A Naturally Randomized Trial Comparing the Effect of Genetic Variants that Mimic CETP Inhibitors and Statins on the Risk of Cardiovascular Disease

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Background

- Mendelian randomization studies consistently demonstrate that LDL cholesterol (LDL-C) appears to be causally associated with the risk of cardiovascular disease
- Numerous randomized trials have demonstrated that reducing LDL-C reduces the risk of CVD by 20% per mmol/L, independent of how LDL-C is lowered
- Notable exception are CETP inhibitors: in ACCELERATE trial evacetrapib reduced LDL-C by 0.75 mmol/L but did not reduce cardiovascular events
    - Challenges the causal effect of LDL-C on cardiovascular disease
    - Raises possibility that clinical benefit of lowering LDL-C depends on how it is lowered

Objectives

- Evaluate the causal effect of lower LDL-C (and other lipoprotein measures) on the risk of cardiovascular events due to genetic variants that mimic the effect of CETP inhibitors
- Compare with effect of lower LDL-C due to genetic variants that mimic the effect of statins (HMG-CoA reductase inhibition), ezetimibe (NPC1L1 inhibition), and PCSK9 inhibitors
- To make inferences about whether the clinical benefit of lowering LDL-C depends on how LDL-C is lowered

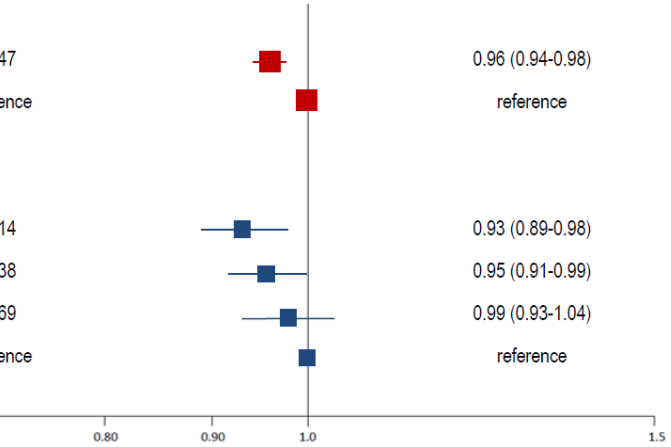
Study Design & Population

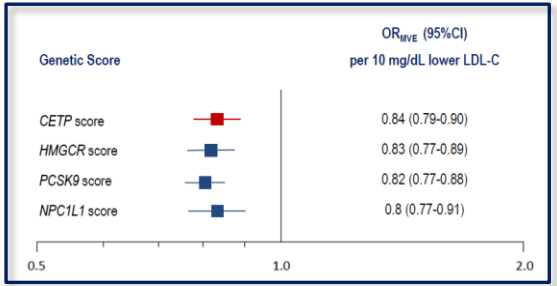
- **Study Design:** naturally randomized trial comparing effect of naturally random allocation to genetic variants that mimic the effect of CETP inhibitors, statins or both
- **Study Population:** 358 205 participants from 77 studies (76 061 cardiovascular events)
  - **Primary analysis:** 102 837 participants from 14 prospective cohort or case-control studies
  - **External Validation analyses:** 189 539 participants from 48 studies
- **Primary outcome:** major vascular events (MVE) defined as the *first* occurrence of non-fatal MI, stroke, coronary revascularization or coronary death

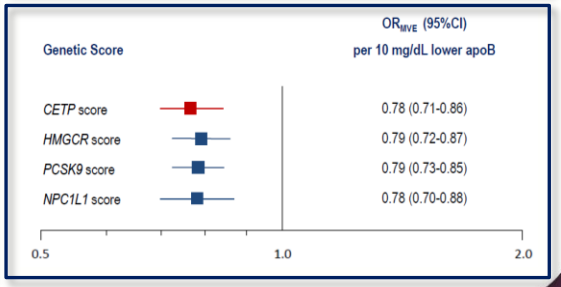
Results: CETP inhibition alone

- Analogous to CETP inhibitor monotherapy
- Concordant reductions in LDL-C and apoB and a lower risk of cardiovascular events that is proportional to the absolute change in LDL-C (same effect on MVE per unit lower LDL-C as variants that mimic statins, ezetimibe, PCSK9 inhibitors)

