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ATHEROSCLEROSIS

PCSK9 inhibition reduces cardiovascular events in high-risk patients

The PCSK9 inhibitor evolocumab has been shown to reduce LDL-cholesterol levels, but whether this reduction translates into a decline in cardiovascular events was previously unknown. Now, findings from the FOURIER trial — presented at the ACC.17 Scientific Sessions and published in *The New England Journal of Medicine* — show that evolocumab reduces the risk of cardiovascular events in patients with atherosclerotic disease who were already receiving statin therapy.

The discovery of PCSK9 as a therapeutic target for atherosclerotic cardiovascular disease has led to the development of monoclonal antibodies that inhibit its action, including evolocumab. "Genetic and exploratory clinical data suggested that LDL-cholesterol reduction with PCSK9 inhibition should lead to lower rates of myocardial infarction and stroke, but we needed to perform a definitive cardiovascular outcomes trial", explains Marc Sabatine, lead investigator of the FOURIER study. The FOURIER investigators sought to assess the efficacy and safety of evolocumab in patients with atherosclerotic cardiovascular disease already receiving moderate-intensity or high-intensity statin therapy.

> "these observations support the use of evolocumab to reduce the risk of cardiovascular events"

FOURIER was a multicentre, randomized, double-blind, placebo-controlled study involving patients from 1,242 sites in 49 countries. The trial included patients with a history of myocardial infarction, nonhaemorrhagic stroke, or symptomatic peripheral artery disease, who had LDL-cholesterol levels of ≥70 mg/dl, and were receiving an optimized regimen of lipid-lowering therapy. Participants were randomly assigned to receive a subcutaneous injection of evolocumab (140 mg fortnightly or 420 mg monthly) or placebo. The primary efficacy end point was a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.

In total, 13,784 patients were assigned to the evolocumab group, and 13,780 to the placebo group. The median follow-up duration was 26 months. At 48 weeks, evolocumab-treated patients had a 59% reduction in LDL-cholesterol levels compared with placebo-treated controls, which translated to a mean absolute reduction of 53 mg/dl. Levels of non-HDL cholesterol, apolipoprotein B, and triglycerides were similarly reduced in the evolocumab group versus the placebo group. Importantly, evolocumab significantly reduced the risk of the primary composite end point, which occurred in 9.8% of evolocumab-treated patients compared with 11.3% of placebo-treated patients (HR 0.85, 95% CI 0.79–0.92, $P<0.001$). The secondary end point of cardiovascular death, myocardial infarction, or stroke was also reduced with evolocumab treatment. "There was a consistent benefit in all the major subgroups studied, including those on high-intensity statin therapy and those starting with low levels of LDL cholesterol," adds Sabatine. "The benefits grew with time, with a 16% reduction in cardiovascular death, myocardial infarction, and stroke in the first year, then a 25% reduction thereafter." Overall rates of adverse events were not different between groups. Although uncommon, injection-site reactions occurred more frequently with evolocumab treatment (2.1% versus 1.6%).

Together, these observations support the use of evolocumab to reduce the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease. These findings also suggest that these patients might benefit from the lowering of LDL-cholesterol levels beyond the current targets.

In an accompanying editorial, Robin Dullaart points out that the efficacy of "PCSK9 inhibition treatment that is started shortly after an acute event still needs to be determined, as does the efficacy of the treatment in other categories of high-risk patients", but anticipates that findings of the FOURIER trial will soon be added to clinical guideline recommendations for the treatment of high-risk patients with atherosclerotic disease.

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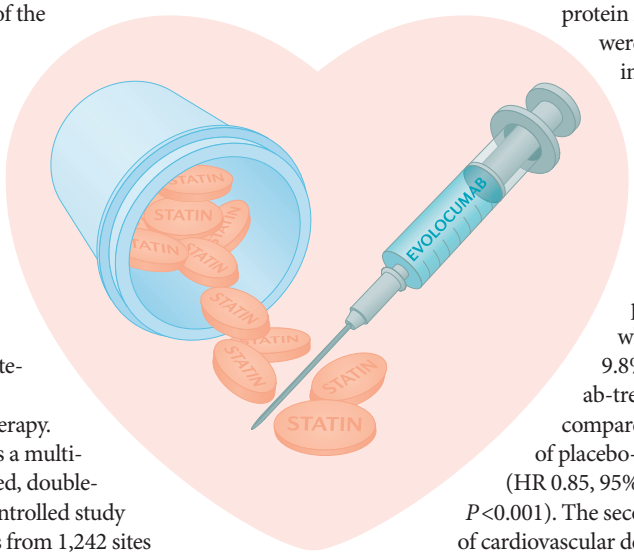

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FURTHER READING Dadu, R. T. *et al.* Lipid lowering with PCSK9 inhibitors. *Nat. Rev. Cardiol.* **11**, 563–575 (2014)