What Do We Know Now That Could Have Changed the History of CETP Inhibition?

Lessons from Previous CETP Inhibitor Trials

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Disclosures

- Research support: AstraZeneca, New Amsterdam Pharma, Amgen, Anthera, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron and LipoScience

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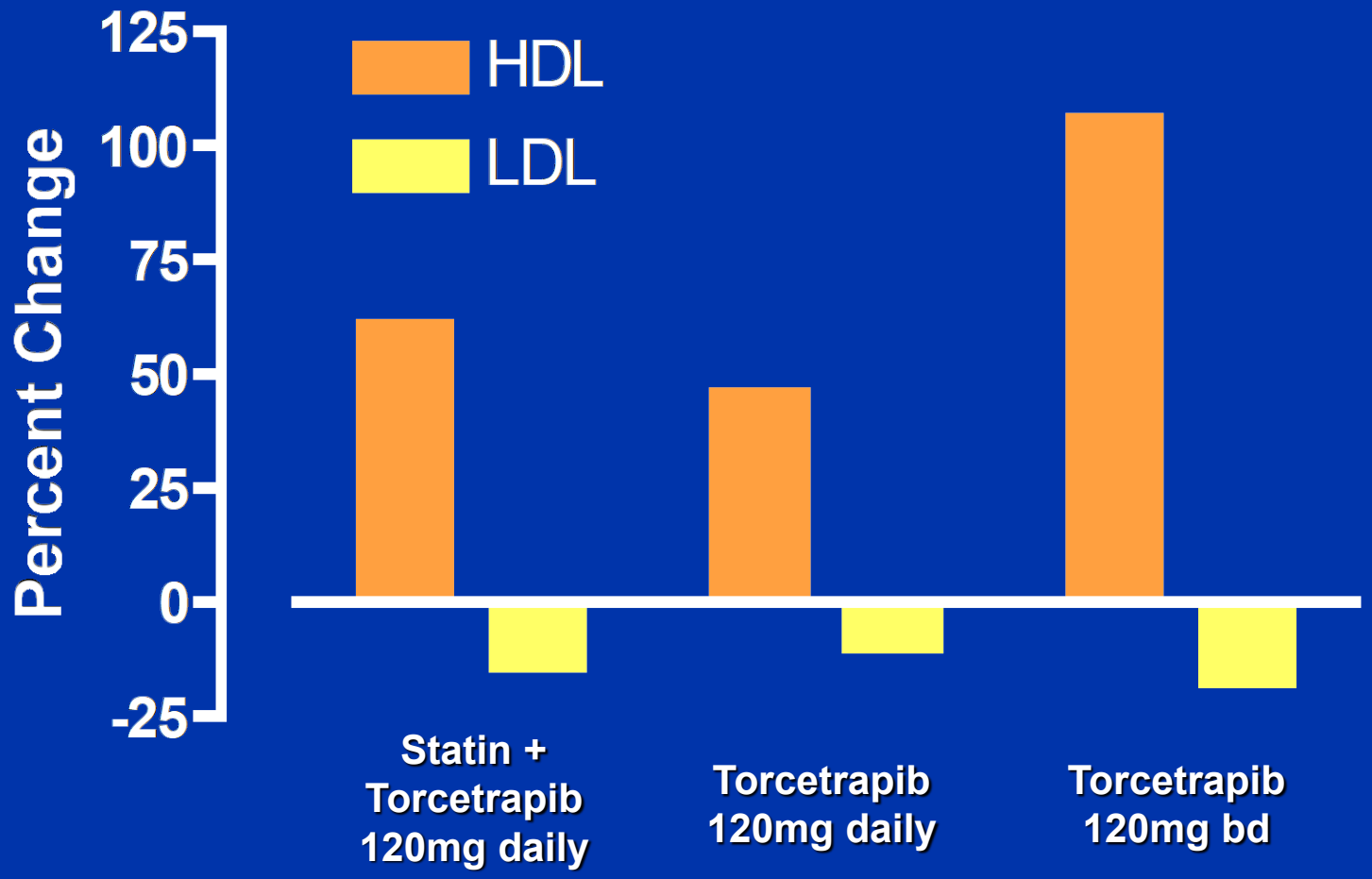
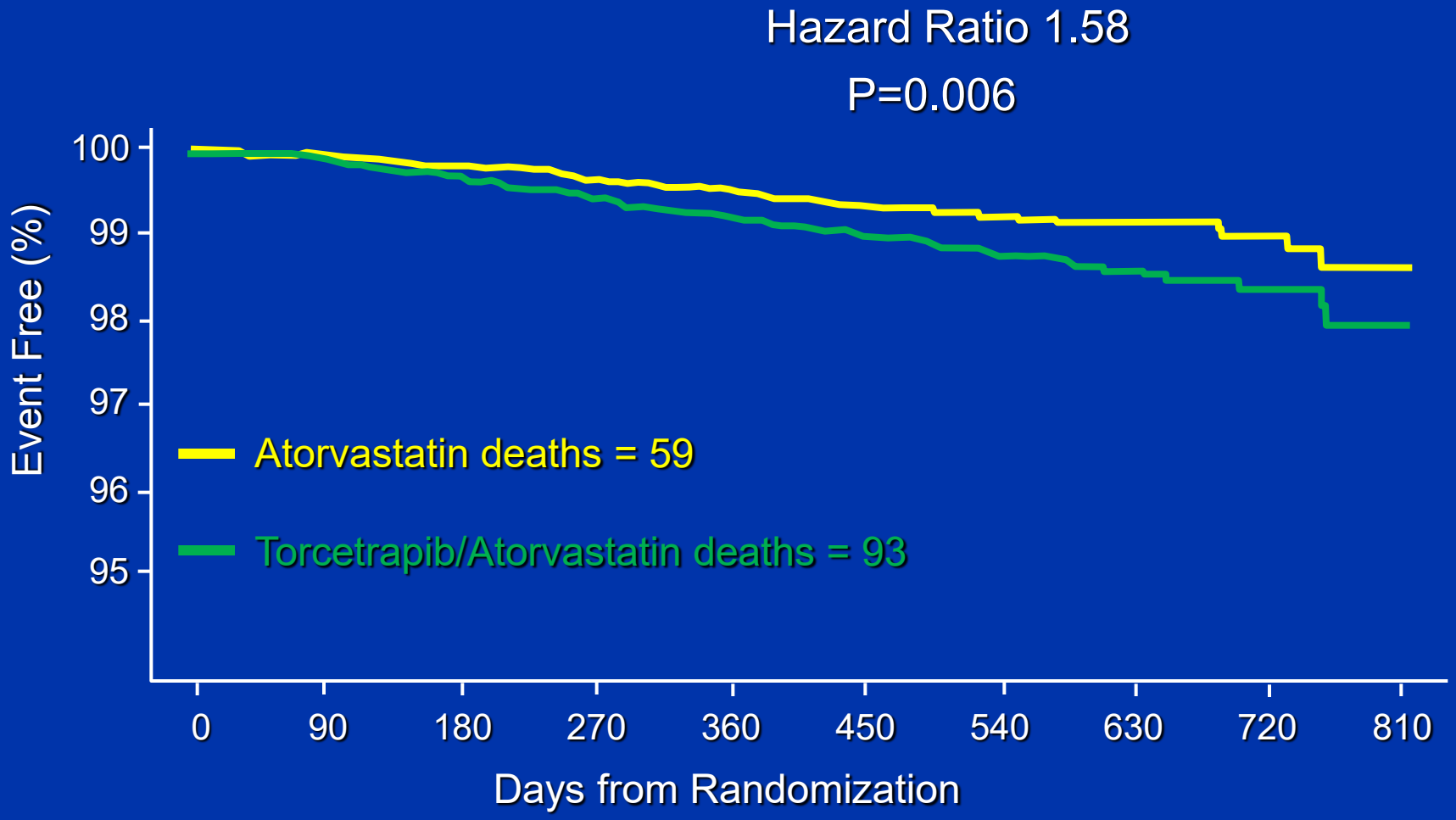
Favorable Effect of CETP Inhibition on Lipid Levels in Humans



