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Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of Ticagrelor *versus* Clopidogrel in patients with stable coronary artery disease. The ONSET/OFFSET study

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Ticagrelor (formerly AZD 6140) is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel according to the laboratory tests. Although the clinical efficacy of ticagrelor has been studied extensively in PLATO, a comprehensive characterization of its antiplatelet onset and offset effect profile in a statistically powered comparison with clopidogrel has not been conducted in patients with coronary artery disease (CAD). Moreover, ticagrelor has not been compared with high-loading-dose clopidogrel in patients. Therefore, the present study was designed to determine the onset and offset of the antiplatelet effect of ticagrelor with the PLATO trial dose compared with high-loading-dose clopidogrel and placebo in stable CAD patients given background aspirin therapy. ❑

Study design

The ONSET/OFFSET study was a multicenter, randomized, double-blind, double-dummy, parallel-group study. The total duration of the study was about 10 weeks and the goal was 50 patients per treatment group (ticagrelor 180 mg loading dose and 90 mg daily, clopidogrel 600 mg loading dose and 75 mg daily and placebo). Samples for platelet function testing were taken at predosing (0 hour) and after the first dose of study drug on visit 2, then throughout the onset period (0.5 to 24 hours after the first loading dose), at the start of the offset period (0 hour, visit 4), and throughout the 10-day offset period. ❑

Results

Fifty-two patients in the ticagrelor group, 51 in the clopidogrel group, and 11 in the placebo group completed the study. The primary end

point for onset, platelet inhibition (IPA) at 2 hours after loading (20 μmol/L ADP, final extent) was greater for ticagrelor than for clopidogrel (88% versus 38%, P<0.0001).

IPA was higher at 0.5 hours after loading with ticagrelor (41% versus 8%, P<0.0001) and at all times in the first 24 hours after loading and in the maintenance phase (P<0.0001); within 1 hour of ticagrelor loading, IPA was greater than the maximum IPA achieved after clopidogrel loading. In the ticagrelor group, IPA did not differ between 2 and 8 hours after loading, whereas in the clopidogrel group, IPA was greater at 8 hours than at 2 hours (P=0.02). The mean time to maximum IPA in the ticagrelor group was 5.8 hours less and the area under the effect curve from 0 to 8 hours after loading (20 μmol/L ADP, final extent) was higher than in the clopidogrel group By 2 hours after loading, a greater proportion of patients achieved >50% IPA (98% versus 31%, P<0.0001) and >70% IPA (90% versus 16%, P<0.0001) in the ticagrelor group than in the clopidogrel group, respectively.

Concordant results were observed with the final and maximum extent of platelet aggregation. At the end of the 6 weeks of treatment, IPA (20 μmol/L ADP, final extent) was significantly higher in the ticagrelor group than in the clopidogrel group (P<0.0001); however, IPA did not differ between the groups at 24 and 48 hours after the last dose. IPA for ticagrelor on day 3 after the last dose was comparable to that for clopidogrel at day 5; IPA on day 5 for ticagrelor was similar to clopidogrel on day 7 and did not differ from placebo (P=NS). Bleeding-related events occurred more frequently in the ticagrelor group (28.1%) than in the clopidogrel (13.0%) and placebo (8.3%) groups. Three patients in the ticagrelor group stopped the study drug owing to dyspnea. ❑

Conclusion

Ticagrelor achieved more rapid and greater platelet inhibition than high-loading-dose clopidogrel in patients with stable CAD. This inhibition was sustained during the maintenance phase and was faster in offset than clopidogrel. These effects may explain why ticagrelor treatment in the PLATO trial was associated with a lower occurrence of the primary end point than seen with clopidogrel therapy, whereas no difference in coronary artery bypass graft–related bleeding occurred between the 2 groups. ❑

Comment on a paper:
Paul A Gurbel, MD; Kevin P Bliden, BS; Kathleen Butler, MD et al – Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of Ticagrelor versus Clopidogrel in patients with stable coronary artery disease. The ONSET/OFFSET Study. *Circulation* 2009; 120:2577-2585