Abstract: P1226

Very low achieved low-density lipoprotein cholesterol level with alirocumab treatment after acute coronary syndrome: ODYSSEY OUTCOMES

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Background: Recent guidelines for cholesterol management recognize uncertainty regarding long-term efficacy and safety of prolonged very low levels of LDL-C on treatment with a PCSK9 inhibitor, including risk of new-onset diabetes. ODYSSEY OUTCOMES used a treat-to-target approach to demonstrate reduction of coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke, or unstable angina (MACE) with the PCSK9 inhibitor alirocumab (ALI) vs placebo (PBO) in 18,924 patients with recent acute coronary syndrome and elevated LDL-C despite intensive statin therapy. ALI was blindly adjusted (75 or 150 mg dose) to target LDL-C 0.6-1.3 mmol/L (25-50 mg/dL). To avoid sustained very low LDL-C, blind substitution of PBO for ALI was intended if 2 consecutive LDL-C levels were <0.39 mmol/L (15 mg/dL). Patients were followed for median of 2.8 years (maximum of 5 years).

Purpose: We report the efficacy and safety of ALI in patients who reached very low LDL-C (consecutively <0.39 mmol/L), compared with matched patients from the PBO group.

Methods: Of 9462 patients randomized to receive ALI, 730 (7.7%) reached very low LDL-C and had substitution of PBO a median 8.3 months after randomization. Using propensity score matching, they were compared (3:1) with 2152 patients initially assigned to PBO. Propensity score matching was also used to compare the incidence of new-onset diabetes in 525 patients without diabetes at baseline who had very low LDL-C levels on ALI with 1675 matched patients in the PBO group. Neurocognitive events and haemorrhagic stroke were also evaluated in relation to very low LDL-C.

Results: Overall, ALI reduced the incidence of MACE (9.5% vs 11.1%; HR 0.85, 95% CI 0.78-0.93; P<0.001). Characteristics used in propensity score matching (and associated with very low LDL-C on ALI) included sex (male), diabetes (present), baseline LDL-C and lipoprotein(a) (lower), region (Asia), statin treatment, smoking, hypertension, and body mass index. Despite being switched to PBO, patients with very low LDL-C on ALI had fewer MACE than matched patients from the PBO group (6.4% vs 8.5%; HR 0.71, 95% CI 0.52-0.98; P=0.039; Figure). Very low LDL-C on ALI was not associated with risk of new-onset diabetes, compared with matched patients from the PBO group (15.1% vs 13.0%; HR 1.10, 95% CI 0.85-1.43;
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Conclusions: The overall efficacy of ALI on cardiovascular outcomes was not diminished by the patients who had blinded substitution of PBO for sustained very low LDL-C. Despite a short duration of active treatment, these patients had fewer MACE than matched controls from the PBO group. No adverse consequence of very low LDL-C was identified. However, because patients with sustained very low LDL-C were switched to PBO, the long-term safety of more prolonged very low LDL-C, including risk of new-onset diabetes, deserves further study.