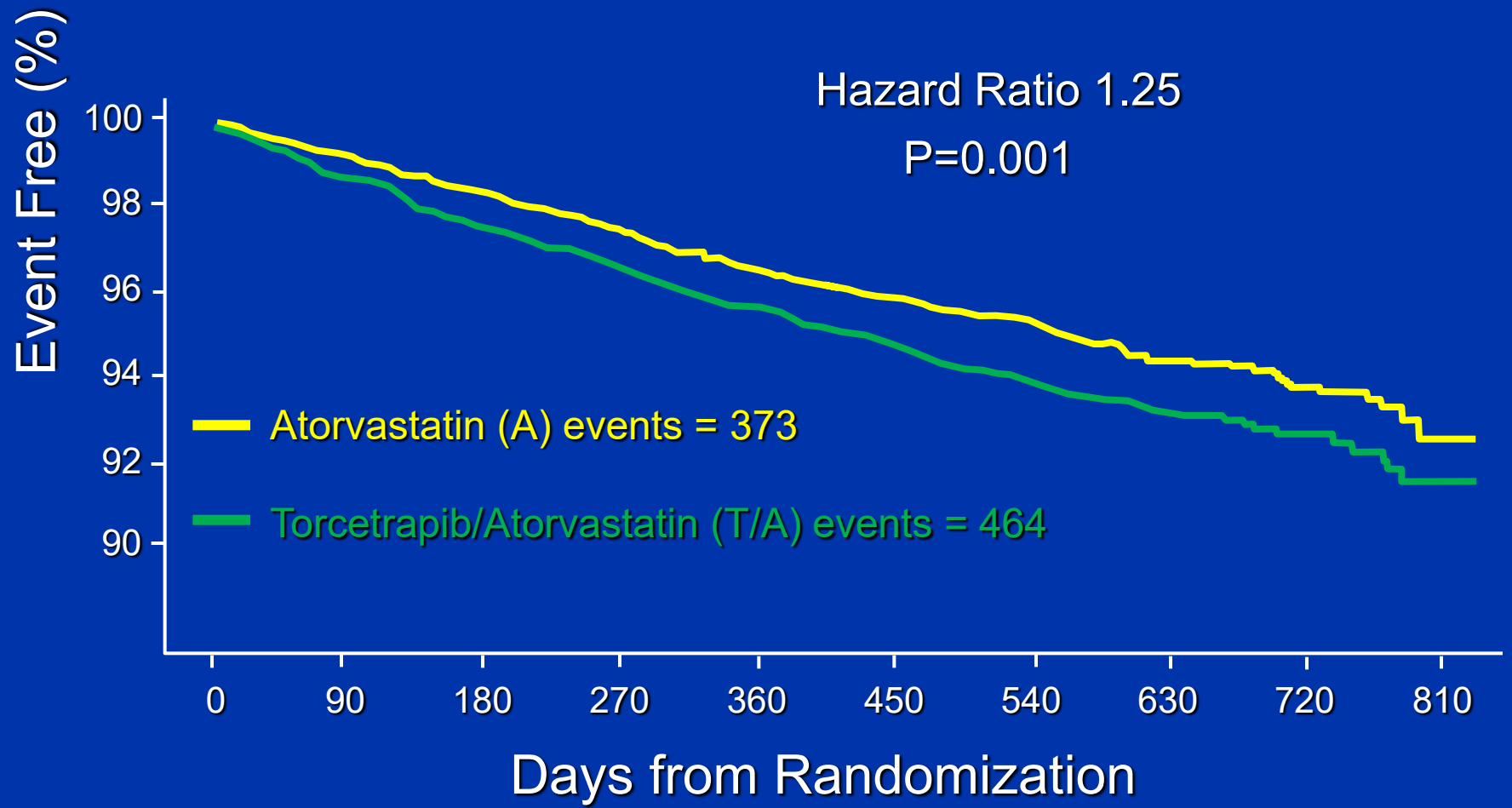
Brousseau *N Engl J Med* 2004; 350:1505-15

