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EDITORIAL COMMENT

Clopidogrel Resistance

More Grist for the Mill*

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Clopidogrel has similar efficacy as aspirin for the prevention of thrombotic vascular events among patients with atherosclerotic vascular disease (1) and is a suitable alternative for those with aspirin intolerance or allergy. When added to aspirin, clopidogrel reduces the incidence of thrombotic vascular outcomes among patients with acute coronary syndromes (2–4) and those undergoing percutaneous coronary intervention (PCI) (5–7). Given the wide prevalence of atherosclerotic vascular diseases and the high event rates, efforts are widespread to improve upon the therapeutic effectiveness of clopidogrel. The observation that many patients have less than expected platelet inhibition with clopidogrel has given rise to the concept of clopidogrel resistance and research to identify and overcome the phenomenon (8).

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The occurrence of a cardiovascular event in a patient prescribed clopidogrel may be designated as a treatment failure, which could result from noncompliance, one or more of the many pathophysiological mechanisms of such events that are independent of clopidogrel's specific platelet inhibition, or from inadequate clopidogrel response. Response variability can occur because of differences in pretreatment platelet function (e.g., as in advancing age, diabetes mellitus, or accelerated platelet turnover) (8) or because of clopidogrel resistance. The latter term should be reserved for situations in which there is incomplete blockade of the platelet membrane $P2Y_{12}$ receptor in a patient who is compliant with clopidogrel therapy. Reliable and valid laboratory assessment of platelet inhibition is dependent upon the baseline platelet reactivity and the choice of platelet agonist and anticoagulant (9). Standardization of methods and high cost remain challenges, as does ensuring that the chosen method is a specific measure of the degree of $P2Y_{12}$ blockade. Light-transmission aggregometry (LTA) has many shortcomings, even when adenosine diphosphate (ADP) is used as the agonist. The platelet vasodilator-stimulated phosphoprotein-phosphorylation assay using flow cytometry may be the most specific available technique (9).

Clopidogrel resistance may result from individual variation in clopidogrel's absorption, metabolism, and combination with its specific platelet receptor. There is substantial variability in the speed and degree of absorption (7). Clopidogrel is a thienopyridine prodrug, which is converted to its active metabolite by several enzymes of the P450 family, including CYP3A4 and CYP2C19 (10). The active metabolite combines irreversibly with the platelet membrane $P2Y_{12}$ ADP receptor, thereby inhibiting this pathway of platelet activation, but leaving the $P2Y_1$ ADP receptor unaffected (9). Drug–drug competition for CYP3A4 can decrease the production of the clopidogrel metabolite (8), as may polymorphisms of the CYP3A4 gene (10). The loss-of-function CYP2C19*2 single nucleotide polymorphism, occurring as either a hetero- or homozygote allele, reduces the conversion of clopidogrel to its active metabolite, and appears to be an important determinant of diminished antiplatelet effect (10,11). Achievement of optimal platelet inhibition occurs only after several days of a maintenance dose of 75 mg/day, but is achieved more rapidly with an oral loading dose (600 mg is more effective than 300 mg, and 900 mg may be more effective) (12). Genetic variations in the $P2Y_{12}$ receptor may alter the therapeutic effectiveness of clopidogrel, although conflicting results have been published (8).

In this issue of the *Journal*, Trenk et al. (13) present the results of a pre-planned substudy of their previously published EXCELSIOR (Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rate) study (14), in which they studied 802 consecutive patients undergoing elective PCI and stent placement. Patients were given clopidogrel (600 mg pre-PCI, then 75 mg/day maintenance) and their residual platelet aggregation (RPA) was measured at baseline and immediately pre-PCI. The median RPA pre-PCI was 14%. The adjusted odds ratio for the composite of death, myocardial infarction (MI), or target lesion revascularization at 30 days among patients whose RPA was above the median of 14% was 9.6 ($p = 0.004$) compared with those whose RPA was below the median. In the present report, 765 patients from the original cohort were grouped according to pre-discharge RPAs above and below 14%. The adjusted hazard ratio (HR) for death or MI occurring between discharge and 1 year was 3.7 ($p = 0.004$), comparing those with RPA >14% to those below. The difference in outcomes was accounted for primarily by the 281 patients with a drug-eluting stent (DES), among whom the HR for death or MI was 7.8 ($p = 0.004$) comparing those with RPAs above

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and below 14%. The analogous HR in the patients with a bare-metal stent was 2 ($p = 0.13$).

