New insights on CETP inhibition from genetic research and clinical trials

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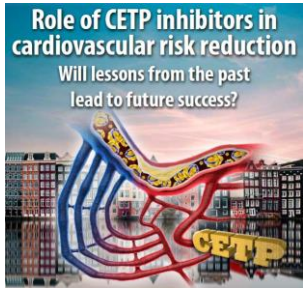
Role of CETP inhibitors in cardiovascular risk reduction - Will lessons from the past lead to future success?



PHYSICIANS' ACADEMY FOR PACE-CME CARDIOVASCULAR EDUCATION

Disclosures

- Dr Kastelein reports consultancies with 89Bio, CiVi Biotech, CSL-Behring, Draupnir Bio, Menarini Ricerce, Madrigal, North Sea Therapeutics, Novartis, Silence Therapeutics, CinCor, Scribe Therapeutics

- Dr Kastelein is acting Chief Medical Officer (CMO) of Staten Biotech and Chief Science Officer (CSO) of NewAmsterdam Pharma

Genomic Validation of LDL-C Reduction and CETP Inhibition for CVD Reduction

CETP loss of function, The Ashkenazi Jewish Longevity Gene Project

Louise Levy, 'supercentenarian' subject of longevity study among Ashkenazi Jews, dies at 112

BY ANDREW SILOW-CARROLL JULY 28, 2023 3:22 PM

Louise Levy was born in 1910 and grew up in Cleveland and New York City; Levy often ascribed her longevity to a daily glass of red wine and a low-cholesterol diet.

The CETP gene variant is associated with exceptional longevity and healthy aging phenotype

CETP I405V genotype and lipoprotein characteristic and plasma CETP levels in families with exceptional longevity vs control

Variable	CETP I405V Genotype VV	CETP I405V Genotype IV	CETP I405V Genotype II	*P* value (VV vs II Genotypes)
HDL				
Concentration, mg/dL	57	55	55	0.53
Large particle size, % of total	56	60	60	0.10
Particle size, nm	9.28	9.09	9.07	0.02
LDL				
Concentration, mg/dL	114	120	123	0.16
Large particle size, % of total	67	58	56	0.02
Particle size, nm	21.29	20.98	20.88	0.002
CETP concentration, mg/mL	1.65	1.92	1.99	<0.001

Individuals with exceptional longevity had significantly higher (up to 3.6-fold) homozygosity for the 405 valine (I405V) allele of CETP (VV genotype) vs controls

CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Barzilai N, et al. *JAMA*. 2003;290(15):2030-2040.

CETP is a genomically-validated target associated with lower cardiovascular risks

The Copenhagen City Heart study demonstrated the link between CETP inactivating mutations and lower cardiovascular risk

Genetic Inhibition of *CETP*, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects

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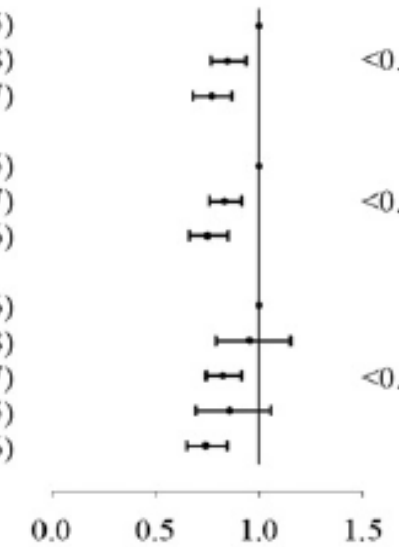
Copenhagen, Denmark

The Copenhagen City Heart Study

- Prospective study in 10,261 individuals
- Up to 34 years follow-up showed:
  - **Carriers of CETP (inactivating) genotpes** exhibited **decreased LDL cholesterol levels**
  - **Carriers of LDL decreasing CETP (inactivating) genotypes had a lower cardiovascular risk** with the following hazard ratios:
    - for any ischemic cardiovascular event: 0.76
    - for ischemic heart disease: 0.65
    - for ischemic cerebrovascular disease: 0.71