Excess Mortality with Torcetrapib



Barter *N Engl J Med* 2007;357:2109-22

ILLUMINATE: Primary Endpoint:
Time to First MCVE*: Kaplan-Meier Plot



*Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

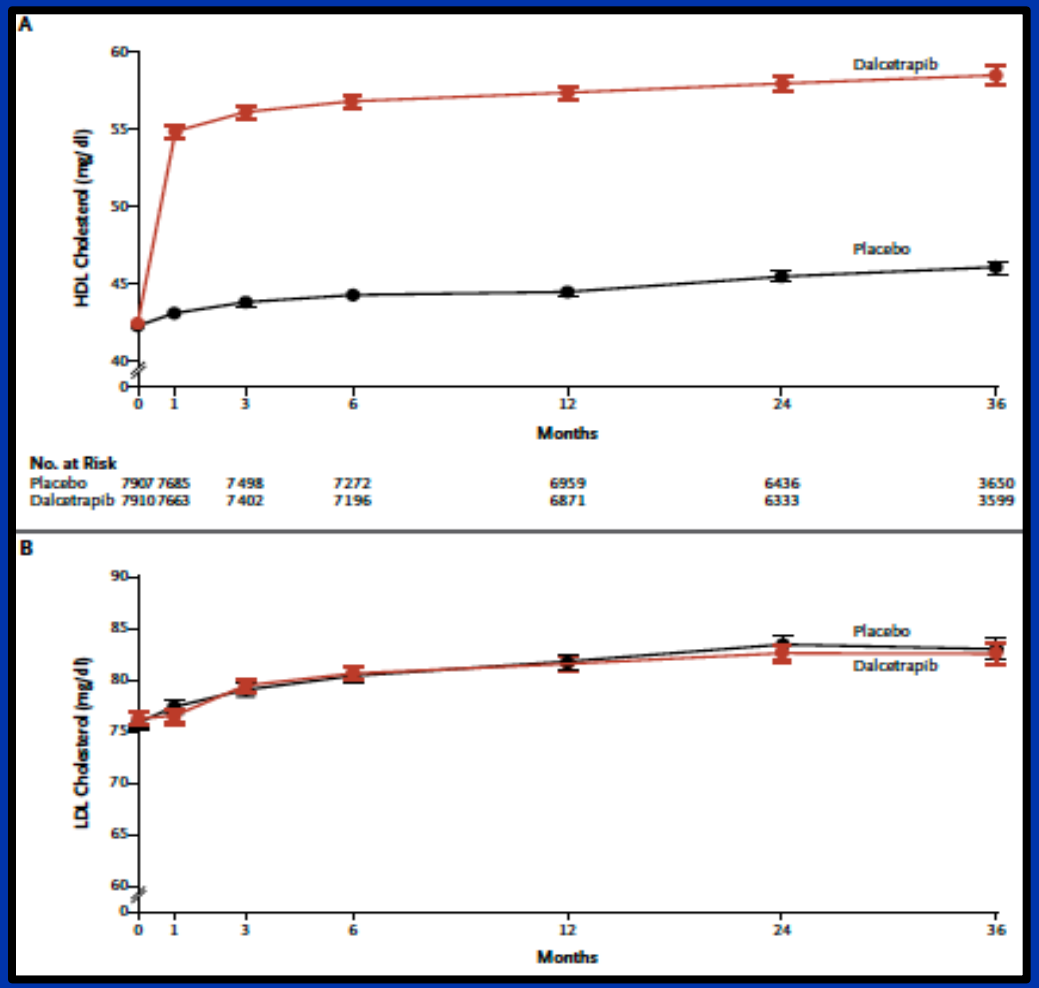
Barter et al, NEJM 2007;357:2109

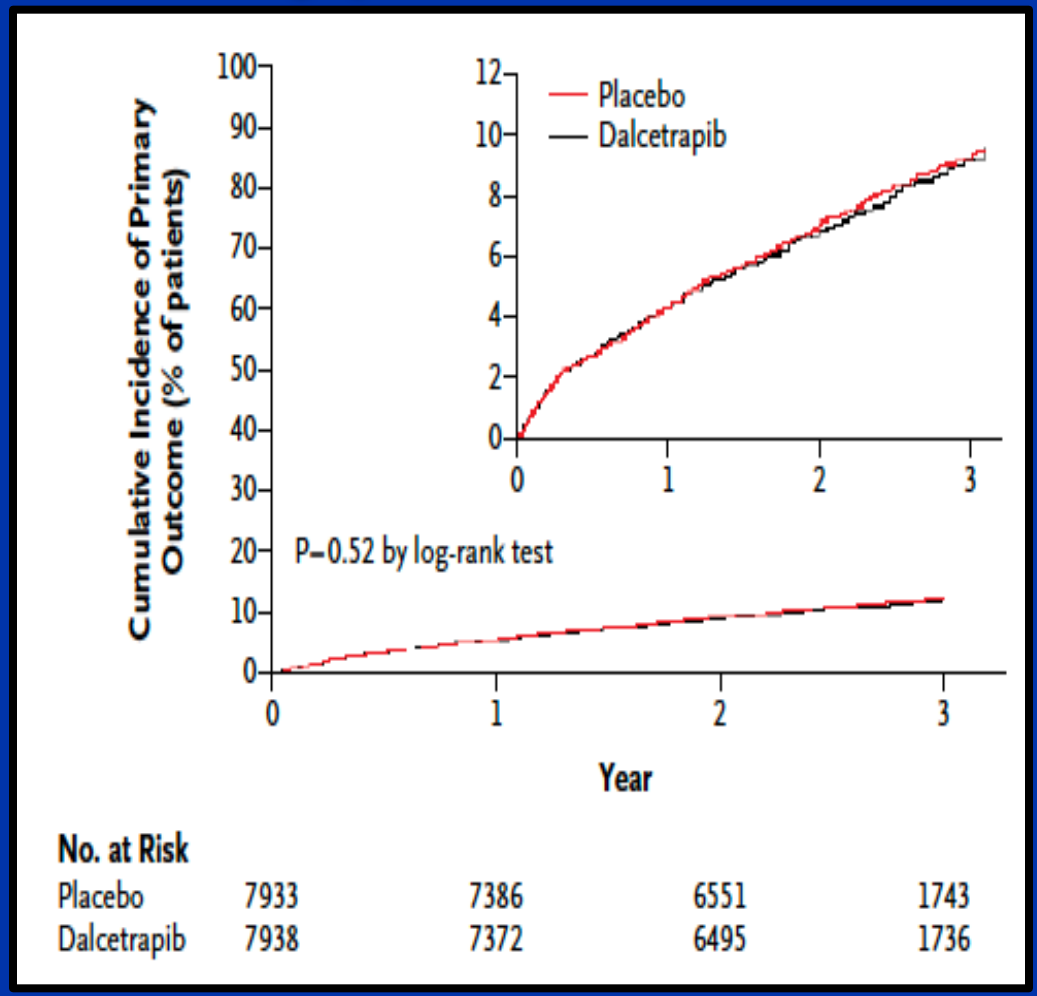
Potential Torcetrapib Off Target Toxicity

- Increase in BP in animals that do not express CETP
- Electrolyte changes consistent with RAAS activation
- Increase adrenal synthesis of aldosterone and cortisol
- Less nitric oxide synthase and greater endothelin expression associate with endothelial dysfunction
- Potential for other CETP inhibitors without such toxicity to undergo clinical development

Torcetrapib was a “One Off”

Dalcetrapib Does Not Reduce CV Risk
The End of the HDL Hypothesis?