Analysis	Δ HDL-C (95% CI)	Δ LDL-C (95% CI)	Δ apoB (95% CI)	OR_{MVE} (95%CI)
Primary Analysis				
CETP score ≥ median	4.62	-2.15	-1.47	0.96 (0.94-0.98)
CETP score < median	Reference	reference	reference	reference
Dose Response				
CETP score quartile 4	7.12	-3.29	-2.14	0.93 (0.89-0.98)
CETP score quartile 3	4.98	-2.32	-1.38	0.95 (0.91-0.99)
CETP score quartile 2	2.37	-0.95	-0.69	0.99 (0.93-1.04)
CETP score quartile 1	reference	reference	reference	reference

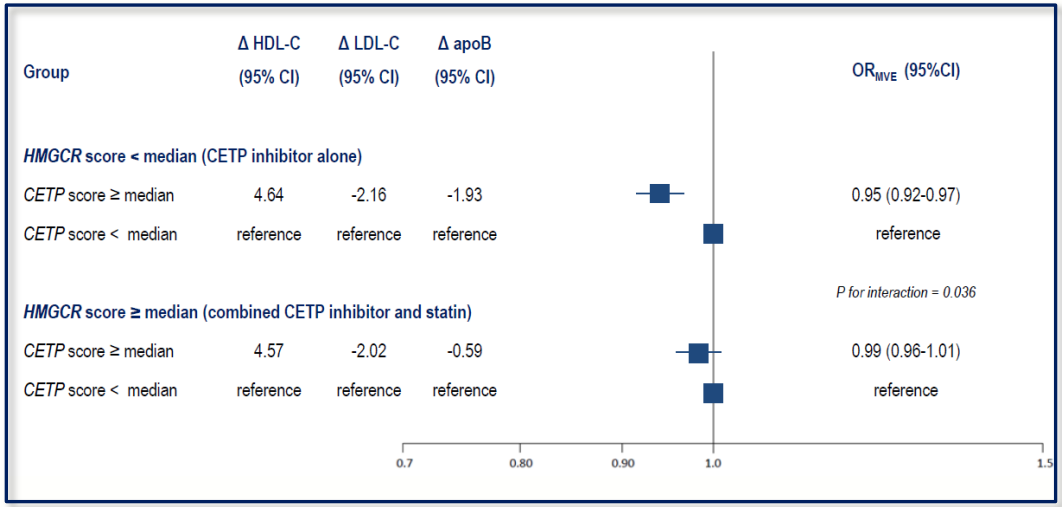


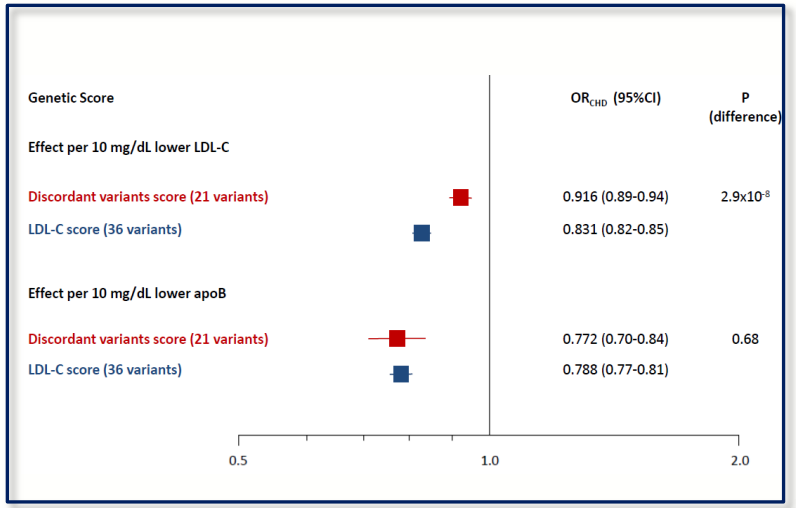




Results: Combined CETP and HMG-CoA reductase inhibition

- Analogous to combined CETP inhibitor and statins (all RCTs have evaluated CETP inhibitors on background of statin therapy)
- Discordant changes in LDL-C and apoB (due to an attenuated change in apoB) and a lower risk of cardiovascular events that is proportional to the absolute change in apoB, *but less than expected per unit lower LDL-C*





