

Abstract 14019: Comparing the Effect Profile of CETP in Individuals of East Asian and European Ancestries

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Abstract

Introduction: Cholesteryl ester transfer protein (CETP) is a lipid drug target under development for CHD in both European and East Asian populations. Previous drug target Mendelian randomization (MR) studies conducted in East Asians failed to show a CHD effect, which has been interpreted as lack of effectiveness of CETP inhibition for CHD prevention in this population.

Hypothesis: In this study, we inferred the effect of CETP inhibition in individuals of European and East Asian ancestries using drug target Mendelian randomization.

Methods: We leveraged genetic associations of CETP variants with major blood lipid fractions for individuals of European (n=1,320,016) and East Asian (n=146,492) ancestries. Colocalization was employed to identify potential cross-ancestry signals of CETP variants for plasma concentrations of LDL-C or HDL-C. Drug target MR was used to estimate ancestry-specific effects of on-target CETP inhibition. Differences between ancestries were evaluated using interaction tests, applying a multiplicity corrected alpha of 1.9×10^{-3} based on the 26 considered traits.

Results: There was strong support (posterior probability=1.00) of a shared causal CETP variant affecting HDL-C in both populations, which was not observed for LDL-C. Employing drug target MR scaled to a standard deviation increase in HDL-C, we found that lower CETP was associated with lower LDL-C, Lp[a], systolic blood pressure and pulse pressure in both groups, but the effects were more pronounced in European individuals (interaction p-values $< 1.9 \times 10^{-3}$). Lower CETP was protective against CHD, angina, intracerebral haemorrhage and heart failure in both ancestries, for example for CHD in East Asians (OR 0.89, 95% CI 0.84;0.94) compared to Europeans (OR 0.95, 95% CI 0.92;0.99, interaction p-value=0.05).

Conclusions: In conclusion, on-target inhibition of CETP is anticipated to decrease cardiovascular disease in individuals of both European and East Asian ancestries.