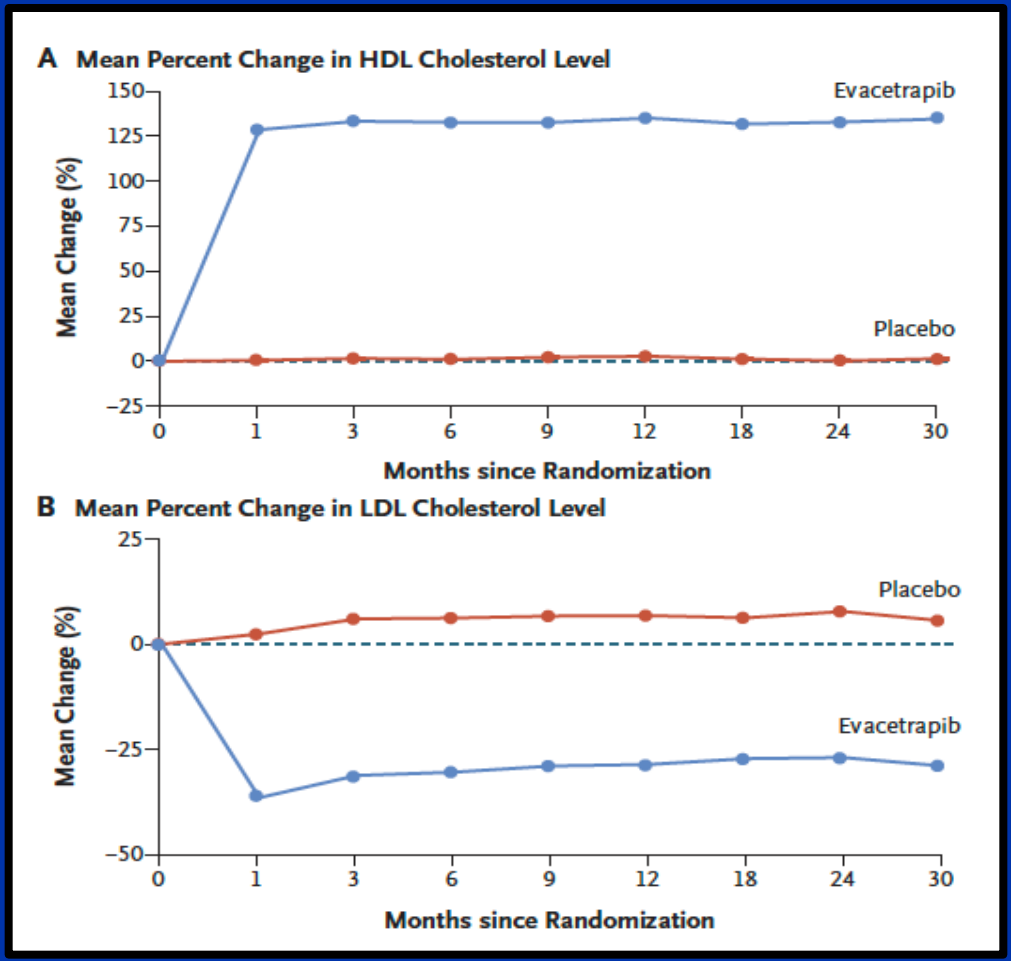


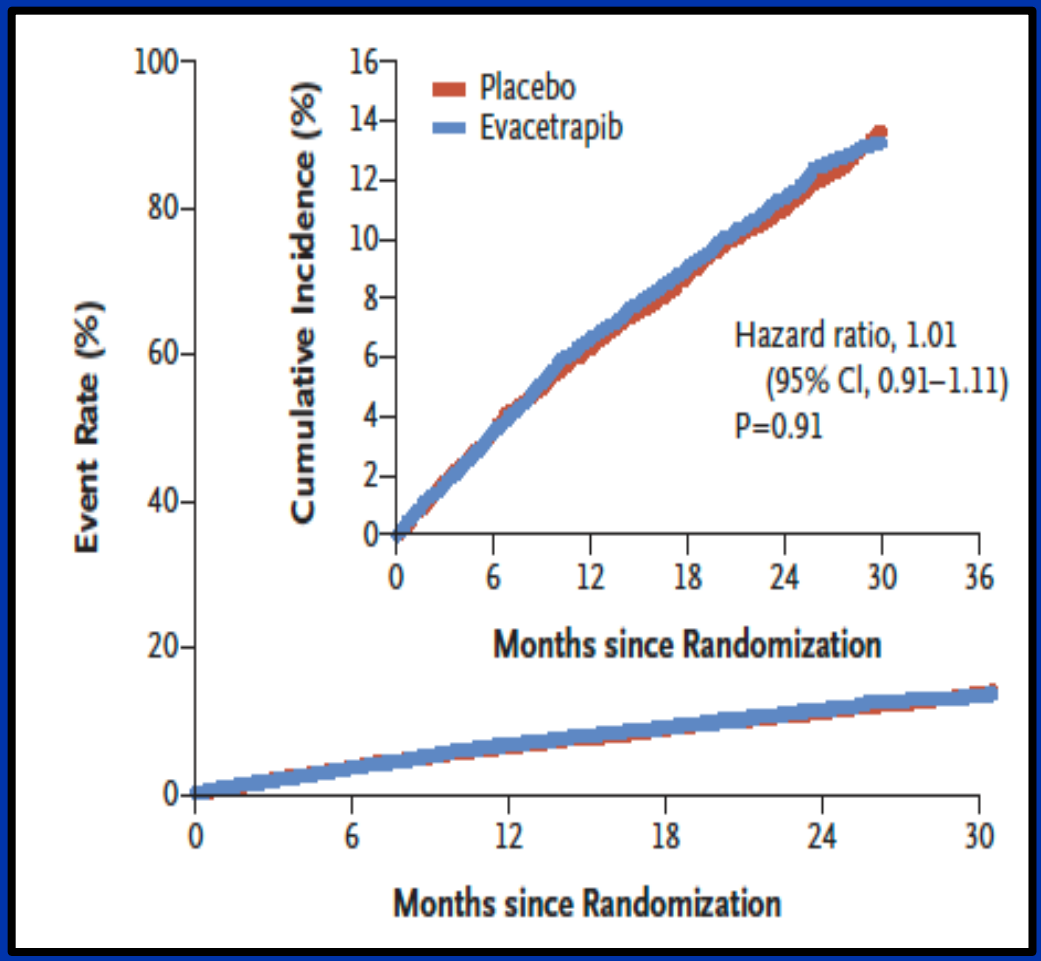


Schwartz, Nicholls et al *N Engl J Med.* 2012;367:2088-99.

Dalcetrapib Did Not Lower LDL-C

Evacetrapib Does Not Reduce CV Risk





Lincoff, Nicholls et al *N Engl J Med.* 2017;376:1933-42.