Conclusions

- The causal effect of LDL on cardiovascular disease is determined by the circulating concentration of LDL particles (as estimated by apoB) rather than by the mass of cholesterol carried by those particles (as estimated by LDL-C)
- Therefore, the clinical benefit of lowering LDL-C may depend on the corresponding reduction in LDL particles as measured by apoB
- Clinical benefit of lowering LDL-C depends on how LDL-C is lowered
  - Therapies that reduce LDL-C by reducing LDL particles (e.g. statins, ezetimibe, PCSK9 inhibitors) should reduce the risk of cardiovascular events proportional to absolute change in LDL-C (or apoB)
  - Therapies that reduce LDL-C without proportionally reducing LDL particles (e.g. combined treatment with CETP inhibitors and statins) should reduce the risk of cardiovascular events proportional to the absolute change in apoB, which may be less than the expected for the observed change in LDL-C

Research

JAMA | Original Investigation

Association of Genetic Variants Related to CETP Inhibitors and Statins With Lipoprotein Levels and Cardiovascular Risk

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Editorial

Supplemental content

IMPORTANCE Some cholesteryl ester transfer protein (CETP) inhibitors lower low-density lipoprotein cholesterol (LDL-C) levels without reducing cardiovascular events, suggesting that the clinical benefit of lowering LDL-C may depend on how LDL-C is lowered.

OBJECTIVE To estimate the association between changes in levels of LDL-C (and other lipoproteins) and the risk of cardiovascular events related to variants in the *CETP* gene, both alone and in combination with variants in the 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) gene.

DESIGN, SETTING, AND PARTICIPANTS Mendelian randomization analyses evaluating the association between *CETP* and *HMGCR* scores, changes in lipid and lipoprotein levels, and the risk of cardiovascular events involving 102 837 participants from 14 cohort or case-control studies conducted in North America or the United Kingdom between 1948 and 2012. The associations with cardiovascular events were externally validated in 189 539 participants from 48 studies conducted between 2011 and 2015.

EXPOSURES Differences in mean high-density lipoprotein cholesterol (HDL-C), LDL-C, and apolipoprotein B (apoB) levels in participants with *CETP* scores at or above vs below the median.

MAIN OUTCOMES AND MEASURES Odds ratio (OR) for major cardiovascular events.

RESULTS The primary analysis included 102 837 participants (mean age, 59.9 years; 58% women) who experienced 13 821 major cardiovascular events. The validation analyses included 189 539 participants (mean age, 58.5 years; 39% women) with 62 240 cases of coronary heart disease (CHD). Considered alone, the *CETP* score was associated with higher levels of HDL-C, lower LDL-C, concordantly lower apoB, and a corresponding lower risk of major vascular events (OR, 0.946 [95% CI, 0.921-0.972]) that was similar in magnitude to the association between the *HMGCR* score and risk of major cardiovascular events per unit change in levels of LDL-C (and apoB). When combined with the *HMGCR* score, the *CETP* score was associated with the same reduction in LDL-C levels but an attenuated reduction in apoB levels and a corresponding attenuated nonsignificant risk of major cardiovascular events (OR, 0.985 [95% CI, 0.955-1.015]). In external validation analyses, a genetic score consisting of variants with naturally occurring discordance between levels of LDL-C and apoB was associated with a similar risk of CHD per unit change in apoB level (OR, 0.782 [95% CI, 0.720-0.845] vs 0.793 [95% CI, 0.774-0.812]; $P = .79$ for difference), but a significantly attenuated risk of CHD per unit change in LDL-C level (OR, 0.916 [95% CI, 0.890-0.943] vs 0.831 [95% CI, 0.816-0.847]; $P < .001$) compared with a genetic score associated with concordant changes in levels of LDL-C and apoB.

CONCLUSIONS AND RELEVANCE Combined exposure to variants in the genes that encode the targets of CETP inhibitors and statins was associated with discordant reductions in LDL-C and apoB levels and a corresponding risk of cardiovascular events that was proportional to the attenuated reduction in apoB but significantly less than expected per unit change in LDL-C. The clinical benefit of lowering LDL-C levels may therefore depend on the corresponding reduction in apoB-containing lipoprotein particles.

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