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PHARMACOTHERAPY

Beneficial effects of evacetrapib

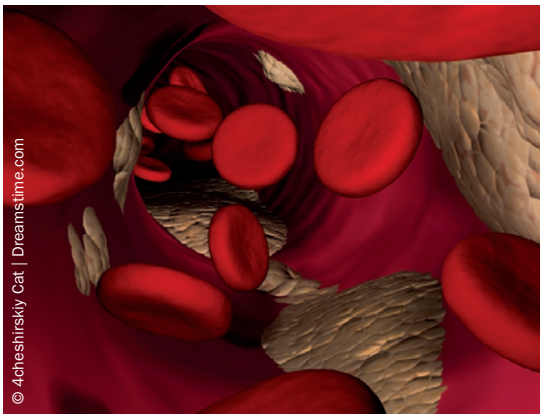
No-one can deny the considerable benefit that statin-induced LDL-cholesterol (LDL-C) reduction has on patients with atherosclerosis. However, in attempts to reduce any residual risk in patients treated with statins, many clinicians are investigating the potential of also increasing HDL-cholesterol (HDL-C) levels. A trial by Stephen Nicholls and colleagues has provided promising results for the cholesteryl ester transfer protein (CETP) inhibitor evacetrapib.

Enrolled patients (aged ≥18 years) had triglyceride levels <400 mg/dl and either low HDL-C levels (<45 mg/dl for men or <50 mg/dl for women) or high LDL-C levels (100–190 mg/dl with 0–1 risk factors, 100–160 mg/dl with ≥2 risk factors and a 10-year coronary risk <10%, or 100–130 mg/dl with ≥2 risk factors and a 10-year coronary risk of 10–20%). The primary analysis included 382 patients randomly assigned to one of ten groups receiving various drug regimens for 12 weeks. All patients were followed up for 4–6 weeks after cessation of the study drug. Evacetrapib administration was generally well tolerated.

Compared with placebo, evacetrapib monotherapy at daily doses of 30 mg, 100 mg, and 500 mg was associated with significant LDL-C reductions of 17.6%, 26.2%, and 39.8%, respectively. The low, medium, and high doses of evacetrapib were also associated with substantial HDL-C increases of 56.7%, 97.6% and 131.9%, respectively. A significant reduction in triglyceride levels (20.1% relative to placebo) was observed only with the 500 mg/dl dose of evacetrapib, and no significant effects on levels of C-reactive protein were found.

The efficacy of evacetrapib in combination therapy with statins was also assessed. Compared with statin monotherapy (which was associated with a reduction in LDL-C levels, as expected, but no significant effect on HDL-C levels), addition of daily evacetrapib 100 mg to daily atorvastatin 20 mg, simvastatin 40 mg, or rosuvastatin 10 mg treatment regimens was associated with 13.9%, 11.2%, and 13.5% greater reductions in LDL-C levels, respectively, and 78.5%, 79.3%, and 88.5% increases in HDL-C levels, respectively. No significant effects on levels of triglycerides or C-reactive protein were noted.

"So it looks like this is a drug we can now take forward into phase III ... with some confidence that it is safe, and we'll find out then if it is efficacious in reducing death, heart attack, and stroke," commented Dr Nicholls in his videoed description of the trial published online in *JAMA* in association with the study report. "Current FDA guidance suggests that drugs that raise HDL need clinical outcome trials to be approved," he went on to highlight, "and so the next step will be ... a very large morbidity and mortality trial in a diverse population —almost certainly a global study—and the study will be designed in such a way [as] to determine whether evacetrapib, given on top of full therapeutic doses of statins, can further reduce morbidity and mortality."



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Original article Nicholls, S. J. *et al.* Effects of the CETP inhibitor evacetrapib administered as monotherapy or in combination with statins on HDL and LDL cholesterol: a randomized controlled trial. *JAMA* **306**, 2099–2109 (2011)