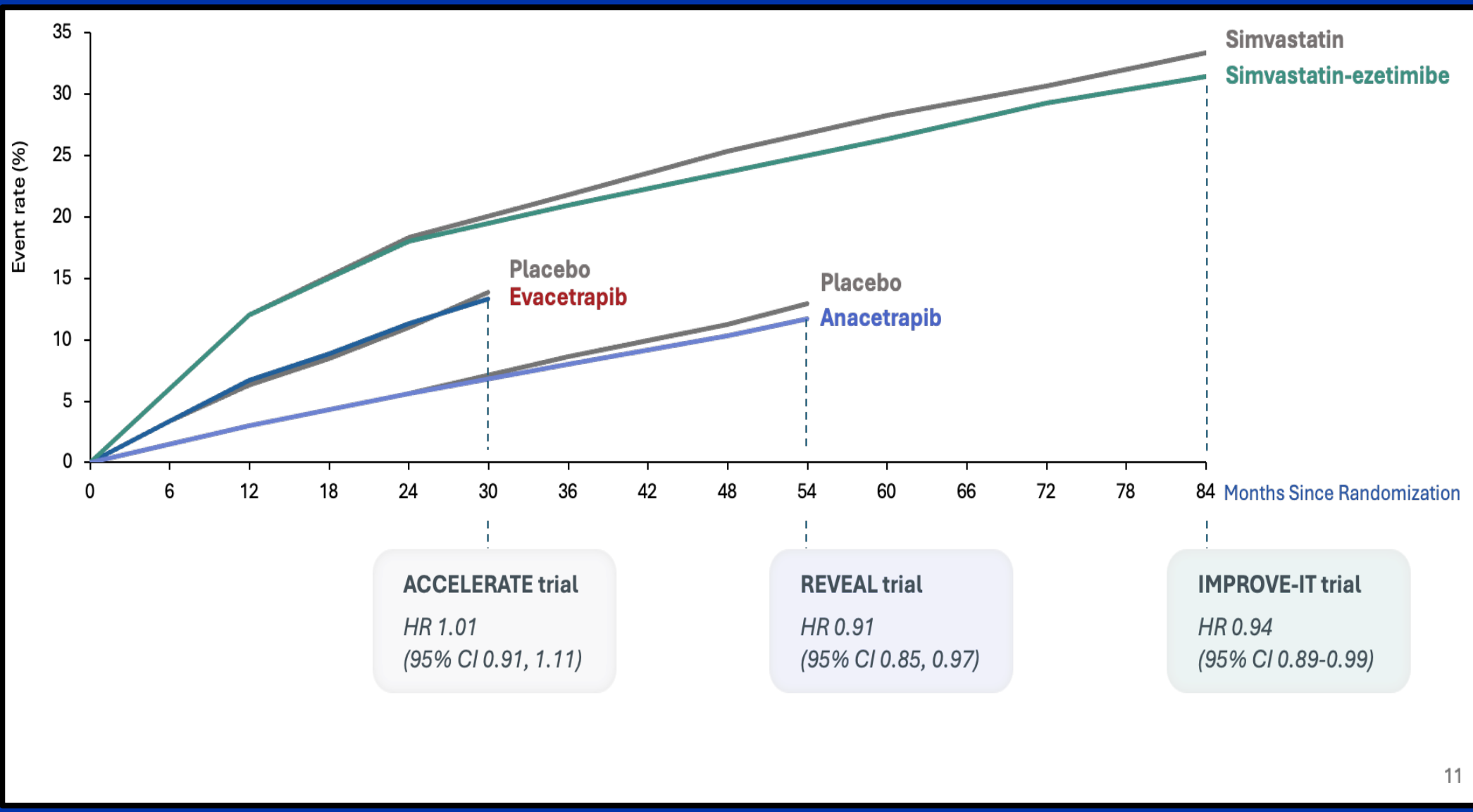
LDL-C Measured with the Wrong Assay

Event or Laboratory Variable	Evacetrapib (N=6038)	Placebo (N=6054)	Hazard Ratio (95% CI)	P Value*
Primary composite end point — no. (%)†	779 (12.9)	776 (12.8)	1.01 (0.91 to 1.11)	0.91
Death from cardiovascular causes	143 (2.4)	166 (2.7)	0.86 (0.69 to 1.08)	0.19
Myocardial infarction	258 (4.3)	259 (4.3)	1.00 (0.84 to 1.18)	0.97
Stroke	94 (1.6)	98 (1.6)	0.96 (0.72 to 1.27)	0.77
Hospitalization for unstable angina	155 (2.6)	146 (2.4)	1.06 (0.85 to 1.33)	0.60
Coronary revascularization	487 (8.1)	485 (8.0)	1.01 (0.89 to 1.14)	0.94
Secondary composite end point — no. (%)‡	437 (7.2)	453 (7.5)	0.97 (0.85 to 1.10)	0.59
All-cause mortality — no. (%)	231 (3.8)	276 (4.6)	0.84 (0.70 to 1.00)	0.04
Lipids — % change§				
HDL cholesterol	133.2±57.2	1.6±17.5	—	<0.001
LDL cholesterol	−31.1±27.6	6.0±29.0	—	<0.001
Median triglycerides (IQR)	−6.0 (−24 to 16.7)	0 (−17.7 to 22.8)	—	<0.001
Apolipoprotein A1	50.5±30.8	1.1±21.5	—	<0.001
Apolipoprotein B	−15.5±22.3	3.8±22.0	—	<0.001
Median lipoprotein(a) (IQR)	−22.3 (−50.6 to 0)	0 (−15.4 to 14.9)	—	<0.001

LDL-C was measured using a direct assay vs preparative ultracentrifugation, which is more sensitive at low absolute LDL-C levels

Lincoff, Nicholls et al *N Engl J Med.* 2017;376:1933-42.

