A large proportion of patients with coronary artery disease treated with elective percutaneous coronary intervention have high residual platelet reactivity and endothelial dysfunction, which might represent the link to the occurrence of ischemic events. This is even more the case for patients with diabetes mellitus, in whom more potent P2Y₁₂ receptor inhibitors have been proposed with promising results in terms of reduced platelet reactivity. Nevertheless, whether this enhanced platelet inhibition also might be beneficial to the endothelial function is yet unknown.

CLOTILDIA (Clopidogrel High Dose Versus Ticagrelor for Antiplatelet Maintenance in Diabetic Patients) was a single-center, prospective, randomized, open label, crossover study, enrolling patients with type 2 diabetes mellitus and stable coronary artery disease treated with percutaneous coronary intervention and drug-eluting stent implantation. Patients were recruited at least 1 month after percutaneous coronary intervention (3.8±2.1 months), while they were still on dual-antiplatelet therapy with aspirin (100 mg/d) and clopidogrel (75 mg/d). At study entry (T0), with the use of a computer-based randomization system, patients were assigned randomly to receive either 90 mg ticagrelor twice daily or clopidogrel 150 mg once daily for 14 days. On day 15 (T1), a crossover was performed to the alternate therapy for an additional 14 days (until T2). At each time point (T0, T1, and T2), all patients underwent ultrasound-based measurement of brachial artery reactivity (including flow-mediated dilation [FMD] and nitroglycerin-mediated dilation [NMD]), and platelet function testing using the VerifyNow P2Y₁₂ assay (Accumetrics).

A total of 42 patients were enrolled in this study; 21 were assigned randomly to receive ticagrelor, and 21 were assigned randomly to receive high-dose clopidogrel. Baseline characteristics were similar in the 2 groups. Values of FMD and NMD at the 3 study time points are shown in the Figure. At T0, no significant differences in FMD and NMD were observed between the 2 groups (FMD, 10.0±4.2% versus 9.7±3.4%, P=0.867; NMD, 12.3±3.3% versus 12.3±3.5%, P=0.968). From T0 to T1, both study groups showed a significant increase in FMD (ticagrelor, P<0.001; high-dose clopidogrel, P=0.049) and NMD (ticagrelor, P<0.001; high-dose clopidogrel, P=0.034). Yet, at T1 patients who received ticagrelor had significantly higher values of both FMD and NMD values than patients who received high-dose clopidogrel (FMD, 16.0±4.4% versus 12.0±3.6%, P=0.009; NMD, 18.8±3.8% versus 15.1±4.5%, P=0.043). From T1 to T2, although a significant decrease was observed in brachial artery reactivity indexes switching from ticagrelor to high-dose clopidogrel (FMD, P<0.001; NMD, P=0.003), a significant further increase was observed crossing over from high-dose clopidogrel to ticagrelor in both FMD (P<0.001) and NMD (0.009). At T2, patients who received ticagrelor in comparison with patients who received high-dose clopidogrel showed significantly higher values of FMD (17.2±5.4% versus 11.2±4.4%, P<0.001) and NMD (18.6±6.4% versus 13.5±5.9%, P=0.020). At the end of the study drug assignment period, both FMD and NMD values were significantly higher with ticagrelor in comparison with high-dose clopidogrel (FMD, 16.6±4.8% versus 10.0±4.2%, P=0.001; NMD, 18.6±6.4% versus 12.3±3.5%, P=0.001).

Correspondence to: Fabio Mangiacapra, MD, PhD, Unit of Cardiovascular Science, Department of Medicine, Università Campus Bio-Medico di Roma, Via Álvaro del Portillo, 200-00128 Rome, Italy. E-mail f.mangiacapra@unicampus.it

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versus 11.6±3.9%, P<0.001; NMD, 18.7±5.2% versus 14.8±4.5%, P=0.007). On the other hand, ticagrelor resulted overall in significantly lower platelet reactivity (28±31 versus 116±58 P2Y12 reaction units, P<0.001) and higher platelet inhibition (87±15% versus 51±22, P<0.001) in comparison with high-dose clopidogrel.

The interaction between platelets and endothelium is well established, and so is the potential benefit that antplatelet drugs exert on the arterial wall, independent of platelet inhibition.2 Clopidogrel, a thienopyridine irreversibly blocking ADP P2Y12 receptor, is able to increase the endothelial cell production of nitric oxide, with an attendant dose-dependent improvement in endothelial function. Ticagrelor is an allosteric antagonist of ADP and, contrary to clopidogrel, reversibly blocks P2Y12 receptor. Torngren et al5 observed that, in patients with a previous acute coronary syndrome, those treated with ticagrelor had significantly better endothelial function than patients on clopidogrel or prasugrel. A possible mechanistic explanation for the improved vasoreactivity achieved with ticagrelor might relate to the increased adenosine availability obtained through the inhibition of adenosine cell uptake and the increased ATP release from human red blood cells.6 Both mediators are in fact able to induce vasodilation: adenosine mediates relaxation of smooth muscular cells, whereas ATP promotes the release of nitric oxide, endothelial hyperpolarization factor, and prostacyclins from the endothelium. Moreover, it has been shown that ticagrelor is able to enhance vasodilation response to adenosine. Finally, another possible mechanism for these off-target effects of ticagrelor could relate to the expression of P2Y12 receptors on vascular smooth muscle cells.

Despite limitations including relatively small sample size, short duration, no washout period between different study phases, and uncertain clinical correlation of changes in these arterial measures, the results of the CLOTILDA study suggest for the first time that, in patients with type 2 diabetes mellitus and stable coronary artery disease treated with percutaneous coronary intervention, antiplatelet therapy with ticagrelor versus high-dose clopidogrel, in addition to aspirin, is able to provide, besides more profound platelet inhibition, a significant improvement in endothelial function and endothelium-independent brachial artery reactivity. Additional studies are warranted to explore the clinical impact of these findings and weigh the opportunity to extend the use of ticagrelor also to patients with stable coronary artery disease who are at high risk, such as those with diabetes mellitus.

**DISCLOSURES**

None.

**AFFILIATIONS**

From Unit of Cardiovascular Science, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy (F.M., E.P., I.C., E.R., G.D.S.); Unit of Endocrinology and Diabetes, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy (A.L.P., P.P.); Cardiovascular Research Center Aalst, OLV Hospital, Aalst, Belgium (E.B.); and Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy (E.B.).

**FOOTNOTES**

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Fabio Mangiacapra, Elena Panaioli, Iginio Colaiori, Elisabetta Ricottini, Angelo Lauria Pantano, Paolo Pozzilli, Emanuele Barbato and Germano Di Sciascio

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