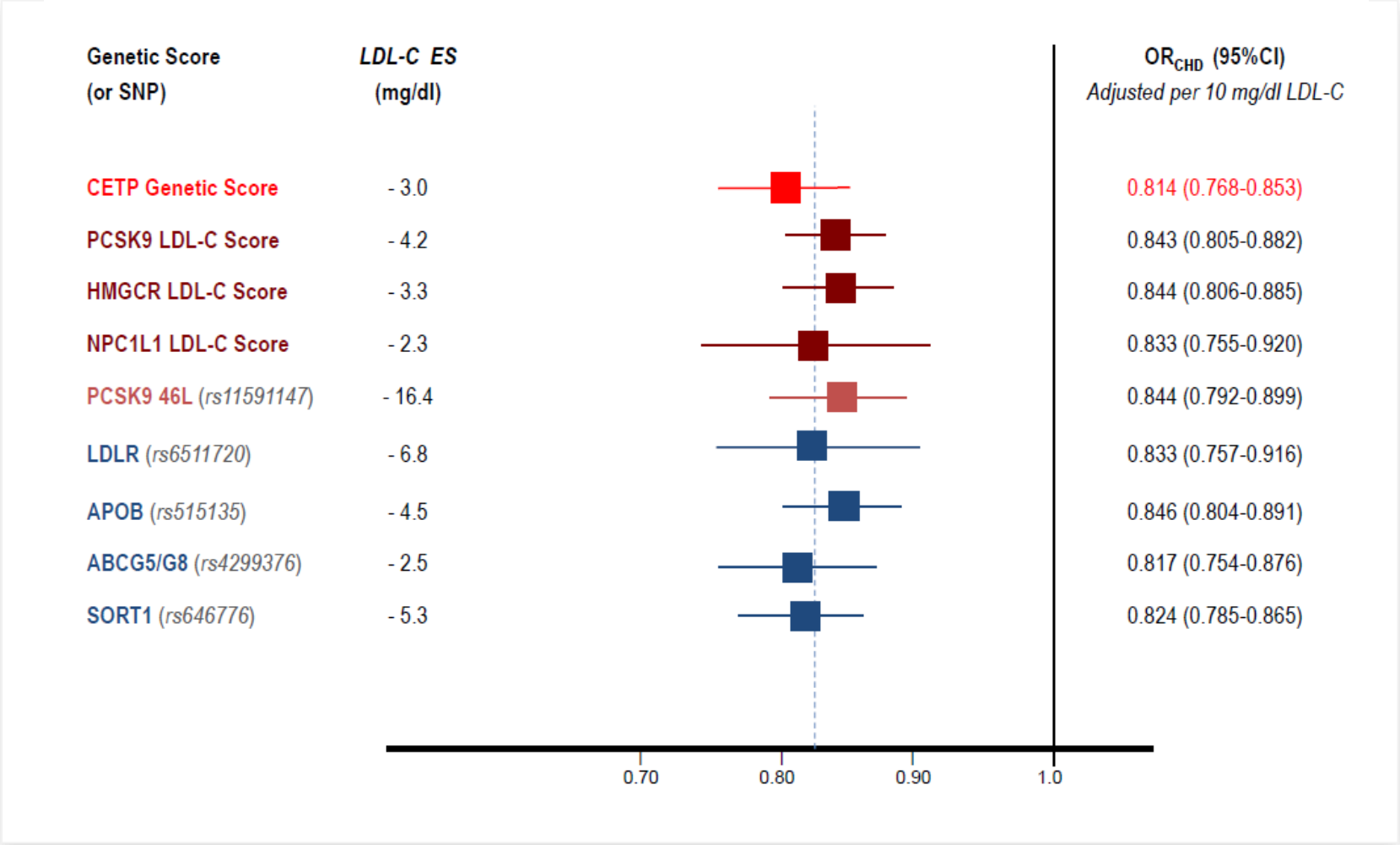
Genotype		Participants (n)	Ischemic Heart Disease (IHD) Events (n)	Incidence rate (95% CI)	Hazard Ratio (95% CI)	P for Trend
-629	CC	2709	620	97 (90-105)		
	CA	5084	1000	83 (78-88)		<0.001
	AA	2468	467	79 (73-87)		
*Taq*1B	GG	3203	737	97 (91-105)		
	GA	5057	977	82 (77-87)		<0.001
	AA	2001	373	78 (70-86)		
-629 + *Taq*1B	Non-carrier	2621	605	98 (90-106)		
	1 A-allele	613	134	91 (77-108)		
	2 A-alleles	4567	883	82 (76-87)		<0.001
	3 A-alleles	508	103	86 (71-105)		
	4 A-alleles	1952	362	77 (70-86)		