Event Curve Separation in Lipid CVOTs

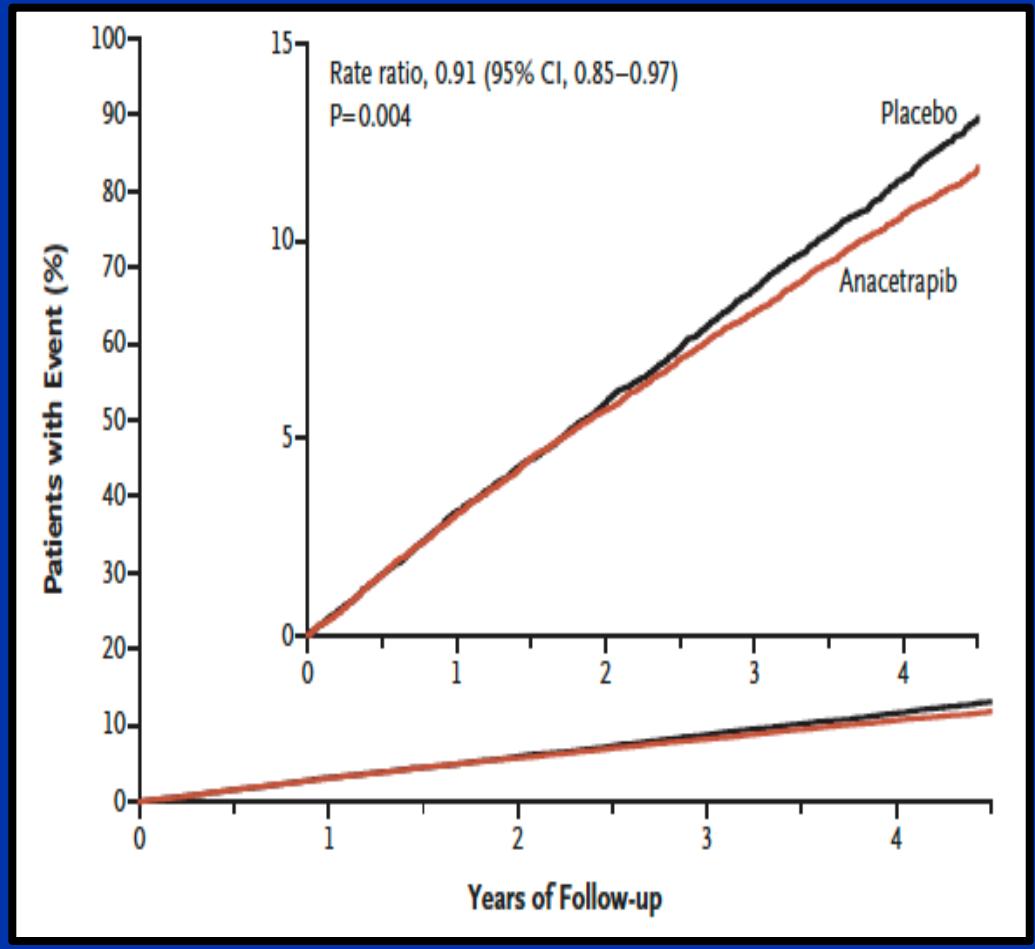


Cannon et al. *N Engl J Med.* 2015;372:2387-97. Lincoff et al. *N Engl J Med.* 2017;376:1933-42. HPS3/TIMI55-REVEAL Collaborative Group. N Engl J Med. 2017;377:1217-27.

Evacetrapib's CVOT was Underpowered and Too Short

Anacetrapib and Reduction in CV Risk

Lipid or Lipoprotein	Anacetrapib (N=15,225)	Placebo (N=15,224)	Absolute Difference†	Relative Difference
				percent
Mean LDL cholesterol (mg/dl)				
Direct method	38	64	−26	−41
Beta quantification‡	53	63	−11	−17
Mean non-HDL cholesterol (mg/dl)	79	96	−17	−18
Mean HDL cholesterol (mg/dl)	85	42	43	104
Mean apolipoprotein A1 (mg/dl)	160	118	42	36
Mean apolipoprotein B (mg/dl)	54	66	−12	−18
Mean triglycerides (mg/dl)	136	146	−10	−7
Mean lipoprotein(a) (nmol/liter)	43	58	−15	−25

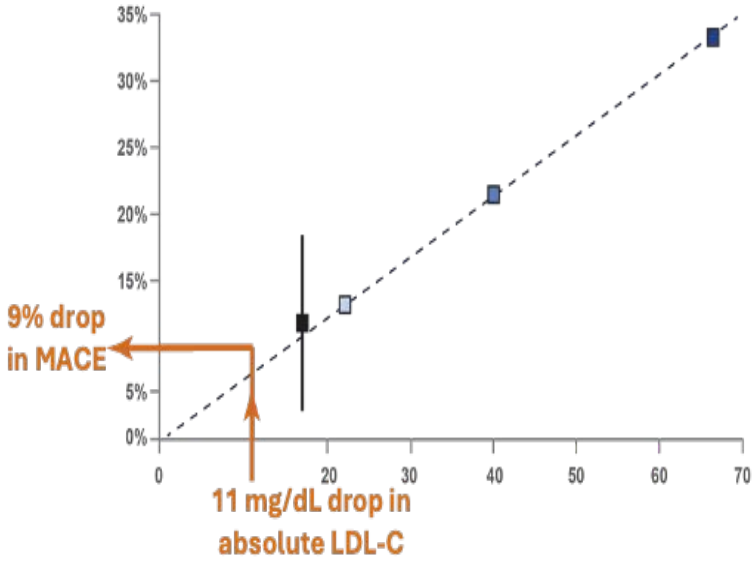


HPS3/TIMI55 – REVEAL Collaborative Group. *N Engl J Med.* 2017;377:1217-27.

Modest CV Benefit with Anacetrapib was Predictable

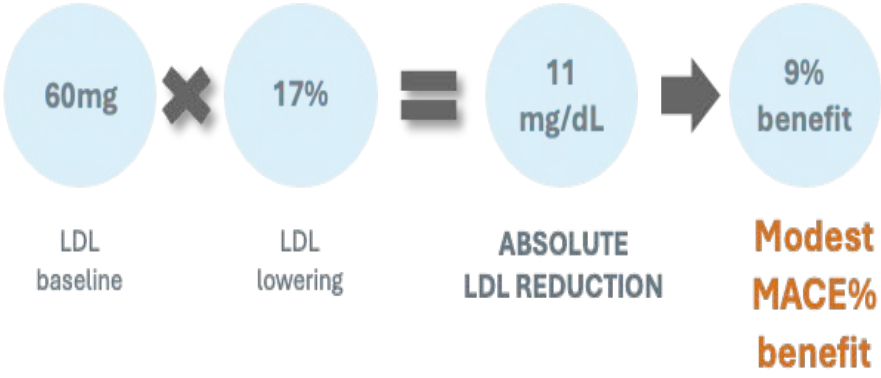
Learning 1: Predictable MACE benefit

- A 6% drop in MACE would be predicted by the CTT metaregression line; 9% observed
- Indicates CETPi behaves like statins and possibly better in reducing MACE

