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EDITORIAL COMMENT

Residual platelet activity in patients managed with clopidogrel: Clinical implications for the management of patients with acute coronary syndrome☆

Atividade plaquetar residual em doentes tratados com clopidogrel. Implicações para a orientação de doentes após sindroma coronária aguda

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Despite its recognized efficacy in the treatment of acute coronary artery disease and of patients undergoing interventional cardiology procedures, clopidogrel is far from a perfect drug. It is a thienopyridine, and its antiplatelet effect is due to irreversible inhibition of P2Y12 receptors, blocking their reactivity to ADP stimulation. Since it is a prodrug that requires two metabolic processes in the liver to produce its active form, patients present considerable variation in response and hence in levels of platelet inhibition. A high proportion do not attain adequate levels, resulting in therapeutic inefficacy; this situation has been given various names – resistance, variability, unresponsiveness – to express the idea that not all patients receive the same therapeutic benefit, which is why thrombotic phenomena can occur even in patients under antiplatelet therapy, suggesting a failure of the therapy itself.

The effect of antiplatelet drugs is influenced by multiple factors, many of them inherent to the individual patient, including a genetic component, as several polymorphisms are known to be associated with loss of drug function.

Curiously, the medical community has been far more concerned with loss of function and consequent residual platelet activity than with excessive function leading to bleeding complications.

The debate on this issue has focused on three main themes: the best laboratory test to determine platelet function, its clinical impact, and the implications for individual patient therapy.

Laboratory methodology

Several studies have been published in recent years aimed at providing a definitive answer to the question of which test, by its ease of performance and discriminatory power, is best in terms of the implications for daily clinical practice.

Various tests have been developed in the search for a simple method which can be performed at the patient's bedside but has sufficient discriminatory power to identify high-risk patients, particularly after coronary stent implantation. Light transmission aggregometry is now considered the standard test, and the bedside platelet assay known as VerifyNow is the most widely used in practice. Studies have compared the value of different tests and found considerable variation. Breet et al.[1] published an interesting study in 2010 comparing four tests in a group of 1069 patients, which demonstrated that all had a low level of accuracy in predicting risk in the 12 months following coronary stent implantation, and none was able to predict bleeding risk.

VerifyNow was used in the two largest clinical trials in this field, GRAVITAS (Gauging Responsiveness with a VerifyNow

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P2Y12 assay: Impact on Thrombosis and Safety)[2] and ADAPT-DES (clinicaltrials.gov NCT00638794), which, together with its relative ease of performance, has contributed to its popularity.

In this issue of the *Journal*, Teixeira et al.[3] analyzed the prognostic value of residual platelet activity in a small series of 70 patients treated with clopidogrel following acute coronary syndrome, with a mean follow-up of four months. A less common laboratory method was used to assess platelet function, the Multiplate system, based on impedance aggregometry, which according to the authors is simpler and avoids the need for centrifugation, since it is performed on whole blood.

This system has been tested and has shown good results compared with light transmission aggregometry.[4,5]

Clinical impact

Research on the clinical impact that such tests could have is of vital importance if they are to be incorporated into daily practice, but unfortunately this question is far from resolved. The findings of clinical trials fall short of demonstrating how useful these tests actually are. There are inherent problems in organizing trials designed to clarify the situation, the main one being that when studying populations with stable disease, the low number of events in these patients means that large-scale studies are required, which are difficult to perform.

Another problem is the total lack of knowledge concerning the value of testing in the context of acute disease, which is understandable since the acute phase carries a high thrombotic risk and requires multiple therapies, making these patient populations more difficult to study.

Therapeutic implications

Although the therapeutic implications are the most interesting aspect, here too there are no clear answers. The GRAVITAS trial again highlighted the prognostic implications for patients who do not attain adequate levels of platelet inhibition, but it remains to be demonstrated whether this information is sufficient to personalize therapy based on laboratory results.

As an alternative to functional studies, the CURRENT-OASIS 7 trial[6] tested a simpler strategy, doubling clopidogrel doses for six days, irrespective of residual platelet activity. The effort required to recruit 25 000 patients was not rewarded by the results, which were completely neutral in the overall population for the primary composite outcome of 30-day cardiovascular death, nonfatal infarction or stroke.

The therapeutic implications have also been affected by the introduction of new antiplatelet drugs with greater proven efficacy, notably prasugrel and ticagrelor, both of which have been tested against clopidogrel in two large research programs. In the TRITON TIMI 38 trial,[7] prasugrel was tested in patients following acute coronary syndrome with known coronary anatomy, who were scheduled for percutaneous coronary intervention. The PLATO trial[8] tested the new drug ticagrelor, also in patients with acute coronary syndrome, but in contrast to the prasugrel study, patients were included irrespective of whether they had been referred for percutaneous intervention.

At the same time, laboratory studies have shown the superiority of both drugs, making it clear that the problem of individual variability has been solved.[9,10] The practical consequence of this has been to consign clopidogrel to a residual role, with the new alternatives being used whenever possible and European guidelines giving them a clear preference.[11,12]

It is against this background that research efforts should be analyzed, aimed at personalizing therapy based on laboratory results.

The role of genetic studies

The identification of genetic polymorphisms that cause clopidogrel to lose its antiplatelet function opened up new prospects in the search for tailored therapy.

A recent meta-analysis[13] of nine clinical trials analyzed the role of the CYP2C19 polymorphism in predicting thrombotic risk. The presence of one reduced-function allele is sufficient to increase the risk of stent thrombosis, which is even greater if both alleles are present (hazard ratio 3.97, 95% confidence interval 1.75–9.02, $p = 0.001$).

The next step is to find genetic tests that can be performed at the bedside and give a rapid result, thus allowing prompt adjustment of therapy. This was the aim of the RAPID GENE trial,[14] which showed the ease of performing point-of-care genetic testing and how carriers of loss-of-function genes benefit from an alternative drug to clopidogrel.

The study by Teixeira et al.[3] also included genotyping, and as expected the presence of the CYP2C19*2 allele was an independent predictor of medium-term outcome, but was not a predictor of poor platelet response to clopidogrel. However, some weaker aspects of the study should be borne in mind when interpreting these results, particularly the small sample size, the patients' apparently low risk given their clinical characteristics, and the defined endpoint, which included unstable angina but not other thrombotic events such as stent thrombosis and stroke.

Conclusion

The problem of varying response to clopidogrel still warrants further clinical trials, but so far all point in the same direction. Platelet reactivity under therapy is a strong risk marker, but it remains to be seen whether modifying this lack of response has a favorable impact on prognosis. There are thus still insufficient reasons to include platelet function tests in clinical practice, except in individual cases or for research purposes.

One thing that is now certain, as reflected in European guidelines, concerns the use of the new antiplatelet drugs prasugrel and ticagrelor, at least in high-risk patients. In the light of current knowledge, they are the only effective way to solve the problem of unresponsiveness to clopidogrel, thus avoiding the need for platelet function tests or genotyping, which are of doubtful clinical value. The differences and similarities between the three antiplatelet drugs have been clearly defined[15] and there is strong evidence that the new drugs, when used as recommended, are superior

to clopidogrel, with a more predictable and homogeneous response that is not affected by genetic factors.[16,17]

Conflict of interest

João Morais was a member of the PLATO trial steering committee, is currently the Portuguese national coordinator of the ACCOAST study and was the lead researcher for the TRILOGY trial. He receives fees for consulting and participating in scientific meetings on antithrombotic therapy (Astra Zeneca, Bayer Health Care, BMS/Pfizer, Lilly/Daiichi Sankyo, and MSD).

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