Archives of Cardiovascular Disease (2010) **103**, 349—353

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

SCIENTIFIC EDITORIAL

Clopidogrel resistance: What's new?

Résistance au Clopidogrel : quoi de neuf ?

Thomas Cuisset [a,*], **Guillaume Cayla** [b], **Johanne Silvain** [c]

[a] *Department of Cardiology, CHU La Timone, 264, rue Saint-Pierre, 13385 Marseille cedex 5, France*
[b] *Department of Cardiology, University Hospital of Nîmes, 30000 Nîmes, France*
[c] *Inserm CMR937, Pitié-Salpêtrière Hospital, AP—HP, Institut de cardiologie, University Paris-6, 75006 Paris, France*

Received 3 May 2010; accepted 3 May 2010
Available online 23 June 2010

KEYWORDS
Antiplatelet therapy;
Clopidogrel resistance;
Acute coronary syndrome;
Platelet function tests;
Genetic polymorphisms

Summary The concept of clopidogrel resistance emerged several years ago. Since then, many studies have been performed to elucidate the mechanisms and potential clinical impact of this biological finding. These studies identified complex mechanisms, including drug—drug interactions, genetic polymorphisms and clinical factors, and showed consistently the clinical relevance of the variability of clopidogrel response, with higher ischaemic risk in low-responders or non-responders, and higher bleeding risk in hyper-responders. Several strategies for overcoming clopidogrel resistance have been evaluated in small clinical studies, but the benefit of tailored antiplatelet therapy has yet to be validated in large randomized trials, which are currently ongoing. Upcoming antiplatelet drugs that are more potent will change the field of antiplatelet therapy in acute coronary syndromes. The future of antiplatelet therapy sounds more complex, with different drugs, and tailored therapy based on platelet tests and/or genetic testing, but it will lead us to propose a more individualized therapy, which hopefully will improve patient outcome.

MOTS CLÉS
Traitement antiplaquettaire ;
Résistance au clopidogrel ;

Résumé Le concept de résistance au clopidogrel est apparu depuis quelques années. Depuis, de nombreuses études ont été menées pour élucider les mécanismes ainsi que les conséquences cliniques de cette entité biologique. Ces études ont démontré un mécanisme complexe, incluant des interactions médicamenteuses, ainsi que des facteurs génétiques et cliniques, et ont montré de façon constante l'impact clinique de cette variabilité de réponse. De nombreuses stratégies ont été proposées pour s'affranchir de cette résistance, mais le bénéfice

Abbreviations: CYP, cytochrome P450; HPI, high on-treatment platelet inhibition; HPR, high on-treatment platelet reactivity; LTA, light transmission aggregometry; PRI, platelet reactivity index; VASP, vasoactive stimulated phosphoprotein.

* Corresponding author.
E-mail address: thomascuisset@voila.fr (T. Cuisset).

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doi:10.1016/j.acvd.2010.05.001

Syndrome Coronarien Aigu ;
Tests plaquettaires ;
Polymorphismes Génétiques

d'un traitement individualisé sur les tests plaquettaires doit encore être démontré dans de larges essais cliniques, actuellement en cours. Les nouvelles molécules antiplaquettaires, plus puissantes, vont bien sûr modifier le traitement antiplaquettaire des syndromes coronariens aigus. Le traitement antiplaquettaire du futur apparaît alors plus complexe avec différentes molécules, voire un traitement individualisé sur les tests plaquettaires et/ou génétiques, mais cela nous amènera à proposer un traitement plus personnalisé à chaque patient, ce qui ne peut qu'améliorer leur pronostic.

The concept of clopidogrel resistance or non-response has emerged from numerous trials over the past decade. To fully understand this concept, its implication for patients and the solutions that are being developed and evaluated, cardiologists should increase the field of their knowledge and take an interest in the pharmacological properties of the second-most-sold drug in the world.

