CETP Inhibition:
How Two Decades of a Deeper Understanding of CETP Biology and Clinical Trials Have Shaped a Novel Approach in CV Risk Prevention

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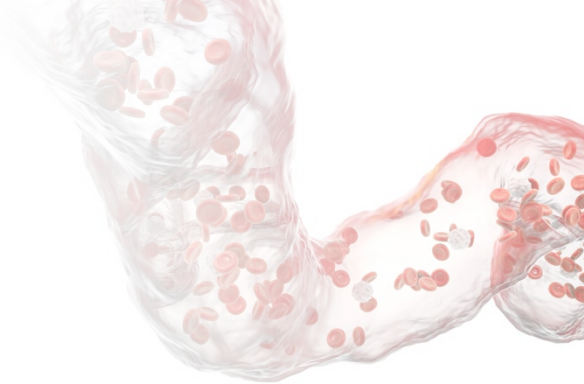
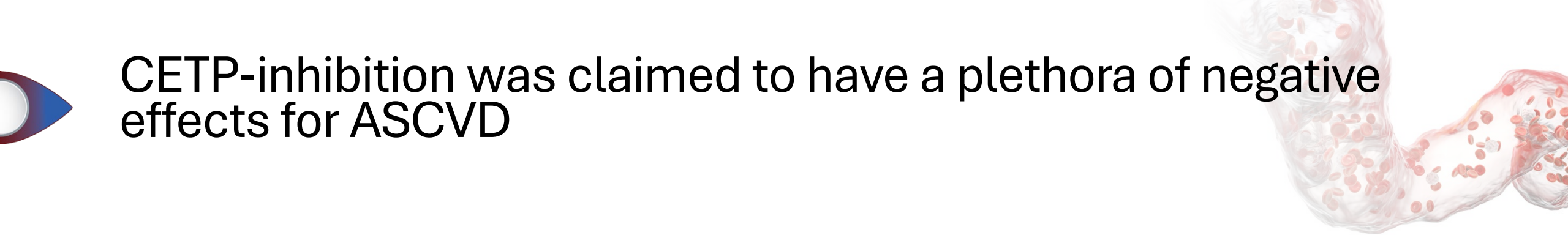
Disclosures



- Dr Kastelein is the Founder and Chief Science Officer (CSO) of NewAmsterdam Pharma

CETP-inhibition was claimed to have a plethora of negative effects for ASCVD



- It produced large dysfunctional HDL-particles, constipated and no longer capable of effluxing excess cholesterol
- These HDL particles lost their capacity for anti-oxidation, were pro-inflammatory and acted like small LDL-particles
- The LDL –particles themselves were ultra small and poly disperse, creating a more atherogenic lipoprotein profile
- None of the CVOT's with CETPi's produced any positive results and, in fact, had multiple safety issues
- The MACE reduction observed in REVEAL was minimal and clinically irrelevant and the long half life of anacetrapib led to safety issues

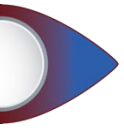
CVD, cardiovascular disease; HDL, high-density lipoprotein.

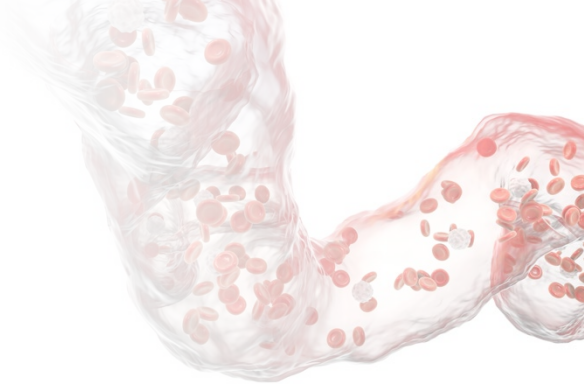
CETP – Sometimes Wisdom Comes With the Years

- CETP biology becoming much better understood
- Importance of Lp(a) and small LDL-particles currently well-defined
- Off-target side effects observed in earlier CETPi drug development eliminated with novel chemistry
- Clinical outcome trials further refined with lessons from previous mistakes

CETPi, cholesteryl ester transfer protein inhibitor; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