Selected genotypes display significant reduction in the Ischemic Heart Disease incidence rate

Johannsen T, Frikke-Schmidt R, Schou J, et al. Genetic Inhibition of CETP, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects. J Am Coll Cardiol. 2012 Nov, 60 (20) 2041–2048. https://doi.org/10.1016/j.jacc.2012.07.045

Association of CETP score with risk of Major Cardiovascular Events

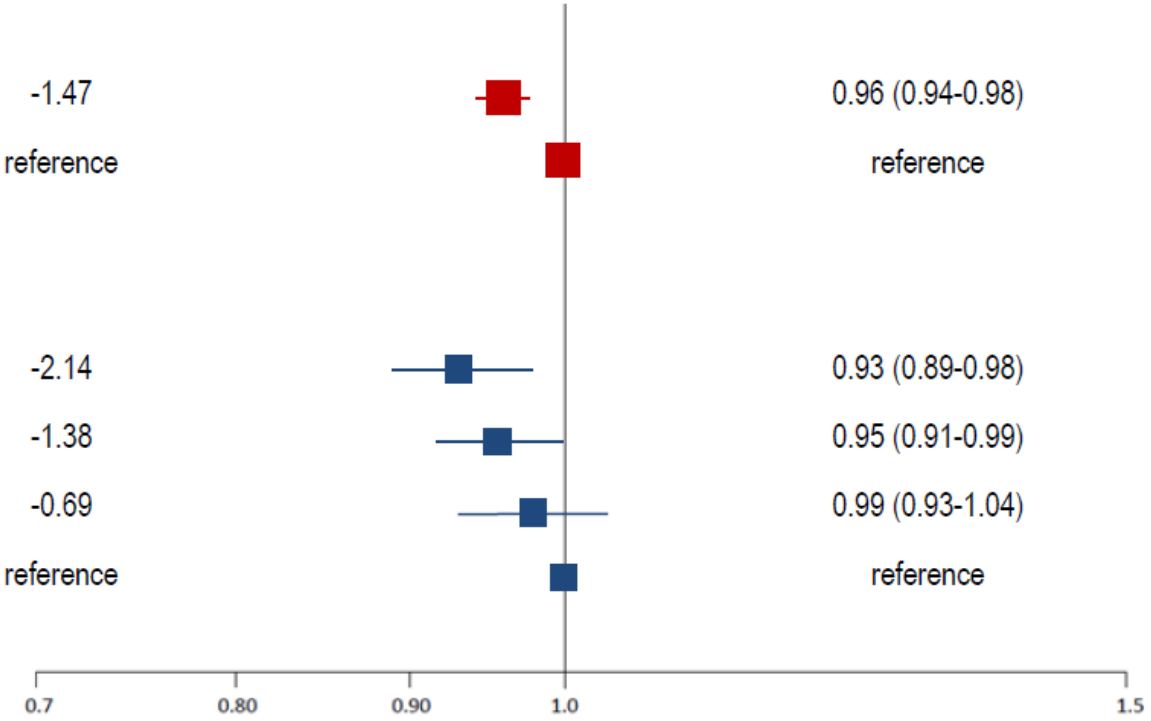


Mendelian randomization analyses suggest that the causal effect of CETP inhibition on the risk of cardiovascular events appears to be determined by changes in the concentration of apoB-containing lipoproteins rather than changes in HDL-C and is consistent with other modalities