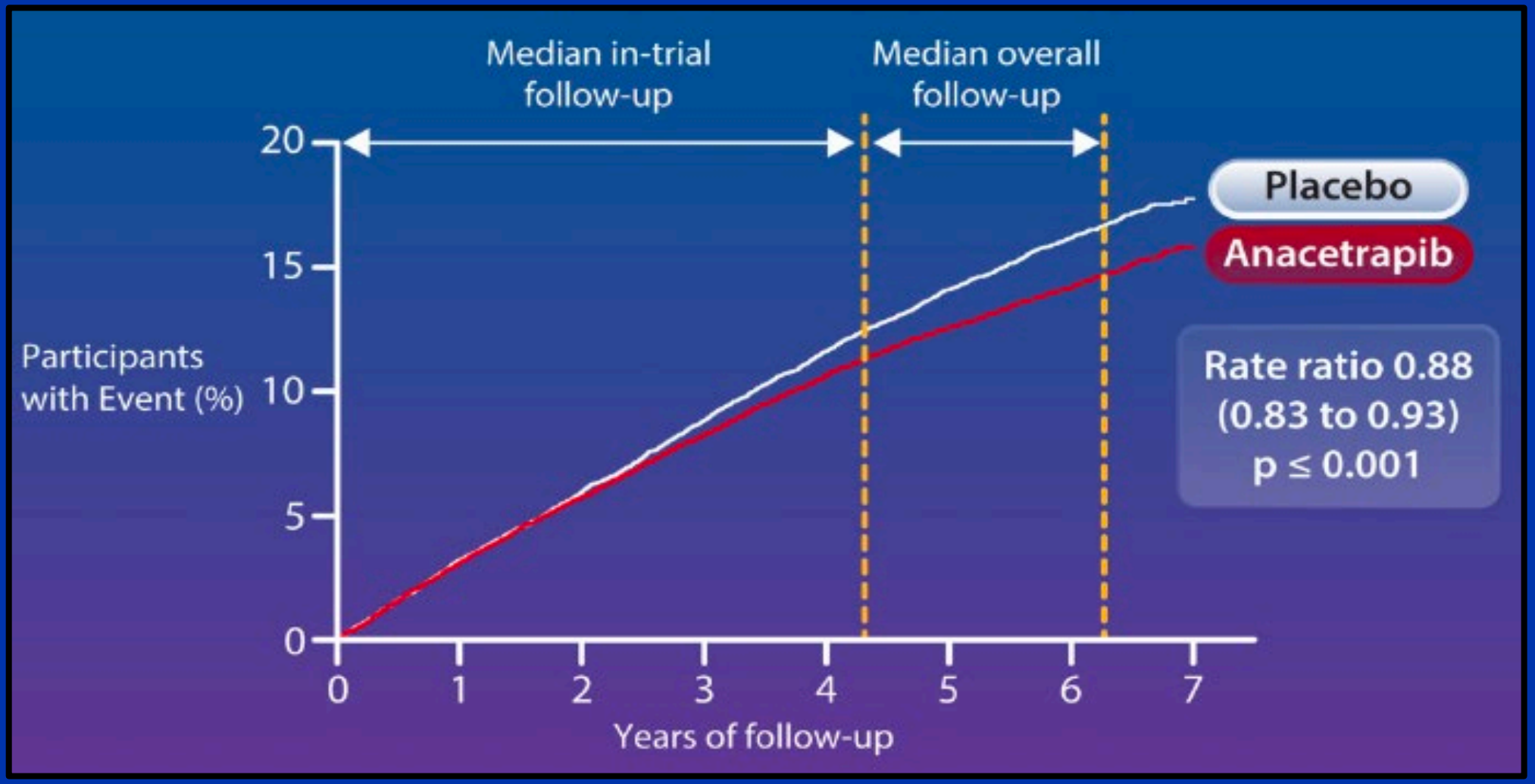


Learning 2: Baseline levels were too low

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



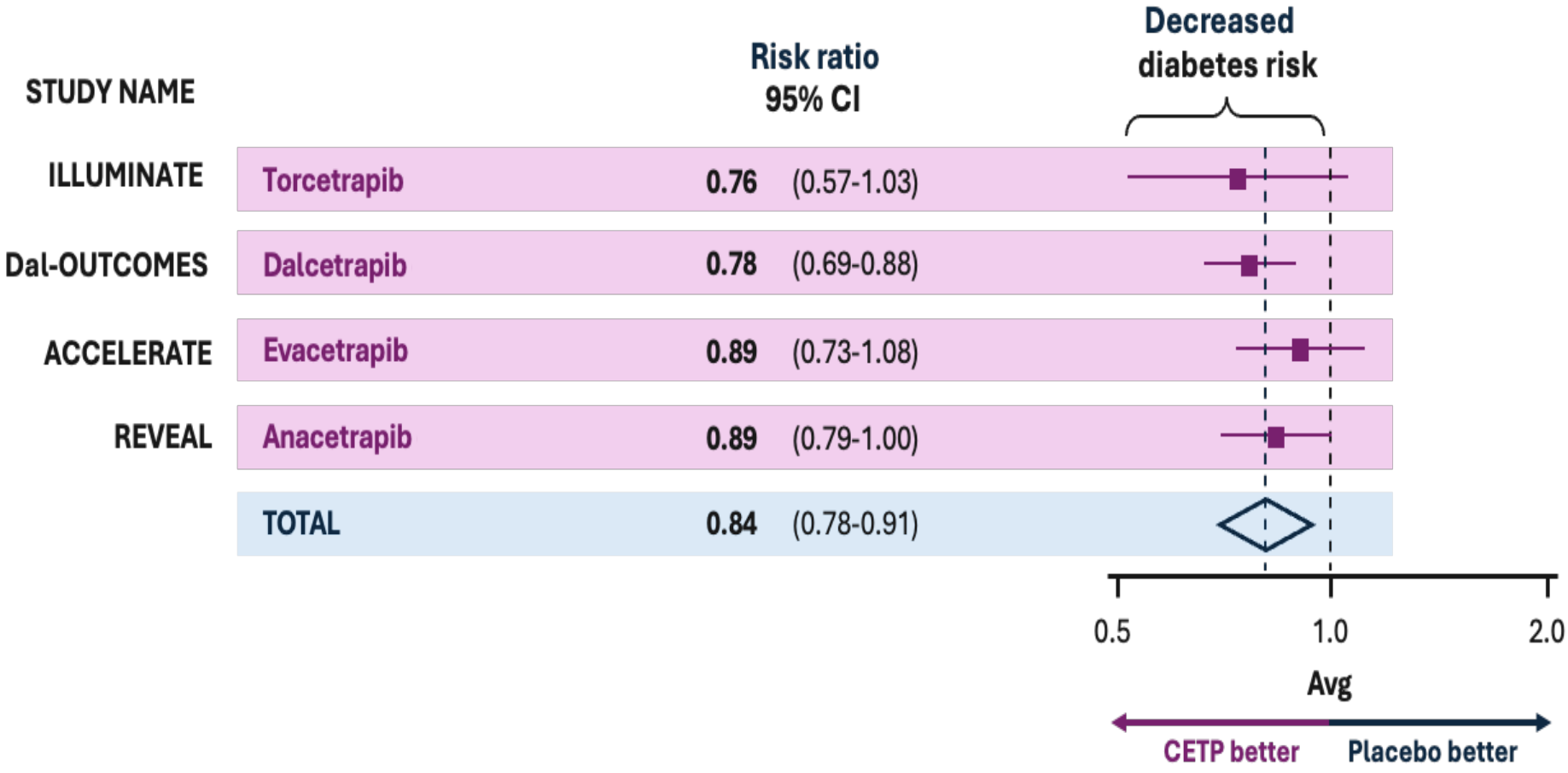
Greater CV Benefits with Anacetrapib on Longer Follow Up



HPS3/TIMI55 – REVEAL Collaborative Group. *Eur Heart J.* 2022;43:1416-24.

