Cilostazol is an inhibitor of phosphodiesterase type III in both platelet and vascular smooth cells with the potential for inhibition of platelet aggregation and proliferative vessel response to coronary stent implantation (1,2).

Studies have shown that adjunctive cilostazol to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention (PCI) may decrease late restenosis and enhance inhibition of adenosine diphosphate (ADP)-induced platelet aggregation, providing a rationale for triple antiplatelet therapy (3–5). The appealing hypothesis that triple antiplatelet therapy may provide more profound platelet aggregation inhibition and, at the same time, less hyperplastic vessel wall response to stent implantation was examined in this issue of the Journal by the CILON-T (Influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent im- plantation) trial investigators in a large cohort of all-comer patients receiving coronary drug-eluting stents (DES) who were randomized to dual or triple antiplatelet therapy (6).

The primary end point of the study, based on the dual effect of cilostazol, was a composite of acute atherothrombotic events and late ischemic events (death, myocardial infarction, stroke, and target vessel revascularization). The secondary end point focused on platelet aggregation inhibition as assessed by VerifyNow P2Y12 assay (Accumetrics, San Diego, California) at discharge, and a poor platelet reactivity to clopidogrel or clopidogrel plus cilostazol was an independent predictor of the primary end point (hazard ratio: 1.61 for every increase in tertile).

This finding is consistent with the results of previous studies on responsiveness in vitro to clopidogrel (7–10).

High residual platelet reactivity on dual antiplatelet treatment is frequent and associated with high risk of thrombotic events in patients receiving coronary DES. The pharmacodynamic response to clopidogrel has a high inter-patient variability. The mechanisms leading to a decreased effect of clopidogrel on platelet aggregation inhibition are multifactorial and include high baseline value of platelet aggregation, diabetes, high body mass index, decreased intestinal absorption, and hepatic activation (11–13). Moreover, variation in platelet function in response to clopidogrel has been associated with interference from other drugs such as statins, proton pump inhibitors, and calcium-channel blockers.

Decreased intestinal absorption and hepatic activation of the drug are affected by genetic polymorphisms that are under intensive investigation (11–13), and it seems unlikely that clopidogrel resistance in patients with genetic polymor-phism can be overcome by increasing the dose of the drug.

Most patients who exhibit high residual platelet reactivity after a 600-mg loading dose of clopidogrel have no or mild improvement of platelet aggregation inhibition with in-
creasing the dose of the drug. In a study based on a series of 215 patients undergoing DES-supported PCI for unprotected left main disease, poor responsiveness to 600-mg clopidogrel loading was the only independent predictor of late cardiac mortality and definite stent thrombosis: clopido
grel nonresponders had a nearly 4-fold increase in the risk of stent thrombosis and cardiac death as compared with clopidogrel responders (14). Patients who were nonre-
sponders to a 600-mg loading dose of clopidogrel at the first in vitro test were prescribed 150 mg daily of the drug or shifted to ticlopidine, and repeat measurement of platelet reactivity after therapeutic adjustments showed some im-
provement in platelet aggregation inhibition in only 36% of patients (14). Similar results in terms of persistent high residual platelet reactivity after increasing the dose of clopidogrel were reported by Pena et al. (15) in a series of 7 patients who suffered stent thrombosis.

Concluded small trials using a double dose of clopidogrel or a standard dose of clopidogrel plus cilostazol have not provided a definite answer about the possibility of achieving more appropriate platelet aggregation inhibition and better clinical outcome in patients undergoing PCI (16–18). However, with the available data, including also the CILON-T trial results, it is unlikely that triple antiplatelet therapy will overcome clopidogrel resistance.

It is still unknown whether more potent antiplatelet agents, such as prasugrel or ticagrelor, that provide a more predictable in vitro platelet aggregation inhibition (19,20) will replace clopidogrel in all patients receiving DES. Again, it is still unknown whether nonresponsiveness to clopidogrel will remain a marker of increased risk of DES thrombosis and more generally of thrombotic events also using new antiplatelet agents.

In the meantime, the possibility to tailor effectively the antiplatelet therapy under the guidance of in vitro tests should be considered as an attractive option.

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