Ference, Brian A., et al. "Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk." Jama 318.10 (2017): 947-956

More potent CETP inhibitors are more efficacious for ASCVD risk reduction

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

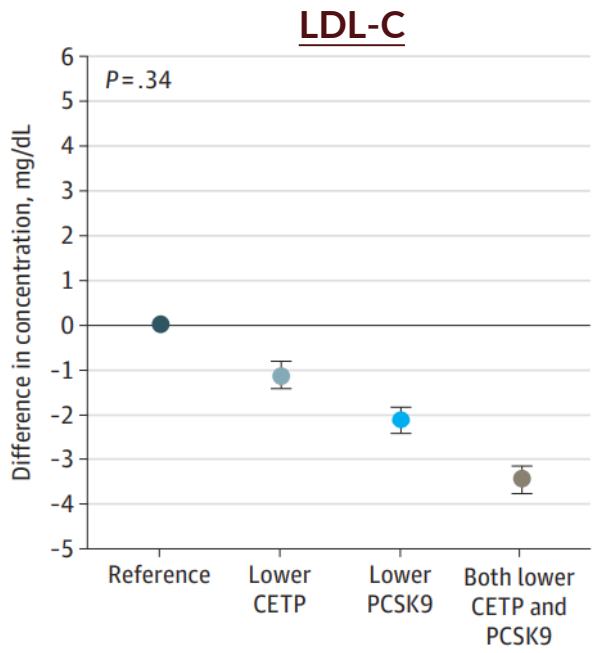


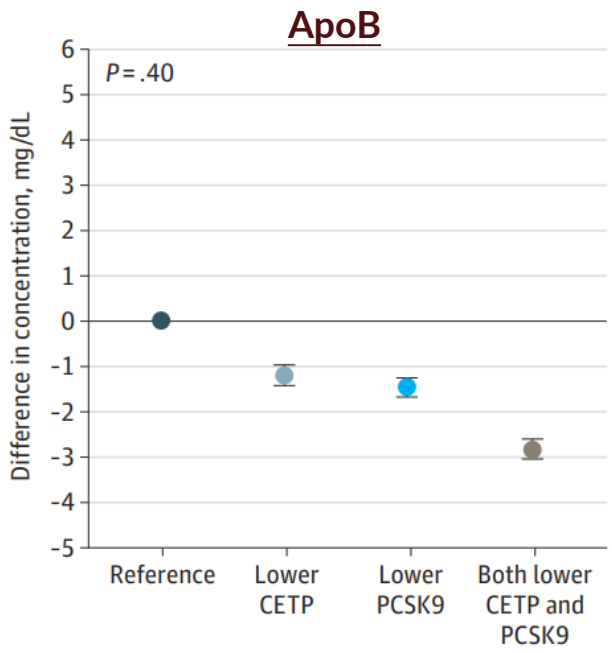
Ference, BA., et al. "Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk." Jama 318.10 (2017): 947-956.

Is there evidence for an additive effect between CETP inhibition and other mechanisms?

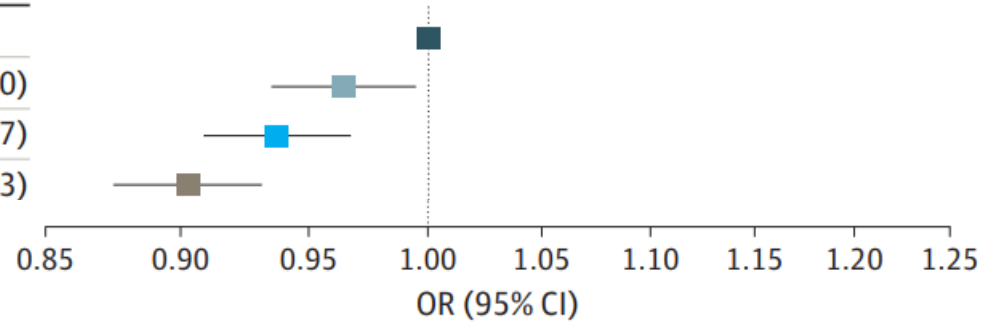
Joint inhibition of CETP and PCSK9 has additive effects on lowering LCL-C, ApoB and a lower risk of CAD

