Nature Reviews Cardiology **8**, 610 (2011); published online 27 September 2011; doi:10.1038/nrcardio.2011.150

CORONARY ARTERY DISEASE

Dalcetrapib safely raises HDL-cholesterol level in the phase IIb dal-PLAQUE trial

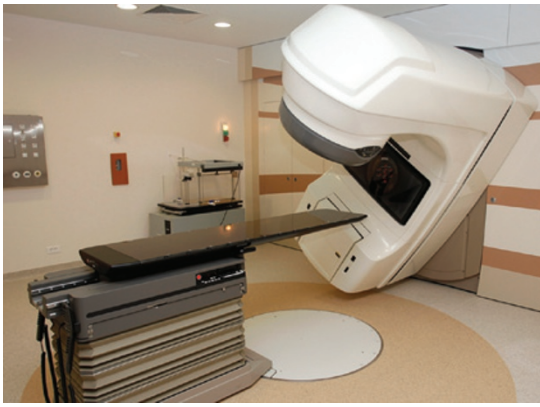
Dalcetrapib, a novel drug that inhibits cholesteryl ester transfer protein (CETP) activity, successfully raises the level of HDL cholesterol in patients with coronary artery disease, and has no detectable proatherogenic or proinflammatory effects, according to the results of the dal-PLAQUE trial published in *The Lancet*.

> "Dalcetrapib ... has no detectable proatherogenic or proinflammatory effects"

The successful treatment of atherosclerotic disease with therapies to lower LDL cholesterol, especially with statins, is well established, but a supplementary approach to reduce plaque burden is to raise the level of HDL cholesterol. In the ILLUMINATE trial, another CETP inhibitor, torcetrapib, effectively increased HDL cholesterol, but was associated with increases in blood pressure, vascular inflammation, and mortality. The phase IIb dal-PLAQUE trial was, therefore, designed to investigate the effect of dalcetrapib on atherosclerotic disease progression, and is part of the dal-HEART programme into the overall safety and efficacy of the drug. The effect of dalcetrapib on vascular function was assessed in a parallel phase IIb trial (dal-VESSEL), the results of which were presented at the 2011 European Society of Cardiology Congress.

The investigators randomly allocated 130 patients with (or at high risk of) coronary artery disease to receive either dalcetrapib 600 mg per day or placebo for 24 months. Concomitant statin use was higher in the placebo group compared with dalcetrapib, but the groups were well matched for baseline LDL-cholesterol levels. dal-PLAQUE was the first multicenter study to use noninvasive, multimodal imaging to assess indices of atherosclerosis as primary end points. MRI was used to evaluate plaque morphology and atherosclerotic progression or regression after 24 months, and PET/CT measurement of ^{18}F-fluorodeoxyglucose uptake identified vascular inflammation after 6 months.

Similarly to the reported findings in dal-VESSEL, the mean HDL-cholesterol concentration increased by 30.9% and 4.0% in the dalcetrapib and placebo groups, respectively. MRI assessment of plaque burden showed no evidence of a proatherogenic effect, and a 4.01 mm^2 reduction in total vessel enlargement, with dalcetrapib therapy compared with placebo. Dalcetrapib treatment had no proinflammatory effect according to PET/CT assessment, and did not increase blood pressure or the frequency of adverse events, compared with placebo.



© Picsfive | Dreamstime.com

The long-term safety and efficacy of dalcetrapib is being assessed in two large, ongoing, phase III trials: dal-PLAQUE 2, in which atherosclerotic disease progression will be measured by coronary IVUS and carotid B-mode ultrasonography; and dal-OUTCOMES, in which overall cardiovascular morbidity and mortality will be recorded. Furthermore, the safety and efficacy of dalcetrapib in approximately 300 patients who have suffered an acute coronary syndrome will be investigated in dal-ACUTE.

Gregory B. Lim

Original article Fayad, Z. A. *et al.* Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodal imaging (dal-PLAQUE): a randomised clinical trial. *Lancet* doi:10.1016/S0140-6736(11)61383-4