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In Very-High-Risk Patients with Vascular Disease, Evolocumab Slightly Reduces Nonfatal MI but Not Mortality

Clinical Question

Does evolocumab (Repatha), a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, reduce the likelihood of cardiovascular events in patients with cardiovascular disease who are already taking a statin?

Bottom Line

In an extremely high-risk group of patients with known vascular disease, taking evolocumab instead of placebo in addition to standard statin therapy for slightly more than two years will prevent one myocardial infarction (MI) for every 83 persons treated and prevent one stroke for every 250 persons treated. At the current cost of the drug in the United States, that amounts to approximately \$2.5 million per nonfatal MI prevented. (Level of Evidence = 1b)

Synopsis

PCSK9 inhibitors lower low-density lipoprotein (LDL) cholesterol levels, but do they have a benefit on patient-oriented outcomes? This trial recruited 27,564 patients with known vascular disease (MI, stroke, or peripheral arterial disease) and at least one major additional risk factor (e.g., diabetes mellitus, smoking, age 65 years or older) or two minor risk factors (e.g., high-density lipoprotein level less than 40 mg per dL [1.04 mmol per L], high-sensitivity C-reactive protein level greater than 2.0 mg per L [19.05 nmol per L], LDL level of

130 mg per dL [3.37 mmol per L] or greater). This was an extremely high-risk group, which is important to keep in mind. All patients had to be taking a high-intensity statin yet still have a fasting LDL level of at least 70 mg per dL (1.81 mmol per L). The mean age of participants was 62 years, 75% were men, 85% were white, and most came from Europe. The most common type of vascular disease was a history of previous MI (81%).

The patients were randomized to receive evolocumab injections (140 mg per week or 420 mg per month at the patient's discretion) or placebo injection. The groups were balanced at the start of the study, and analysis was by intention to treat. The drug certainly lowers the LDL level, from a median of 92 mg per dL (2.38 mmol per L) at baseline to approximately 30 mg per dL (0.78 mmol per L) within one month. After a median follow-up of just over two years, the primary composite outcome of cardiovascular death, MI, stroke, hospitalization for unstable angina, or revascularization occurred less often in the evolocumab group (9.8% vs. 11.3%; $P < .001$; number needed to treat [NNT] = 67 for 26 months to prevent one event).

As always, it is important to look at individual outcomes. There was no difference in the likelihood of cardiovascular death (1.8% for evolocumab vs. 1.7% for placebo) or all-cause mortality (3.2% vs. 3.1%). The bulk of the benefit came from fewer nonfatal MIs (3.4% vs. 4.6%; $P < .001$; NNT = 83 over 26 months) and a small decrease in nonfatal stroke (1.5% vs. 1.9%; $P = .01$; NNT = 250 over 26 months). There were no differences in serious adverse events, including neurocognitive events, between groups. The drug sells for \$14,100 per year in the United States, compared with approximately \$7,000 per year in the United Kingdom and Canada.

Study design: Randomized controlled trial (double-blinded)

Funding source: Industry

Allocation: Concealed

Setting: Outpatient (any)

Reference: Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.

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