Mendelian randomization study to explore the associations of combined reduction of CETP and PCSK9





Coronary artery disease (35 002 cases)	OR (95% CI)
Higher CETP and PCSK9	1 [Reference]
Lower CETP	0.96 (0.94-1.00)
Lower PCSK9	0.94 (0.91-0.97)
Lower CETP and PCSK9	0.90 (0.87-0.93)



Cupido, AJ et al., Joint Genetic Inhibition of PCSK9 and CETP and the Association With Coronary Artery Disease A Factorial Mendelian Randomization Study, JAMA Cardiology, August 3, 2022. doi:10.1001/jamacardio.2022.2333

Novel Mendelian Randomization Data

Genetic study design: Mendelian Randomization

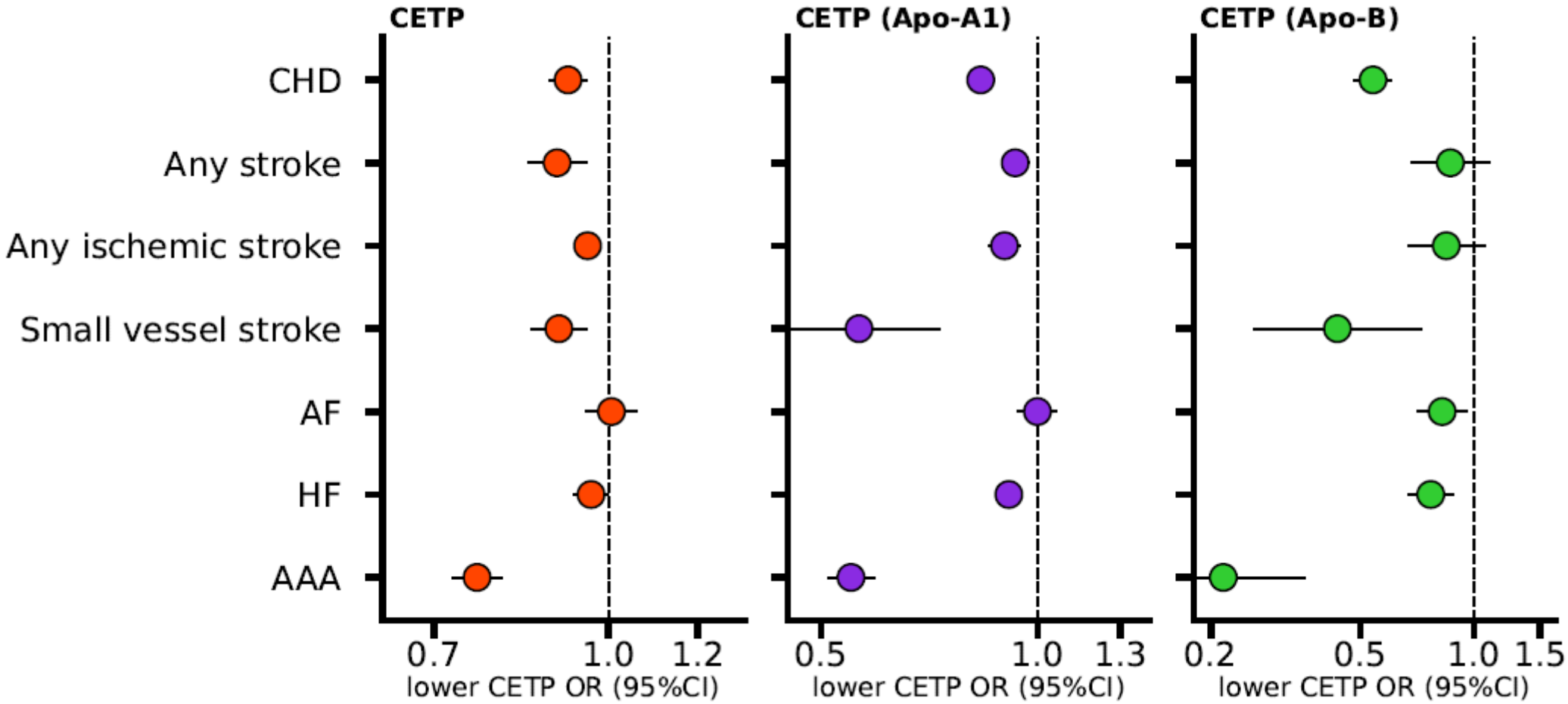
- Selected genetic instruments within and around *CETP* (the gene)
- Instruments weight using: CETP concentration or Apo-A1

