Ticagrelor monotherapy beyond 1 month versus standard dual antiplatelet therapy after drug-eluting coronary stenting: a pre-specified per-protocol analysis of the GLOBAL LEADERS trial

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Background: In the GLOBAL LEADERS trial, the intention-to-treat (ITT) effect of ticagrelor monotherapy after 1 month of dual antiplatelet therapy (DAPT) was not superior to that of 12-month DAPT followed by aspirin alone in the prevention of 2-year all-cause mortality or new Q-wave myocardial infarction (MI) after coronary stenting. Intention-to-treat analyses can be affected by incomplete protocol adherence. We present a pre-specified per-protocol analysis.

Purpose: To determine whether 1 month of ticagrelor plus aspirin followed by 23 months of ticagrelor monotherapy is superior to 12 months of DAPT followed by aspirin alone in the per-protocol population of the GLOBAL LEADERS (NCT01813435).

Methods: The GLOBAL LEADERS compared two antiplatelet strategies after drug-eluting stenting for stable coronary artery disease or acute coronary syndromes. Per-protocol population consisted of randomized patients fulfilling enrollment criteria and receiving protocol-mandated treatment. Adherence to the allocated antiplatelet therapy was evaluated at discharge, 30 days, and 3, 6, 12, 18, and 24 months, with non-adherence reasons categorized following a hierarchical approach. A protocol-deviation was defined in the case of high perceived bleeding/thrombotic risk, a medical decision without evident clinical reason, patients unwilling to take study drugs, prescription error, logistical issues, unclear reasons. Baseline characteristics, including (but not limited to) age, sex, diabetes, prior PCI, were used to construct time-varying inverse probabilities for not deviation from the protocol to reconstruct a study population with no protocol-deviations. Protocol deviators were artificially censored at the time at which they deviated. The primary endpoint was the composite of 2-year all-cause mortality or non-fatal new Q-wave MI. We used a weighted pooled logistic regression to estimate the per-protocol rate ratio (RR) of experimental vs. control treatment for the primary endpoint.

Results: Of the 15,968 randomized patients, 805 out of 7,980 (10.1%) in experimental group and 537 out of 7,988 (6.7%) in control group were classified as protocol deviators and artificially censored by month 12, not contributing events in the second year. The events for the adherence-adjusted analysis were 279 in experimental group and 325 in control group (25 and 24 less than in ITT analysis, respectively). The estimated adherence-adjusted RR was 0.87 (95% CI: 0.74–1.02; p=0.09), comparable to the ITT RR (0.87; 95% CI: 0.75–1.01; p=0.07).

Conclusion: At per-protocol analysis, ticagrelor monotherapy after 1 month of DAPT was not superior to conventional treatment, in line with the previously reported ITT effect. Similar per-protocol and ITT effects can be accounted for similar per-protocol and ITT populations, as a substantial proportion of patients were non-adherent due to clinically grounded reasons (anticipated in the protocol) and, accordingly, not considered as protocol deviators.