Firstly, clopidogrel, as part of the thienopyridine class, is a prodrug. It undergoes a series of transformations to yield an active metabolite, which is the real P2Y12 inhibitor. After its absorption, approximately 85% of the clopidogrel dose is hydrolyzed by esterases to an inactive metabolite and cannot be converted into the active metabolite. The remaining 15% undergoes a two-step oxidation by a series of hepatic cytochrome P450 s (CYPs) to generate the active metabolite, which is able to bond irreversibly with the P2Y12 receptor and therefore inhibit platelet aggregation.

Among the hepatic enzymes that contribute to this metabolic process, a key enzyme — CYP2C19 — has been shown to have many isoforms, which produces large variability in its catalytic activity. This variability translates into different rates of conversion of clopidogrel into its active compound, which can attenuate (2C19*2, 2C19*3) or enhance (2C19*17) the pharmacodynamic effect of the drug [1,2]. Recently, the loss-of-function variant 2C19*2, which is present in about 30% of Caucasians and up to 60% of the Asian population, has been associated with decreased activation of clopidogrel, resulting in a reduced antiplatelet effect [3,4]. More importantly, the ''genetic resistance'' induced by the carriage of at least one CYP2C19*2 allele translates into a significantly increased risk of recurrent cardiovascular events, including a dramatic threefold increase in stent thrombosis in patients receiving clopidogrel therapy [5—7]. To make it even simpler, several other mechanisms have been identified that induce a decreased response, including drug-to-drug interactions through the same hepatic cytochrome (P450), as described recently with proton pump inhibitors [8,9], and clinical factors such as diabetes and being overweight [10].

These recent findings clearly support the need for platelet function tests, to identify non-responder candidates for treatment adaptation (under the hypothesis that tailored therapy will lower recurrent events), and more potent antiplatelet agents to overcome the non-response to clopidogrel, such as prasugrel, which is less sensitive to cytochrome polymorphism, or ticagrelor, which inhibits the P2Y12 receptor directly and avoids hepatic metabolization.

Several methods have been used to assess clopidogrel-induced antiplatelet effects but only three tests have been studied extensively in the clinical research setting. Light transmission aggregometry (LTA) is still considered as the gold standard method and has been used largely in prospective studies, to evaluate response to clopidogrel and predict cardiovascular events. Flow cytometry assessment of the phosphorylation of Vasoactive Stimulated Phosphoprotein (VASP), an intracellular actin protein, is also well correlated with inhibition induced by clopidogrel, and has the advantage of being very specific for the P2Y12 receptor. Unfortunately, these two tests require equipment and technicians, and are both time- and cost-consuming. The VerifyNow system (Accumetrics, Inc., San Diego, CA. USA) is a fully automated, point-of-care test, which is easy to use and can measure platelet response to clopidogrel in a few minutes. This assay has been well correlated with LTA [11—13] and VASP Platelet Reactivity Index (PRI), and is probably the optimal assay for platelet measurement in a clinical setting because of its potential availability in catheterization laboratories. Nevertheless, the utility of such a test remains to be proven in large, randomized, clinical studies.

The clinical relevance of the concept of clopidogrel resistance or non-response has been investigated broadly. Several clinical studies, using the above-mentioned platelet function tests, have demonstrated that patients with High on-treatment Platelet Reactivity (HPR) or clopidogrel resistance have an increased risk of ischaemic events, including stent thrombosis [14,15].

Mateztky et al. were the first to demonstrate, in a small population of patients with ST-elevation myocardial infarction, that patients in the first quartile of response to clopidogrel (considered as non-responders to clopidogrel) were at high risk of having a recurrent cardiovascular event at 6 months [16]. In this study, clopidogrel response was defined as the variation of platelet inhibition from a baseline value. This method, which evaluated the relative response to clopidogrel, is not always suitable for daily clinical practice because baseline samples are not often available due to chronic clopidogrel therapy or night admission. Moreover, studies have shown good correlation between non-response to clopidogrel (small difference between pre-treatment and post-treatment values) and HPR, which only necessitates one post-treatment platelet measurement. Therefore HPR was considered as a good estimate of thrombotic risk and enables high-risk patients with non-response to clopidogrel to be defined [17].

The recent POPULAR study is the largest and most complete study conducted so far, evaluating the potential additive predictive value of several platelet tests in the