Using the EXCELSIOR cohort, the authors set out to determine whether the loss-of-function CYP2C19*2 polymorphism is associated with high RPA after the administration of clopidogrel. They measured RPA in citrated blood, drawn before clopidogrel (baseline), before PCI (at least 2 h post-600 mg clopidogrel load), and before hospital discharge (after at least 1 maintenance dose of clopidogrel 75 mg/day). Platelets were stimulated using ADP (at 5 and 20 μmol/l), with RPA determined by LTA at 5 min and expressed as both absolute and relative inhibition compared with baseline. Before PCI, RPA was inhibited by a mean of 74.2% in the *1/*1 wild-type homozygotes, but only by 51.6% in the *2 allelic variant group ($p < 0.001$). At hospital discharge, the mean inhibitions of RPA were, respectively, 83.7% and 74.5% ($p < 0.001$); this reduced difference suggests the rate of metabolic conversion is the primary mechanism of differences in RPA. Surface protein expression of a number of markers of platelet activation after stimulation by ADP 20 μmol/l was reduced pre-PCI and pre-discharge, more so in the *1/*1 group than in the *2 allelic variant group. There were no differences in baseline RPA or surface marker expression, ruling out this important source of variability (7).

The authors were unable to determine if the *2 allelic variant is predictive of death or MI. The incidence at 1 year was 3.4% among the *1/*1 homozygotes compared with 2.0% among the *1/*2 heterozygotes ($p = 0.372$). Among the patients with at least 1 DES, the incidence of death or MI was 2.1% among the homozygotes and 3.3% among the carriers. The rates of these events were low, and there was insufficient power to detect modest but still important differences between the groups, although it might have been helpful to look at the overall incidence of death or MI from the PCI to 1 year.

Do these observations enhance our understanding of clopidogrel resistance? Do they provide new approaches to patient management? Do they open new avenues of research? The observations of the predictive value of high RPA after clopidogrel therapy for subsequent thrombotic events extend the short-term observations of the EXCELSIOR study (14) and confirm those made in other sizeable studies (15,16). However, for the present, the clinical utility of the observations is minimal. The determination of RPA by LTA is a complex test with considerable variability from one laboratory to another, and it is not specific for clopidogrel's blockade of the $P2Y_{12}$ receptor (9). The clinician needs a rapid, inexpensive, reliable, and specific test for the pre-PCI assessment of short- and long-term risk. A finding of high short-term risk might prompt the addition of an intravenous glycoprotein IIb/IIIa inhibitor during the procedure. A finding of high long-term risk (perhaps those patients with the highest RPAs and those receiving a DES) might prompt raising clopidogrel dose or using prasugrel, a more potent thienopyridine with less response variability (17). Prasugrel has a greater overall risk of bleeding, but if patients with relatively high clopidogrel resistance could be identified, it is conceivable that substituting prasugrel might increase efficacy without substantially increasing bleeding. Clinical trials of various management strategies incorporating assessments of platelet inhibition are required to sort out the options for patients with apparent clopidogrel resistance. For the present, professional societies recommend that platelet function assessment be confined to research studies. New drugs such as AZD6140 and cangrelor, which directly target the $P2Y_{12}$ receptor and are reversible, may provide options with less response variability than clopidogrel, obviating complex and expensive assessments of platelet reactivity (18).

The observations of greater RPA among the carriers of the *2 allelic variant provide extensive new data on the impact this loss-of-function single nucleotide polymorphism has on clopidogrel's platelet inhibition. The effect in heterozygotes is a reduction and slowing of clopidogrel action. Additional experiments are required to clarify whether a higher loading dose and/or longer-term administration of clopidogrel might lead to greater inhibition of residual platelet reactivity. Measurements of the clopidogrel metabolite would also help to clarify the mechanism of reduced inhibition. The mean RPA of the carriers of the *2 allele is higher than that of the *1/*1 homozygotes, but there is extensive overlap of the values in the 2 groups. Therefore, even if the genotyping could be accomplished at reasonable speed and cost, intensification of antithrombotic therapy might subject many *2 patients to unnecessary bleeding risk, and more intense therapy would be denied to many among the *1/*1 homozygotes with relatively high RPA. The clinical importance of the observations will remain uncertain unless a clear relationship can be established between the presence of the allelic variant and increased thrombotic vascular events.

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