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Obesity Summit 2018: PCSK9 inhibitors: FOURIER study- Govind Kulkarni- Pulse Diabetes, Obesity & Cardiac Relief Center, India

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Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers Low-Density Lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain. Methods: We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive Evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction or stroke. The median duration of follow-up was 2.2 years. Results: At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with Evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, Evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with Evolocumab (2.1% vs. 1.6%). Conclusion: In our trial, inhibition of PCSK9 with Evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. LDL cholesterol is a well-established and modifiable risk factor for cardiovascular disease. Monoclonal antibodies that inhibit PCSK9 have emerged as a new class of drugs that effectively lower LDL cholesterol levels. Evolocumab, a member of this class, is a fully human monoclonal antibody that reduces LDL cholesterol levels by approximately 60%. Genetic studies have shown that carriage of PCSK9 loss-of-function alleles is associated with lower LDL cholesterol levels and a reduced risk of myocardial infarction. Moreover, exploratory data from longer-term follow-up in phase 2 and phase 3 trials of PCSK9 inhibitors showed significant reductions in cardiovascular outcomes. However, there were little more than 100 events in these studies combined. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) was a dedicated cardiovascular outcomes trial that tested the clinical efficacy and safety of Evolocumab when added to highintensity or moderate-intensity statin therapy in patients with clinically evident atherosclerotic cardiovascular disease.

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