Evaluate Vantage

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ACC 2019 – Anacetrapib analysis throws doubt on Dalcor play

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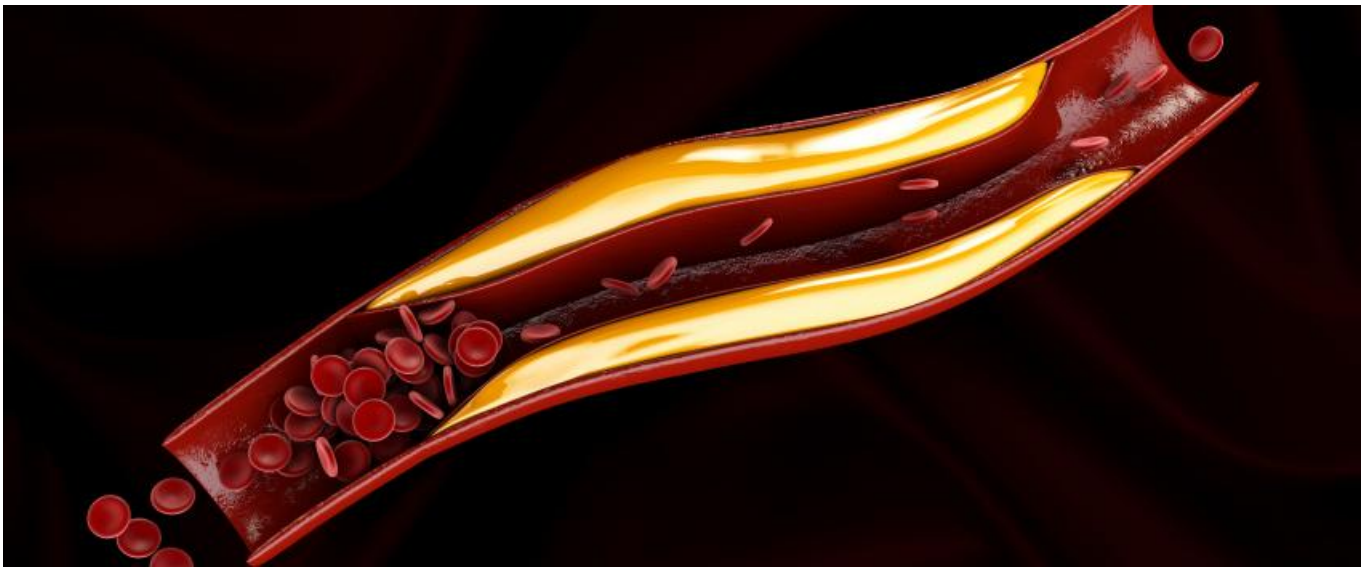

No genetic correlation was seen with Merck & Co's CETP inhibitor, but Dalcor believes that things will be different for dalcetrapib.

Dalcor's case for picking up Roche's failed CETP inhibitor dalcetrapib rested on a single finding from the Dal-Outcomes trial: that subjects with a specific genetic polymorphism saw a 39% decline in cardiovascular events. But a new analysis from a pivotal trial of a similar asset, Merck & Co's anacetrapib, throws into doubt the hypothesis that these patients could in fact benefit from the drug class.

In the Reveal trial of anacetrapib patients with the relevant genotype had a similar rate of cardiovascular events as those without this profile, according to a presentation at the American College of Cardiology conference yesterday. Dalcor said, however, that the sector should not assume that its trial of dalcetrapib, DalGene, will fail, arguing that it recruited sicker patients, and that the two drugs differ in how they alter cholesterol levels.

"The drugs are different and the patient populations are different," Dalcor's chief executive, Fouzia Laghrissi-Thode, told *Vantage* immediately after the ACC presentation of the anacetrapib data.

More revealing

The Reveal trial, fully unveiled at the 2017 European Society of Cardiology meeting, found a 9% reduction in major vascular events with anacetrapib plus statins. Although statistically significant, the level of benefit was clinically disappointing and well below that of the PCSK9 inhibitors Repatha and Praluent. The results effectively put an end to research on CETP inhibitors in the broad cardiovascular disease population (*ESC 2017 – Merck still won't Reveal its hand, August 29, 2017*).

A remaining question was whether Merck's Reveal trial would find a benefit in patients with the AA genotype at rs1967309 in the ADCY9 gene, a possibility raised by analyses of the Dal-Outcomes trial of dalcetrapib, run by Roche. The answer was a clear no.

Reveal enrolled 30,000 patients, and of those 19,210 had ADCY9 genotype data available. Those with the AA genotype did not have a meaningfully different change from baseline in HDL or non-HDL cholesterol at the study's midpoint.

Of 1,520 AA patients randomised to take anacetrapib on top of statins, 12.7% had a major vascular event,

compared with 13.5% of 1,520 subjects taking statins alone, yielding a non-significant hazard ratio of 0.93. The trial's researchers added that there was no sign that anacetrapib had an effect on individual components of the major vascular events composite, including myocardial infarction, stroke or cardiovascular death.

Testing

Ms Laghrissi-Thode was undaunted, however, and contended that the benefit of dalcetrapib might only be seen in the sicker AA patients. Reveal's trial population had been stable, excluding patients with recent myocardial infarctions or strokes. Dal-Outcomes, and now Dal-Gene, have specified that patients need to have suffered a major coronary event in the preceding three months.

The two agents differ in pharmacological profile, she added. Dalcetrapib raises LDL-scavenging HDL by 30% and has no effect on LDL. More potent inhibitors like anacetrapib and Eli Lilly's evacetrapib have doubled HDL but have also lowered LDL; however, there has been speculation that any benefit has come from their LDL-lowering effect (*Lilly's evacetrapib failure the end of the road for CETP?, October 12, 2015*).

Dal-Gene completed its enrolment of 6,100 patients last year and is headed for a futility analysis later this year. If it the trial passes that test then a primary readout should happen at the end of 2020 or early 2021.

These results should put to rest any remaining arguments over the role CETP inhibition could play in cardiovascular disease, some 14 years after Pfizer discontinued the first major agent, torcetrapib. "If the hypothesis is valid and execution is flawless, Dal-Gene should be successful," says Ms Laghrissi-Thode.

The hypothesis now looks even shakier than before.