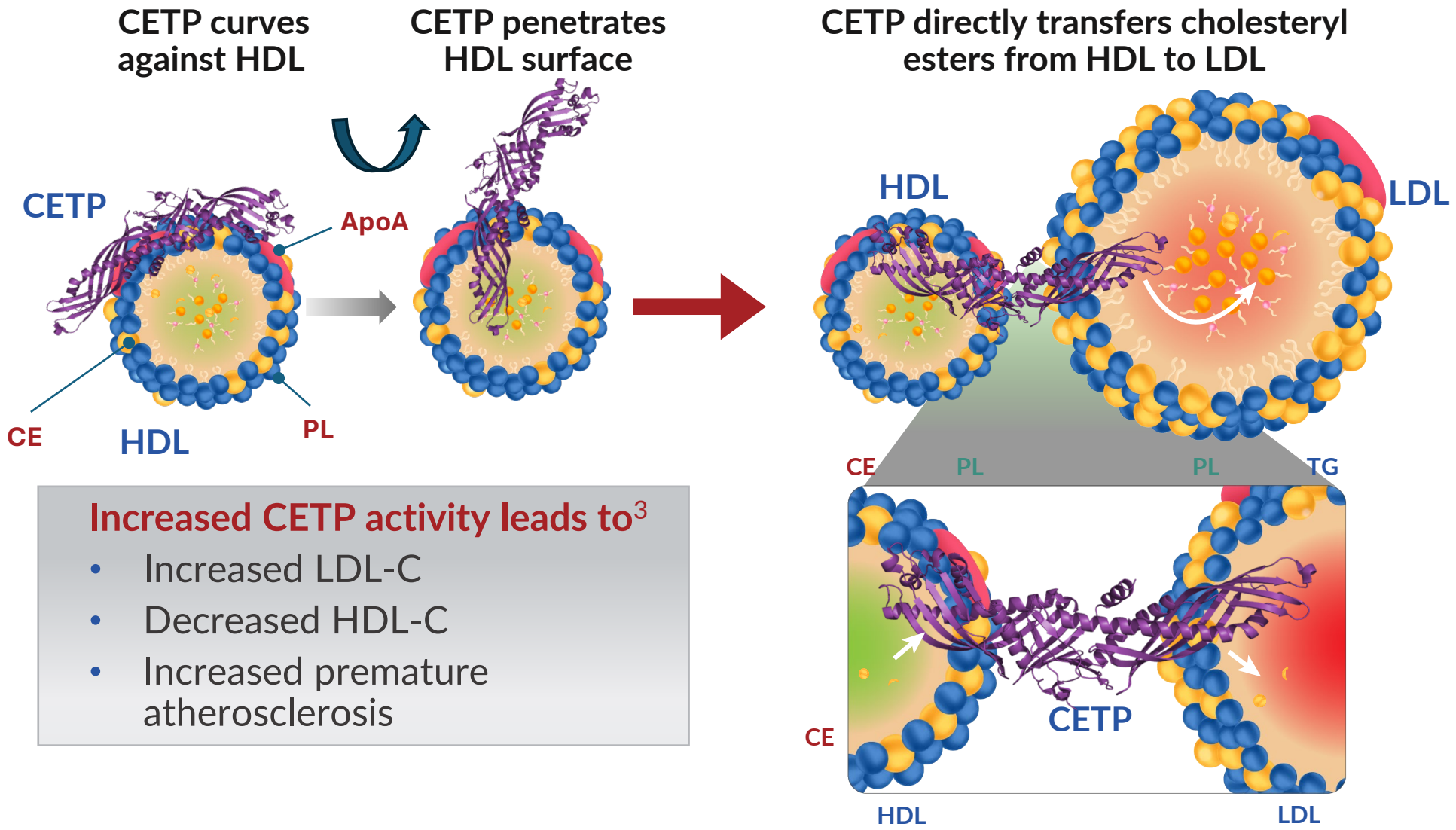
Note: Figures adapted from Zhang M et al. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2017;1862(12):1606-1617. doi:10.1016/j.bbalip.2017.09.004; and from Lei D et al. *J Biol Chem*. 2016;291(27):14034-14044. doi:10.1074/jbc.M116.715565





Atherosclerosis and the Biology of CETP Inhibition

CETP Activity Decreases Circulating HDL-C Levels[1,2]



Increased CETP activity leads to[3]

