

## EDITORIAL COMMENT

## No Role for Triple Antiplatelet Therapy?\*

David Antoniucci, MD

Florence, Italy

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).

See page 280

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 implantation) 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 at 6 months.

There was no difference between groups in the rate of the primary end point (8.5% in the triple antiplatelet therapy and 9.2% in the dual antiplatelet therapy), and as expected, target vessel revascularization was the most frequent event of the primary end point (6.6% and 7.2%, respectively). Thus, in patients receiving DES, cilostazol had no effect on the risk of clinically driven target vessel revascularization

due to restenosis. This study result is not consistent with the results of 2 trials comparing triple antiplatelet therapy with dual antiplatelet therapy in patients at high risk of restenosis, such as patients with diabetes (DECLARE [Drug-Eluting stenting followed by Cilostazol treatment reduces Late REstenosis]–Diabetes trial) and patients with long lesions (DECLARE-Long trial) (4,5).

Both studies showed a decrease in angiographic late loss in patients randomized to adjunctive cilostazol. This difference was associated with a better clinical outcome due to a decreased rate of repeat revascularization. With the available data from the CILON-T, the DECLARE-Diabetes, and the DECLARE-Long trials, it is not possible to explain these contradictory results. However, considering that all 3 studies were open-label designed, used first-generation DES, had a short clinical follow-up, and that, at best, cilostazol may provide a reduction in late loss with an order of magnitude of approximately 0.10 mm, it seems unlikely a significant role of this drug for the prevention of restenosis with the last-generation DES.

With regard to platelet aggregation inhibition, the CILON-T study confirmed that triple antiplatelet treatment is associated with an increased platelet reactivity inhibition as compared with standard antiplatelet treatment, but this effect did not translate into any clinical benefit. However, a substantial percentage of patients randomized to triple antiplatelet therapy had still a high residual platelet reactivity as assessed by VerifyNow at discharge, and a poor platelet response 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 in patients receiving DES (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 polymorphism 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-

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiology, Careggi Hospital, Florence, Italy. Dr. Antoniucci has reported that he has no relationships to disclose.

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: clopidogrel 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 nonresponders 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 improvement 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.

---

**Reprint requests and correspondence:** Dr. David Antoniucci, Division of Cardiology, Careggi Hospital, Viale Morgagni I-50139, Florence, Italy. E-mail: [david.antoniucci@virgilio.it](mailto:david.antoniucci@virgilio.it).

---

#### REFERENCES

1. Pan X, Arauz E, Krzanowski JJ, Fitzpatrick DF, Polson JB. Synergistic interactions between selective pharmacological inhibitors of phosphodiesterase isozyme families PDE III and PDE IV to attenuate proliferation rate of vascular smooth muscle cells. *Biochem Pharmacol* 1994;48:827-35.
2. Goto S. Cilostazol: potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding. *Atheroscler Suppl* 2005;6:3-11.
3. Lee BK, Lee SW, Park SW, et al. Effects of triple antiplatelet therapy with aspirin, clopidogrel and cilostazol on platelet aggregation and P-selectin expression in patients undergoing coronary artery stent implantation. *Am J Cardiol* 2007;100:610-4.
4. Lee SW, Park SW, Kim YH, et al. Comparison of triple versus dual antiplatelet therapy after drug-eluting stent implantation (from the DECLARE-Long trial). *Am J Cardiol* 2007;100:1103-8.
5. Lee SW, Park SW, Kim YH, et al. Drug-eluting stents followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus: the DECLARE-Diabetes trial (a randomized comparison of triple antiplatelet therapy with dual antiplatelet therapy after drug-eluting stent implantation in diabetic patients). *J Am Coll Cardiol* 2008;51:1181-7.
6. Suh J-W, Lee S-P, Park K-W, et al. Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the CILON-T (Influence of Cilostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation) trial. *J Am Coll Cardiol* 2011;57:280-9.
7. Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007;49:2312-7.
8. Gurbel PA, Becker RC, Mann KG, Steinhubl SR, Michelson AD. Platelet function monitoring in patients with coronary artery disease. *J Am Coll Cardiol* 2007;50:1822-34.
9. Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J* 2008;29:992-1000.
10. Marcucci R, Gori AM, Panizza R, et al. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12 month follow-up. *Circulation* 2009;119:237-42.
11. Simon T, Verstuyft C, Murielle M-K, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-75.
12. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA* 2009;302:849-57.
13. Angiolillo DJ, Alfonso F. Platelet function testing and cardiovascular outcomes: steps forward in identifying the best predictive measure. *Thromb Haemost* 2007;98:707-9.
14. Migliorini A, Valenti R, Marcucci R, et al. High residual platelet reactivity after clopidogrel loading and long-term clinical outcome after drug-eluting stenting for unprotected left main coronary disease. *Circulation* 2009;120:2214-21.
15. Pena A, Collet J-P, Hulot J-S, et al. Can we override clopidogrel resistance? *Circulation* 2009;119:2854-7.
16. Jeong Y-H, Lee S-W, Choi B-R, et al. Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity. *J Am Coll Cardiol* 2009;53:1101-9.
17. Jeong Y-H, Kim I-S, Park Y, et al. Carriage of cytochrome 2C19 polymorphism is associated with risk of high post-treatment platelet reactivity on high maintenance-dose clopidogrel of 150 mg/day: results of the ACCEL-DOUBLE (Accelerated Platelet Inhibition by a Double Dose of Clopidogrel According to Gene Polymorphism) study. *J Am Coll Cardiol Interv* 2010;3:731-41.
18. Jeong Y-H, Hwang J-Y, Kim I-S, et al. Adding vilostazol to dual antiplatelet therapy achieves greater platelet inhibition than high maintenance dose clopidogrel in patients with acute myocardial infarction: results of the adjunctive cilostazol versus high maintenance dose clopidogrel in patients with AMI (ACCEL-AMI) study. *Circ Cardiovasc Interv* 2010;3:17-26.
19. Wiviott SD, Trenk D, Frelinger AL, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial. *Circulation* 2007;116:2923-32.
20. Gurbel PA, Bliden KP, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: the RESPOND study. *Circulation* 2010;121:1188-99.

---

**Key Words:** cilostazol ■ DES ■ platelet reactivity.