domains of P2Y12 and inhibits ADP binding.

High on-treatment platelet reactivity: beyond the concept of 'resistance'

The issue of the optimal dosage of clopidogrel, and aspirin, to reduce the ischemic events is linked to the issue of the so-called 'resistance' to antiplatelets. It has been clearly demonstrated that there is a great variability in the entity of inhibition of platelet function induced by these drugs. Pharmacologists define 'resistance' to a drug on the basis of the measurement of the metabolite, which is the specific target of that drug: cAMP for clopidogrel and thromboxane for aspirin. On the other hand, clinicians are interested in the evaluation of how the entity of platelet function inhibition induced by antiplatelets affects the risk of recurrent ischemic events. Therefore, we believe it is crucial to overcome the concept of resistance with that of high on-treatment platelet reactivity. A growing body of evidence is linking the entity of platelet inhibition on clopidogrel with cardiovascular recurrences [2]. Ongoing clinical trials are evaluating if an antiplatelet treatment tailored on the entity of platelet inhibition will be a good strategy in terms of safety and efficacy. These studies will give us the crucial information on the possible utility of a monitoring of antiplatelets in order to prevent clinical events.

Clopidogrel

Clopidogrel is a prodrug that is metabolized by cytochrome P450 into an active metabolite, which irreversibly inhibits binding of ADP to the P2Y12 receptor on the platelet. Only 15% of the dose of clopidogrel absorbed is metabolized into the active drug, in particular by cytochrome P3A4 (CYP3A4).

"The issue of the optimal dosage of clopidogrel, and aspirin, to reduce the ischemic events is linked to the issue of the so-called 'resistance' to antiplatelets."

Genetic polymorphisms have been investigated in order to evaluate a possible genetic determinant of the entity of platelet inhibition induced by clopidogrel. Recently, an allelic variant of *CYP2C19*2* (allele 681A) was found to be associated with an impaired platelet inhibition after clopidogrel administration in healthy subjects. In 1419 acute coronary syndrome patients on dual antiplatelet therapy, we found that allele *2C19*2* of *CYP2C19* gene is an independent predictor of high on-clopidogrel platelet reactivity with the risk of adverse clinical events (stent thrombosis and cardiovascular deaths) in the patients enrolled in the Low Responsiveness to Clopidogrel and Sirolimus- or Paclitaxel-Eluting Stent Thrombosis (RECLOSE) trial [3]. Four papers contemporarily published in the literature demonstrated and confirmed that this

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allelic variant is associated with the risk of major adverse coronary events in high-risk vascular patients [4–7].

We and others have found that diabetes, acute coronary syndrome, obesity and reduced systolic ventricular function are associated with a significantly higher prevalence of high on-clopidogrel platelet reactivity [8]. Acute coronary syndrome is characterized by an enhanced platelet reactivity caused by a higher platelet turnover, documented by the presence of reticulated platelets, which are an important determinant of the entity of platelet inhibition [9]. Diabetes and heart failure are known to be associated with a higher platelet reactivity too. In addition, inflammation, measured by number of white cells, erythrocyte sedimentation rate and the balance between pro- and anti-inflammatory cytokines, has been associated with diabetes, acute coronary syndrome and heart failure, and it has been demonstrated to be a predictor of on-therapy platelet reactivity [10].

Evidence suggests that poor responders to clopidogrel experience more frequent cardiovascular events than responders. However, one limitation considering these results is that each study had different definitions for an individual's response to clopidogrel on the basis of the amount of agonist used, the assay used and the timing of the blood sampling.

Several studies have been published that have confirmed the association between residual platelet reactivity on clopidogrel and the enhanced risk of adverse clinical events [2]. In particular, data from the RECLOSE trial showed that a reduced response to clopidogrel (measured by light transmittance aggregometry (LTA) induced by ADP 10 µmol) is an independent predictor of stent thrombosis and cardiovascular death in 804 patients undergoing PCI with implantation of a drug-eluting stent [11]. From a subsequent analysis of the same cohort of patients, we found that the contemporary reduced response to both aspirin (measured by LTA induced by arachidonic acid) and clopidogrel is the most important predictor of the same end points (stent thrombosis and cardiovascular death) [12]. This result underlines that a 'global' platelet hyperreactivity identifies vulnerable patients at higher risk of recurrences. Great attention has been focused on the clinical validation of the point-of-care tests that do not need a specialized laboratory. Price *et al.* demonstrated on 380 patients undergoing PCI with stent implantation that residual platelet reactivity on clopidogrel measured by VerifyNow P2Y12 is associated with a significantly higher risk of adverse clinical events at a 6-month follow-up [13]. The Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-Platelet Reactivity Predicts Outcome (ARMYDA-PRO) study reported a significant association between high on-clopidogrel platelet reactivity (measured by VerifyNow P2Y12) and 30-days MACE on 160 patients undergoing PCI [14]. Finally, we demonstrated on a larger number of patients (683 acute coronary syndrome patients) that high on-clopidogrel platelet reactivity measured by VerifyNow P2Y12 is associated with a higher risk of cardiovascular death and nonfatal myocardial infarction at a 12-month follow-up [15].

Management of antiplatelets' drug resistance

At present, there is little evidence to guide treatment of the patients with laboratory evidence of a high on-clopidogrel platelet reactivity to antiplatelet drugs or thrombosis occurring during antiplatelet therapy. Empirical strategies include increasing the dose of the antiplatelet agent or adding a second antiplatelet drug.

> "*Evidence suggests that poor responders to clopidogrel experience more frequent cardiovascular events than do responders.*"

It has been shown that a higher platelet inhibition with increased dosage of clopidogrel, combining synergistic medications and evaluating medications potentially hinder the p450 conversion of clopidogrel into its active form. Gurbel and colleagues demonstrated that loading with clopidogrel 600 mg decreased platelet reactivity in comparison with 300 mg [16]. In a similar trial, von Beckerath evaluated different doses of clopidogrel in 60 patients who had ischemic heart disease undergoing elective PCI, and found that clopidogrel 600 mg increased platelet inhibition over a 300-mg loading dose. Loading doses greater than 600 mg of clopidogrel did not increase platelet inhibition, most likely due to limited absorption. In the OPTIMUS study, Angiolillo evaluated patients with Type 2 diabetes mellitus and coronary artery disease and found that a dose of clopidogrel 150 mg is associated with a reduced platelet inhibition in patients with a residual platelet reactivity on standard therapy [17]. The ongoing trials, Gauging Responsiveness with A VerifyNow® Assay Impact on Thrombosis and Safety (GRAVITAS) and Dual Antiplatelet Therapy Tailored on the Extent of Platelet

Inhibition (DANTE) will establish whether an increase in the clopidogrel maintenance dose (150 vs 75 mg daily) is necessary in patients with residual platelet reactivity on clopidogrel (i.e., if a treatment tailored on the extent of platelet inhibition is associated with a reduced number of recurrences).

Furthermore, new P2Y12 receptor antagonists are currently available. Prasugrel is a third-generation thienopyridine that is associated with greater active metabolite generation, superior inhibition of ADP-induced platelet aggregation and less response variability than clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38), prasugrel was compared with clopidogrel in patients with moderate- to high-risk acute coronary syndromes undergoing PCI [18]. The prevalence of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke was lower with prasugrel treatment compared with clopidogrel (12.1 vs 9.9%). However, there were higher rates of bleeding in the prasugrel group. TRITON conclusively demonstrated that superior P2Y12 blockade produces superior reduction in ischemic events in acute coronary syndromes: *ad hoc* studies are needed to establish the effect of prasugrel in patients with high on-clopidogrel platelet reactivity.

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