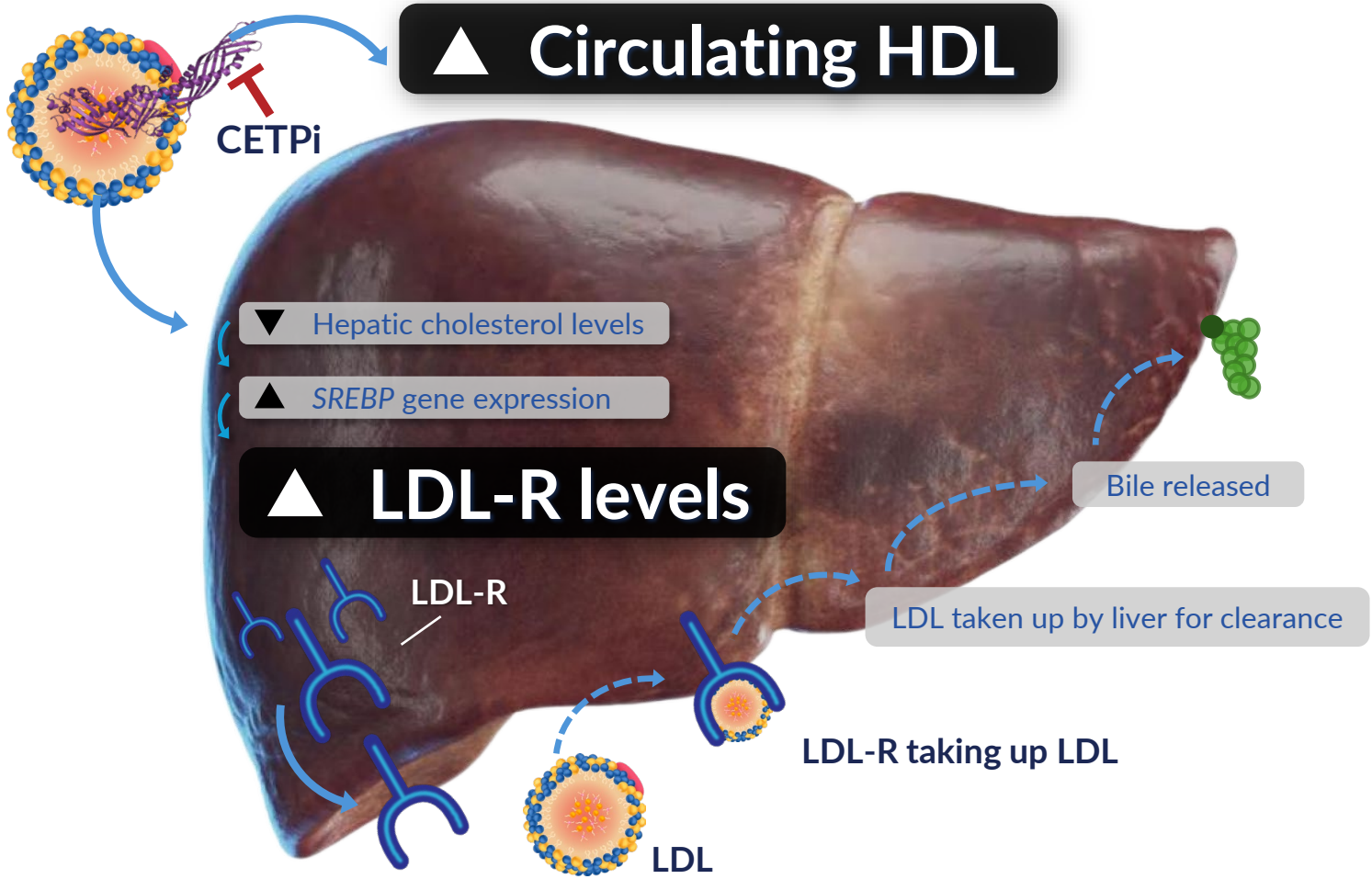
- Increased LDL-C
- Decreased HDL-C
- Increased premature atherosclerosis

TG, triglyceride.

1. Zhang M et al. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2017;1862(12):1606-1617. 2. Lei D et al. *J Biol Chem*. 2016;291(27):14034-14044. 3. Barter PJ, Rye KA. *J Lipid Res*. 2012;53(9):1755-1766.

CETP Inhibition Decreases LDL and Increases HDL in Circulation[1,2]

Positive feedback loop of beneficial changes in cholesterol balance



Decrease in hepatic cholesterol

Increase in hepatic LDL receptors

Increased fractional catabolic rate of LDL and ApoB*

Decrease in plasma LDL levels

+

Increase in plasma HDL levels

CETPi, CETP inhibitor; LDL-R, low-density lipoprotein receptor; SREBP, sterol regulatory element binding protein.