- Inference of the study: CETP activity
- Results presented as: lower CETP concentration, higher Apo-A1and lower apoB100 concentration – mimicking CETP inhibition
- Positive control outcomes: CVD, including small vessel disease traits
- Goal: explore CETP effect on dementia related traits

Note: Data sets range from approximately 4K up to 1,4M individuals

Data on file

Cardiovascular Outcomes



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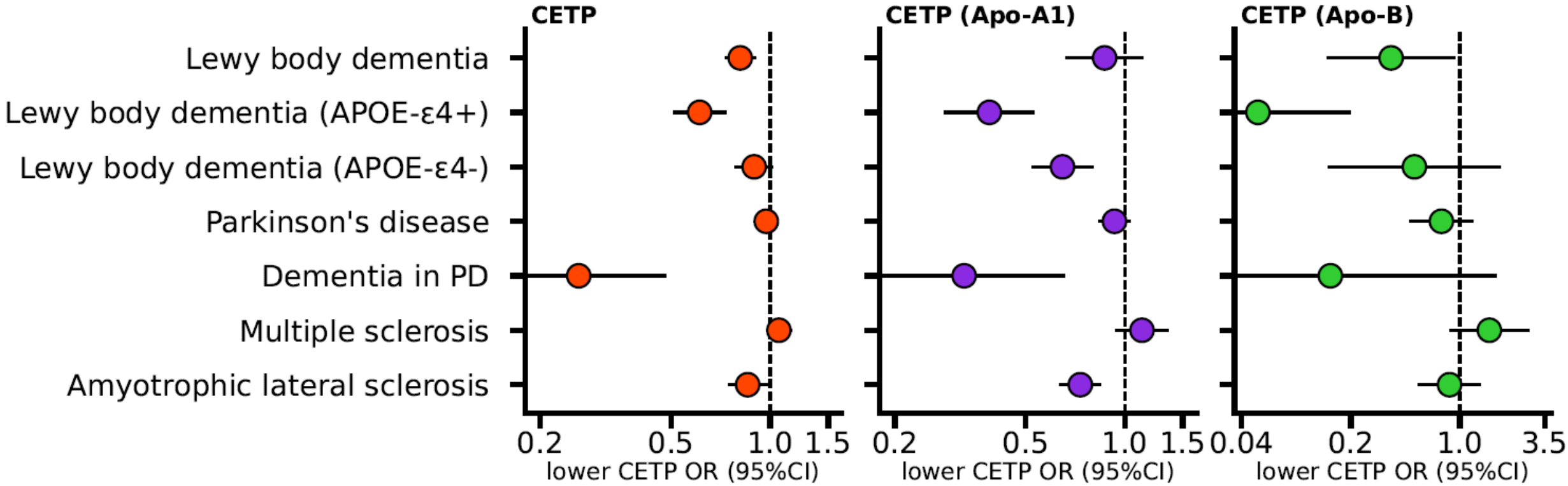
Dementia Related Outcomes



