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Dyspnea in ticagrelor treated patients in the all-comer randomized GLOBAL LEADERS study and its association with clinical outcomes

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Funding Acknowledgement: Study founded by European Cardiovascular Research Institute, which received unrestricted grants from Biosensors Int., AstraZeneca, Medicines Company.

Background: Dyspnea represents a drug adverse effect reported with a higher frequency for ticagrelor, as compared with other P2Y12 antagonists. The impact of dyspnea on clinical outcomes has not been yet evaluated in the context of aspirin-free therapies after percutaneous coronary intervention (PCI).

Purpose: The study aimed to evaluate the incidence of dyspnea and its associations with demographic characteristics and clinical outcomes in patients undergoing PCI treated with ticagrelor either as monotherapy or as a part of a dual antiplatelet therapy (DAPT) in the GLOBAL LEADERS cohort.

Methods: This is a sub-analysis of the randomized all-comer GLOBAL LEADERS study (n=15991), comparing the experimental strategy of ticagrelor monotherapy following one-month DAPT after PCI with the reference strategy of 12-month DAPT followed by 12-month aspirin monotherapy. The incidence of dyspnea reported as adverse event (AE) and its relation to demographic characteristics and 2-year clinical outcomes was evaluated (intention-to-treat analysis). Multivariable Cox proportional hazards models were performed, including randomized treatment and incidence of first dyspnea event as a time-dependent covariate. The primary endpoint was a composite of 2-year all-cause mortality or centrally adjudicated, new Q-wave myocardial infarction (MI). Patient-oriented clinical endpoints (POCE) comprised all-cause death, any stroke, MI or revascularization, whereas net adverse clinical events (NACE) included POCE and Bleeding Academic Research Consortium (BARC)-defined bleeding type 3 or 5.

Results: Overall, dyspnea was reported as an AE in 2101 patients (13.2%) up to two years of follow-up, with a higher frequency in the experimental arm (16.4%) as compared with the reference group (11.1%) (hazard ratio [HR]1.70, 95% confidence interval [CI] 1.56–1.86, p=0.001).

Predictors of dyspnea AE up to 2 years by multivariate analyses were: chronic obstructive pulmonary disease (HR1.71, 95% CI 1.56–1.87, p=0.001), female gender (HR1.31, 95% CI 1.18–1.44, p=0.001), hypertension (HR1.31, 95% CI 1.19–1.44, p=0.001, prior coronary artery bypass grafting (HR1.30, 95% CI 1.10–1.54, p=0.003), left ventricle ejection fraction below 40% (HR1.22, 95% CI 1.04–1.42, p=0.012), presentation with acute coronary syndrome (HR1.19, 95% CI 1.09–1.29, p=0.001) and body mass index ($\geq$27kg/m^2) (HR1.17, 95% CI 1.08–1.28, p=0.001).

In patients who reported dyspnea AE, the two-year rates of the efficacy and safety endpoints in the experimental and reference arm were: for the primary endpoint 3.4% vs. 4.3% (p adjusted=0.807), for POCE 15.8% vs. 17.6% (p adjusted=0.218), for NACE 17.2% vs. 19.6% (p adjusted=0.082), for BARC 3 or 5 type bleeding 17.2% vs. 19.6% (p adjusted=0.082), respectively.

Conclusions: The occurrence of dyspnea AE up to two years after PCI appeared not to affect the safety of the experimental treatment strategy of 23-month ticagrelor monotherapy following one-month DAPT after PCI.