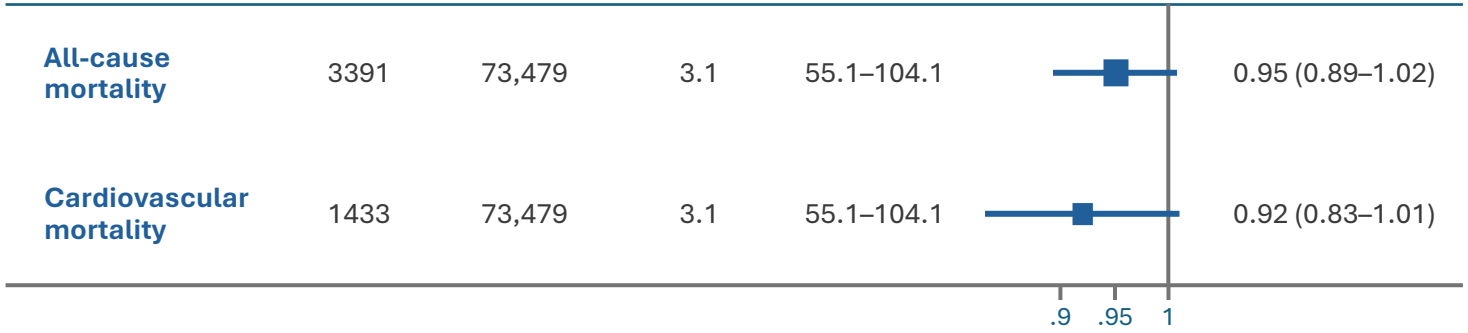
*Fractional catabolic rate is defined as the fraction of the intravascular pool of LDL catabolized per day.[3]

1. Millar JS et al. *J Clin Invest.* 2015;125(6):2510-2522. 2. van der Tuin SJ et al. *J Lipid Res.* 2015;56(11):2085-2093. 3. Benn M et al. *J Biol Chem*. 2005;280(22):21052-21060.

HDL-C Increases Seen With CETP Inhibition Are Safe Based on Various Trials[1]

Association Between Increased Plasma HDL-C in Response to Treatment With CETP Inhibitors and the Risk of All-Cause and CV Mortality (100,000 Patient-Years of Exposure)[1]

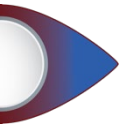
Outcome	No. Events	No. Total	Median follow-up (years)	Range of HDL-C with treatment	HR (95% CI)
All-cause mortality	3391	73,479	3.1	55.1–104.1	0.95 (0.89–1.02)
Cardiovascular mortality	1433	73,479	3.1	55.1–104.1	0.92 (0.83–1.01)

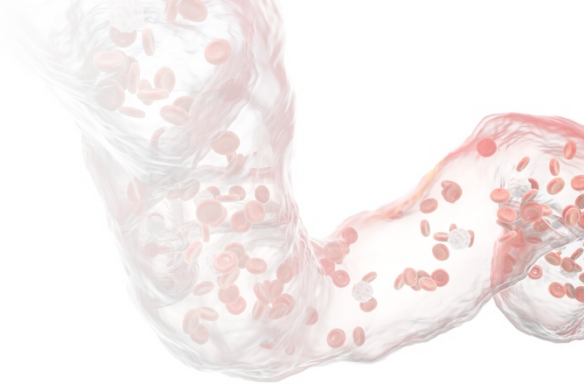


Neither the change in HDL-C nor the **absolute HDL-C level reached** in the ≈15,000 patients on anacetrapib in REVEAL **appears to have had as large an effect on coronary events after 4.1 or after 6.3 years of follow-up** as anticipated based on observational studies[2,3]

REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification.

1. Taheri H et al. *Cardiology*. 2020;145(4):236-250. 2. HPS3/TIMI55–REVEAL Collaborative Group. *N Engl J Med*. 2017;377(13):1217-1227. 3. HPS3/TIMI55-REVEAL Collaborative Group et al. *Eur Heart J*. 2022;43(14):1416-1424. 4. Kastelein JJP et al. *Curr Atheroscler Rep*. 2024;26(2):35-44.





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

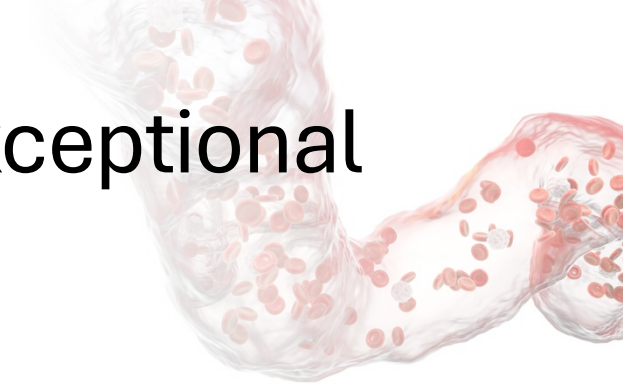
CETP Loss of Function, the Ashkenazi Jewish Longevity Gene Project