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New Insights on CETP Inhibition from Clinical Trials

Torcetrapib was a "one off "

Dalcetrapib did not move the needle on LDL-C

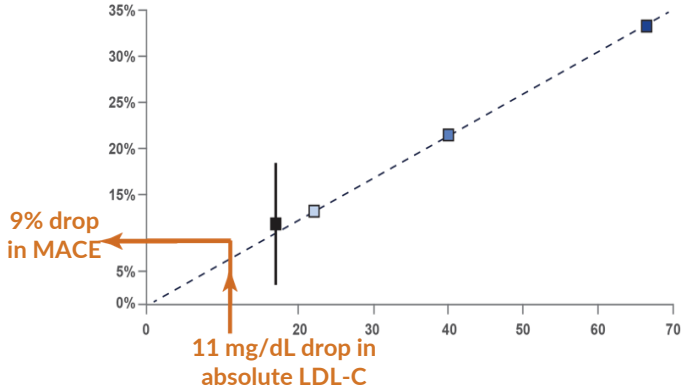
Evacetrapib 's CVOT was underpowered and too short

Anacetrapib: REVEAL study results were initially misinterpreted based on the reported 41% LDL-C Reduction versus the actual 17% reduction

- At 4.1 years, two important learnings:

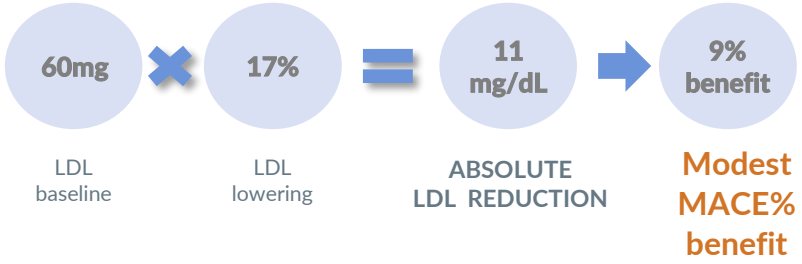
Learning 1: Predictable MACE benefit

- 9% drop in MACE is exactly predicted by the CTT metaregression line
- Indicates CETPi behaves like statins in reducing MACE



Learning 2: Baseline levels were too low

- Baseline 60 mg/dL already below U.S. guideline goals
- Modest drug LDL-lowering potency (17%) resulted in very small absolute reduction (only 11 mg/dL)



- During extended follow up (median 2.2 years): 20% additional MACE risk reduction
- Overall a 12% reduction in MACE at 6.3 years

Anacetrapib's long half-life causes it to continue to have effects in patients (patients remained randomized)

