Editorial

Evacetrapib and cardiovascular outcomes: reasons for lack of efficacy

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Cholesteryl ester transfer protein (CETP) inhibitors are a drug class targeting the enzyme CETP (1). The first CETP inhibitor, torcetrapib, was discontinued because of increased cardiovascular events that were attributed to off-target adverse effects (increased aldosterone and blood pressure) (2). The development program of another CETP inhibitor, dalcetrapib, which did not have the off-target adverse effects of torcetrapib, was terminated due to futility (insufficient efficacy) concerning cardiovascular outcomes (3). Recently, the results of the ACCELERATE trial, that examined the effects of the CETP inhibitor evacetrapib, were published. ACCELERATE was a multicenter, randomized, double-blind, placebo-controlled phase 3 trial, that randomly assigned 12,092 patients with high cardiovascular risk to receive either evacetrapib (130 mg/d) or matching placebo on top of standard medical treatment (4). Evacetrapib treatment resulted in a substantial improvement of lipid profile; after 3 months, a 37.1% absolute decrease in the mean low-density lipoprotein (LDL) cholesterol levels and a 131.6% absolute increase in the mean high-density lipoprotein (HDL) cholesterol concentration compared with placebo were observed. Despite this lipid profile improvement, the primary end-point (the composite of death from cardiovascular causes, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina) did not differ between evacetrapib and placebo after a median of 26 months (12.9% in the evacetrapib group and 12.8% in the placebo group; hazard ratio 1.01, 95% confidence interval, 0.91–1.11; P=0.91), leading the data and safety monitoring board to terminate the trial early because of a lack of efficacy (4).

The failure of the ACCELERATE trial may be attributed to certain on-target and off-target adverse effects:

(I) On-target adverse effects. Even though an increased cholesterol efflux capacity has been repeatedly demonstrated with evacetrapib administration (5-7), it has been speculated that CETP inhibitors are associated with dysfunctional HDL particles (8). Additionally, in the ACCELERATE trial study population included high-risk patients with established atherosclerotic cardiovascular disease in whom dysfunctional HDL particles may predominate (9). It should be mentioned that evacetrapib is associated with an increase of larger cholesterol-rich HDL particles, which may be less atheroprotective compared with smaller HDL particles (10,11) due, at least in part, to increased viscosity, that is associated with elevated cardiovascular disease risk (12). Furthermore, an increase in apolipoprotein E and apolipoprotein CIII levels has been observed after evacetrapib administration in the ACCELERATE trial (5). Elevated apolipoprotein CIII levels are associated with increased cardiovascular risk according to both population and genomic studies (13,14). It has been suggested that elevated

levels of remnant lipoproteins, small dense LDL particles and low-grade inflammation may explain this association. Additionally, it is well known that apolipoprotein CIII exhibits direct proinflammatory effects in the arterial wall by activating vascular cell adhesion molecule-1 and nuclear factor kB (15). It has been suggested that drug-associated larger HDL particles can provide increase amounts of apolipoprotein CIII to the arterial wall. Furthermore, apolipoprotein CIII-enriched HDL particles have been shown to exhibit less functional activity (that is impairment of HDL-mediated cholesterol efflux capacity) (16). It is worth mentioning that increased Apo E levels have been related with ischemic heart disease in men (17).

It should be mentioned that the decrease in LDL cholesterol levels observed with evacetrapib in the ACCELERATE trial (a 37.1% absolute difference compared with placebo) is not mediated by an increased LDL receptors activity known to be associated with a decreased cardiovascular risk, as studies with statins, ezetimibe and PCSK9 inhibitors have shown. Additionally, these reductions in LDL cholesterol were associated with smaller decreases in LDL particles number and apolipoprotein B levels (a decrease of apolipoprotein B by only 15% was noticed in the ACCELERATE trial) (4,18).

(II) Off-target adverse effects. A small increase in systolic blood pressure levels (by 1.2 mmHg) was observed after evacetrapib administration in the ACCELERATE trial that could explain, at least in part, the inability of the drug to reduce cardiovascular events in high risk patients. It has been shown that these drugs can increase aldosterone biosynthesis in adipocytes (19). However, no data concerning hormonal changes in the ACCELERATE trial have been reported yet, while a previously published study showed that evacetrapib was not associated with changes in mineralocorticoid or electrolyte levels (20). Finally, an increase in C-reactive protein levels (by 8.6%) was also found in the ACCELERATE trial potentially leading to an increased inflammatory response (4).

Thus, the lack of efficacy of evacetrapib in the ACCELERATE trial may be associated with many on-target and off-target adverse effects. Many of these effects are common characteristics between CETP inhibitors pointing to the possibility that may be class-specific. However, it was recently announced that the REVEAL outcomes trial of the CETP inhibitor anacetrapib met its primary cardiovascular end-point (21). The final results, which will be revealed in the next few months, will show if this positive result concerning the primary cardiovascular end-point is due to better efficacy or less on-target/off-target adverse effects of anacetrapib compared with other CETP inhibitors.

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Footnote

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