CETP inhibition in the REVEAL trial: could we aim higher?

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Submitted: 1 June 2018
Accepted: 3 June 2018

Arch Med Sci 2020; 16 (5): 1229–1230
DOI: https://doi.org/10.5114/aoms.2020.97968

We have read the recent data on the Randomized EValuation of the Effects of Anacetrapib through Lipid-modification (REVEAL) trial with great interest [1]. Apart from the well-controlled baseline low-density lipoprotein cholesterol (LDL-C) levels, there are at least two potential factors that could have minimized the effect size of anacetrapib in the trial [1]. First, according to the population-based studies, both very low and very elevated high-density lipoprotein cholesterol (HDL-C) levels are associated with increased mortality [2, 3]. In the REVEAL study [1], a minor proportion of individuals had a low HDL-C at baseline. Since this category is the one that could benefit from any putative effect of HDL-C being raised by anacetrapib, it is possible that the risk of mortality would be lower if the drug were tested in a population with very low baseline HDL-C levels. Second, the risk reduction in coronary events with anacetrapib was expected based on the magnitude of non-HDL-C, but not LDL-C (beta-quantification assay) reduction. This might reflect the superiority of LDL particle number over LDL-C for determining cardiovascular (CV) risk [4, 5], and could explain the small effect of anacetrapib, which may mainly affect the cholesterol content of LDL particles rather than their removal by LDL receptors.

The results of the REVEAL study also raise a critical question on their clinical relevance taking into account only 9% relative risk reduction (RRR) and 1% absolute risk reduction of the primary endpoint [1]. There was also no significant effect on major atherosclerotic events [1]. Moreover, opposite to statin therapy [6], as well as combination therapy with evolocumab [7], for which the significant effect on CV outcomes appears after 12 months, in the case of anacetrapib significant reduction of main CV outcomes was observed after 3 years [1]. Therefore, currently the main question is which population might benefit the most from anacetrapib as an add-on to statin therapy. The good safety profile and very good adherence to therapy (almost 90%) suggest that one of the groups might be non-adherent patients (even over 60% after 2 years of statin therapy) [8] as well as those with statin intolerance [9, 10]. Finally, some other subgroups might benefit from anacetrapib, e.g. elderly patients at high and very high CV risk, as the mean age in the study was 67, with a high proportion of individuals over 70 years old.

Conflict of interest

Maciej Banach has served on the speaker's bureau and as an advisory board member for Amgen, Sanofi, Aventis and Lilly. Dimitri P. Mikhailidis has given talks and attended conferences sponsored by MSD, Libytec and AstraZeneca.

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