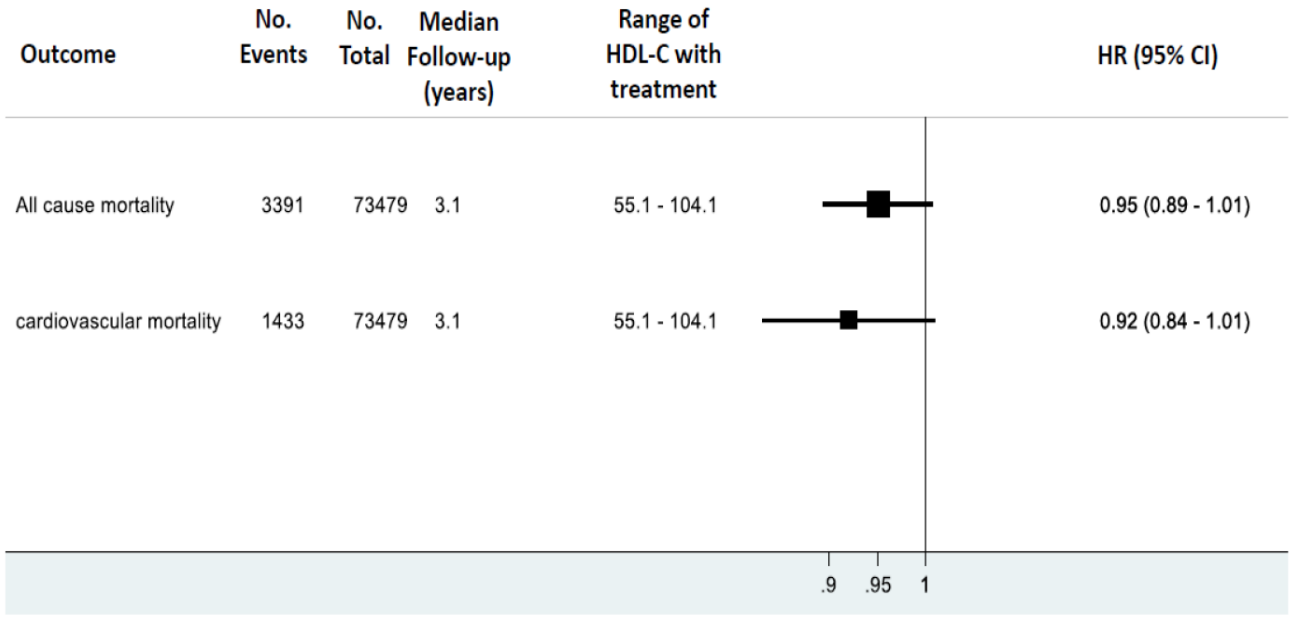
*At both time readouts, REVEAL showed statistically significant decreases across all composites of MACE**

The HPS3/TIMI55–REVEAL Collaborative Group, Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease, September 28, 2017, N Engl J Med 2017; 377:1217-1227, DOI: 10.1056/NEJMoa1706444

The HPS3/TIMI55-REVEAL Collaborative Group, REVEAL Collaborative Group, Long-term safety and efficacy of anacetrapib in patients with atherosclerotic vascular disease, European Heart Journal, Volume 43, Issue 14, 7 April 2022, Pages 1416–1424, https://doi.org/10.1093/eurheartj/ehab863

HDL-C increase is not linked to any efficacy or safety parameter in the REVEAL trial

Association between increased therapeutically achieved plasma HDL-C in response to treatment with CETPi and the risk of all-cause and CV mortality



Brian Ference (U Cambridge) specifically investigated the increase in HDL-C in REVEAL, finding that:

Neither the delta HDL-C increase nor the absolute HDL-C level reached in the 15,000 patients on anacetrapib in REVEAL can be linked to any efficacy or safety parameter after 4.1 or after 6.3 years of follow-up

- This analysis examined 100,000 patient years of exposure
- This is supportive of the initial finding that REVEAL trial MACE result lies squarely on the non-HDL metaregression (i.e., no room for an HDL effect)

The HPS3/TIMI55–REVEAL Collaborative Group, Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease, September 28, 2017, N Engl J Med 2017; 377:1217-1227, DOI: 10.1056/NEJMoa1706444

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Conclusions

- There is overwhelming genomic evidence that demonstrate reduced cardiovascular risk in individuals with naturally lower CETP activity
- The cardiovascular benefit of lower CETP activity is linked to lower LDL-C / ApoB, not higher HDL-C, and seems to be independent and additive to other biological pathways that lower LDL-C / ApoB
- In addition to confirming a cardiovascular benefit, new large scale mendelian randomization data suggest that lower CETP activity may have benefit in neuro-degenerative diseases
- There is plausible rationale why the first 3 CETP inhibitors did not demonstrate a benefit in reducing MACE
- The 4th CETP inhibitor, anacetrapib, demonstrated a significant 9% reduction in MACE at 4.1 years and an additional significant 20% reduction in the 2.2 year follow up, in line with expectations based on its modest LDL-C lowering
- Genomic evidence and the results of REVEAL support the further investigation of the CETP inhibitor class