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



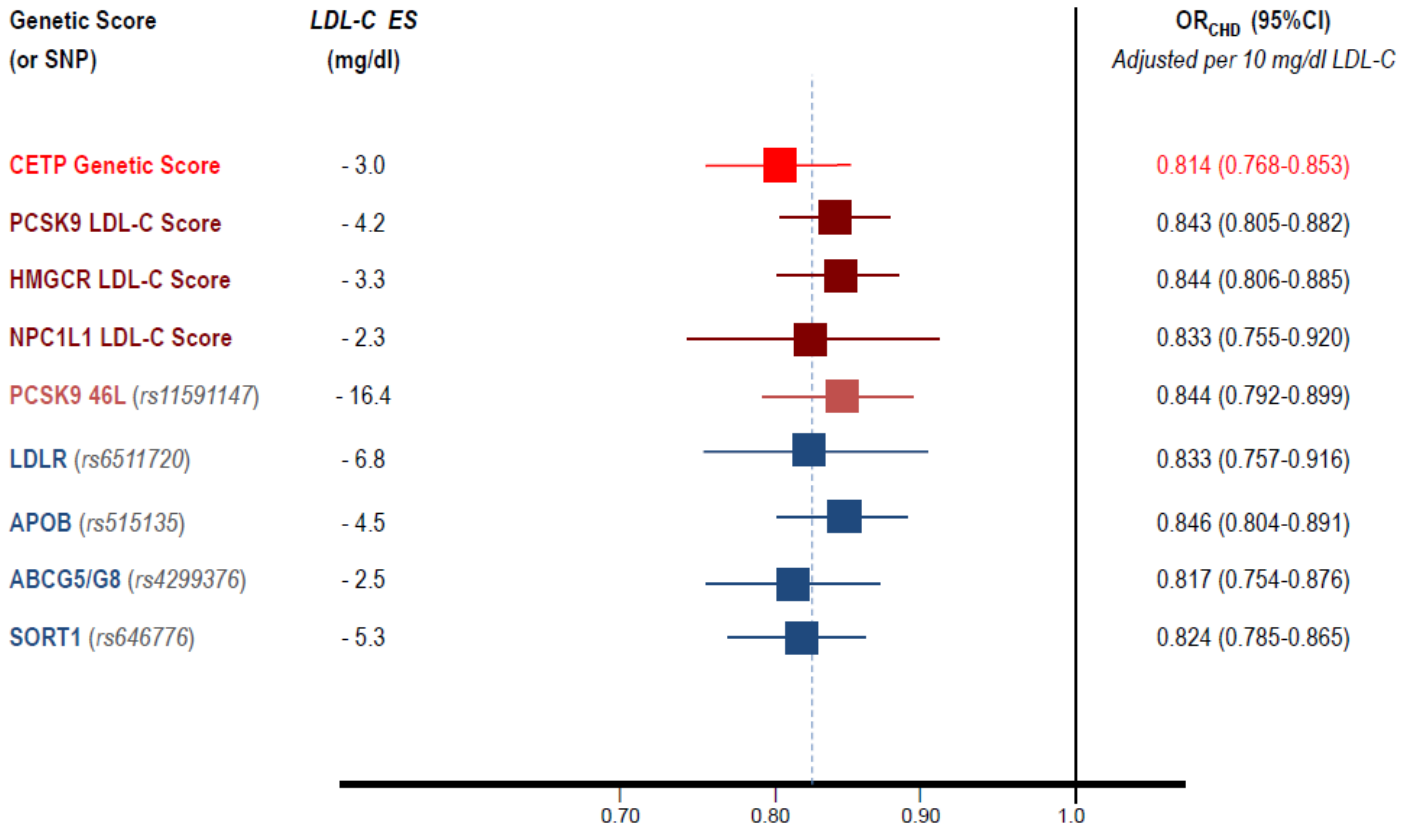
CETP I405V genotype and lipoprotein characteristic and plasma CETP levels in families with exceptional longevity vs control

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

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

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

HDL-C, high-density lipoprotein cholesterol; HMGCR, hydroxymethylglutaryl coenzyme A reductase; NPC1L1, Niemann-Pick C1-like 1.

Ference BA et al. *JAMA*. 2017;318(10):947-956. doi:10.1001/jama.2017.11467

Conclusions

Low CETP activity has overwhelming evidence for its association with ASCVD manifestations

- This relationship is based on apoB containing lipoproteins

CETP inhibition is also investigated as a strategy for prevention of AMD and septicaemia related mortality