SCIENTIFIC EDITORIAL

Clopidogrel resistance: What’s new?

Résistance au Clopidogrel : quoi de neuf ?

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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.

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MOTS CLÉS
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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

\textit{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.

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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 P450s (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 (CYP2C19*17) or enhance (CYP2C19*2) the pharmacodynamic effect of the drug [1,2]. Recently, the loss-of-function variant CYP2C19*2, which is present in about 30% of Caucasians and up to 60% of the Asian population, has been associated with decreased activity in its catalytic ability. This variability 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].

Matezky 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 context of stent thrombosis.
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assessment of risk or recurrent ischaemic events [18]. The first conclusion of this study is that there is only a small additive value to platelet function tests in ischaemic risk assessment compared with clinical and angiographic risk models. Nevertheless, the platelet function test remains useful as an independent risk marker for clinicians. The second conclusion is that only some tests were able to predict recurrent events (LTA, VerifyNow, PlateletWorks [Helena Laboratories, Beaumont, TX, USA]) while others were not (PFA-100 [Siemens Healthcare Diagnostics, Deerfield, IL, USA]). Unfortunately VASP PRI was not evaluated in this head-to-head comparison study, but should still be considered as an efficient test on the basis of other clinical studies [19]. The most difficult problem remaining after all these studies is that there is still no consensus on the definition of clopidogrel resistance or non-response [20]. The threshold for defining non-responders or patients with HPR is still unknown and will be difficult to address, as the level of platelet response varies from one day to the next and from acute situations to stable patients.

Looking at the other side of platelet response, clinicians interested in bleeding complications have noticed that some patients can be hyper-responders, and have published data supporting the association between High on-treatment Platelet Inhibition (HPI) and bleeding complications [2,21]. Therefore, the concept of an “optimal” therapeutic range of platelet inhibition was born, and might help to reduce both ischaemic and bleeding complications in coronary patients treated with clopidogrel.

Over the past decade, different strategies have been evaluated to overcome HPR and clopidogrel resistance, with the ultimate goal of obtaining an optimal antiplatelet therapy regimen that is both highly efficient and safe. As a result of the development of new antiplatelet agents and the outcomes of recent mechanistic studies and clinical trials, we now know that there is still a lot of work to do to get close to the perfect antiplatelet regimen, and that “one does not fit all” in terms of antiplatelet therapy. The prescription of dual antiplatelet therapy, with aspirin (75–325 mg) associated with clopidogrel (300 mg loading dose/75 mg maintenance dose) for all coronary patients can be considered as obsolete.

The first solution to avoid variability of clopidogrel response with conventional doses (300 mg/75 mg) is to increase doses in every patient, to provide a higher degree of platelet inhibition and a lower rate of HPR or non-response [11,22]. In terms of evidence-based medicine and clinical efficiency, the results of the randomized CURRENT-OASIS-7 trial now support an increase in the loading dose of clopidogrel to 600 mg and in the maintenance dose to 150 mg in acute coronary syndrome patients treated with percutaneous coronary intervention [23,24]. However, the absence of benefit in patients treated medically and the fear of bleeding complications with high doses have not yet convinced all cardiologists to change their habits.

The second solution is to provide a tailored therapy based on a platelet function test. Small-randomized studies already support the benefit of tailored therapy in the setting of percutaneous coronary intervention in patients with HPR, with either repeated loading doses of clopidogrel 600 mg [25] or the use of glycoprotein IIb/IIIa antagonists [26,27]. However, the benefit of individualized therapy based on a platelet function test will have to be confirmed in large, clinical trials, and the VerifyNow system has been chosen to demonstrate the superiority of tailored therapy in patients receiving a drug-eluting stent in the ongoing ARC-TIC (NCT00827411) and GRAVITAS (NCT006645918) studies. Recent advances in the pharmacogenetics of clopidogrel and the development of fast genetic testing (<2 h) provide the realistic prospect of a personalized choice of tailored dose adjustment for each individual patient, based on genetic and/or platelet function testing [28].

The third solution is to use new drugs, which are more potent and have less interindividual variability. Platelet inhibition can be obtained by inhibiting several platelet receptors but the P2Y12 receptor has proven to be a key target in the prevention of complications; hence, several new drugs have been developed to target the P2Y12 adenosine diphosphate receptor and obtain a high level of platelet inhibition. Some of these drugs are new thienopyridines (prasugrel and elinogrel) and some are non-thienopyridine inhibitors (ticagrelor and cangrelor). Faster onset of action will be provided by intravenous agents that do not require absorption or metabolism, such as cangrelor and elinogrel, but fast-acting oral drugs, such as ticagrelor and prasugrel, also provide faster speed and a higher level of inhibition than clopidogrel, even when using high doses (up to 900 mg) [29,30].

Two of these new drugs will soon be obtainable — prasugrel, which is already available, and ticagrelor, which is undergoing Food and Drug Administration approval — as they demonstrated better efficacy in two large, randomized trials (TRITON-TIMI 38 and PLATO) compared with classic dual antiplatelet therapy based on aspirin and clopidogrel [31,32]. Both drugs produced similar relative reductions (19% and 16%, respectively) in the primary ischaemic endpoint (death, myocardial infarction and stroke) in an acute coronary syndrome population, and even greater reductions in subgroups, such as in patients with ST-segment elevation myocardial infarction, those treated with percutaneous coronary intervention and diabetic patients, where the risk profile is higher. Additionally, ticagrelor was the third drug, after aspirin in the ISIS-2 trial and clopidogrel in the COMMIT trial, to demonstrate a significant absolute reduction in terms of mortality in acute coronary syndrome patients in a controlled study. On the safety side, progress has been less notable and several unresolved issues remain. Unfortunately, power is not always enough, and prasugrel and ticagrelor have both raised major concerns on the safety front, with constant increases in major bleeding (of 22% and 25%, respectively) observed in the main trials (at least for major, non-coronary artery bypass graft bleedings with the universal TIMI definition). This detrimental effect was not observed in certain subgroups of patients [33] and will probably lead to treatment algorithms according to age, weight, clinical presentation (ST-segment elevation vs. non-ST-segment elevation myocardial infarction) and diabetic status [34].

In conclusion, the future of antiplatelet therapy seems complex, with genetic testing, platelet function testing, tailored therapy and new, faster and stronger antiplatelet inhibitors, which will probably make our treatment decision a little more difficult; but we now have several solutions for treating clopidogrel resistance, which hopefully should ben-
eft our coronary patients, who still bear an unacceptably high risk of recurrent events.

Conflict of interest

Dr Cuisset has received consultant fees from Daiichi-Sankyo and Eli Lilly, and lecture fees from AstraZeneca, Abbott Vascular, Biotronic, Boston Scientific, Cordis, Daiichi-Sankyo, Eli Lilly, sanofi-aventis and Servier. Dr Cuyla has received research grants from Fédération Française de Cardiologie, consultant fees from Eli Lilly, Daiichi-Sankyo, Abbott Vascular and CLS Dade Behring and lecture fees from Daiichi-Sankyo, Eli Lilly, AstraZeneca, Abbott Vascular, Servier and CLS Dade Behring. Dr Silvain has received research grants from sanofi-aventis, Daiichi-Sankyo, Eli Lilly, Inserm, Fédération Française de Cardiologie and Société Française de Cardiologie, consultant fees from Daiichi-Sankyo and Eli Lilly and lecture fees from AstraZeneca, Daiichi-Sankyo and Eli Lilly.

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