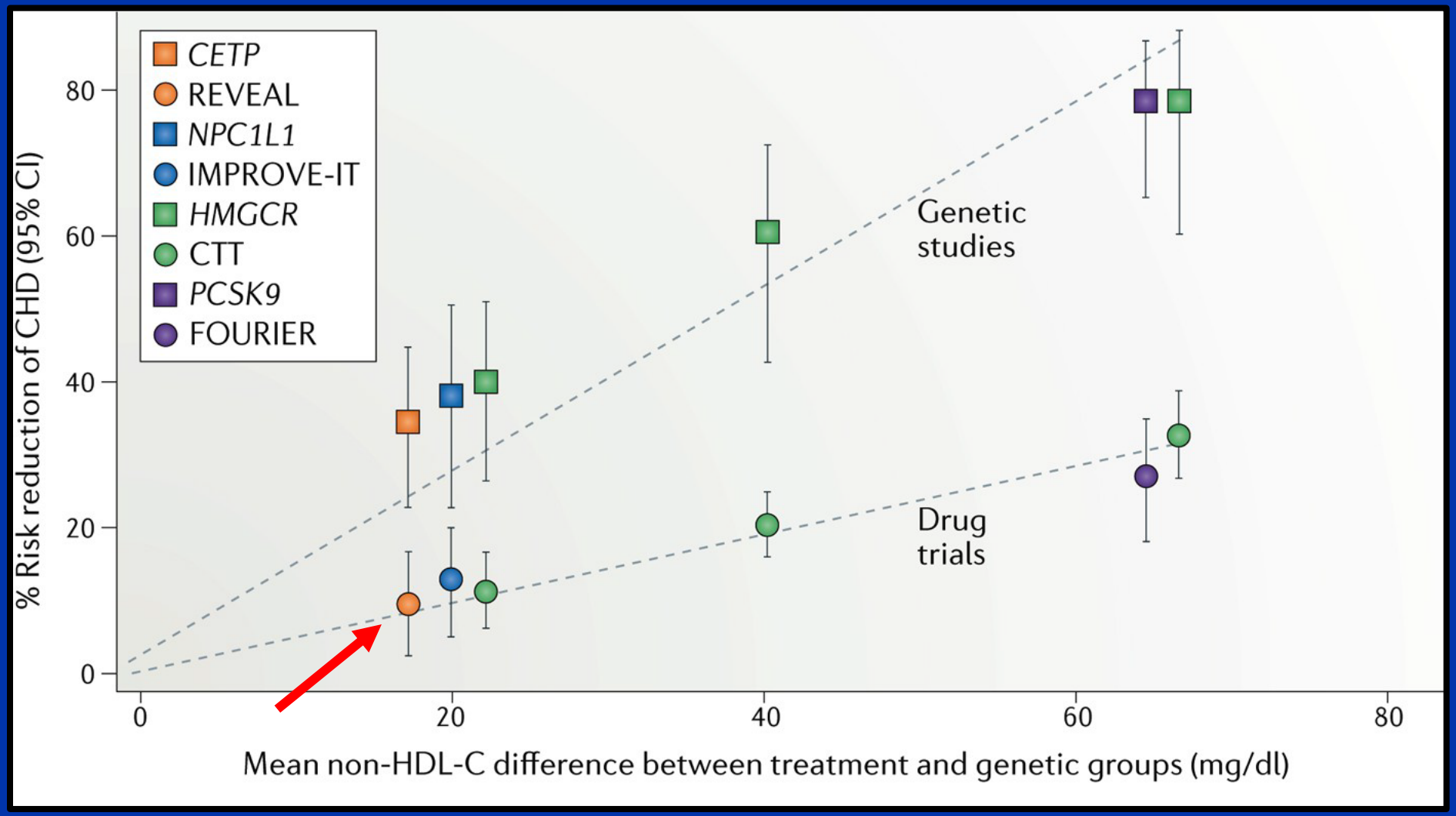
Anacetrapib's CVOT Worked as Expected with No Safety Concerns

Reduction in Diabetes Risk with CETP Inhibitors



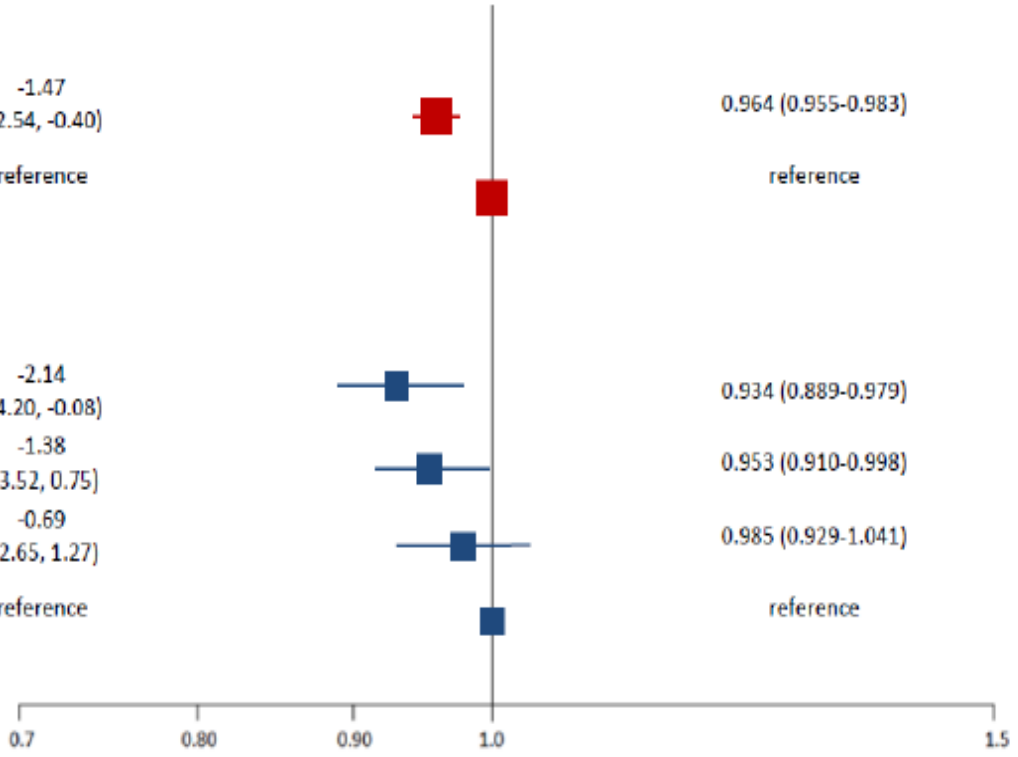
Sattar N et al. *Lancet*. 2010;375:735-42..Dangas K et al. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:622-32. Nurmohamed NS et al. *Cardiovasc Res*. 2022;118:2919-31.

REVEAL: Non-HDL-C Lowering and CV Benefit with Anacetrapib



CETP Variants Associate with Cardiovascular Risk

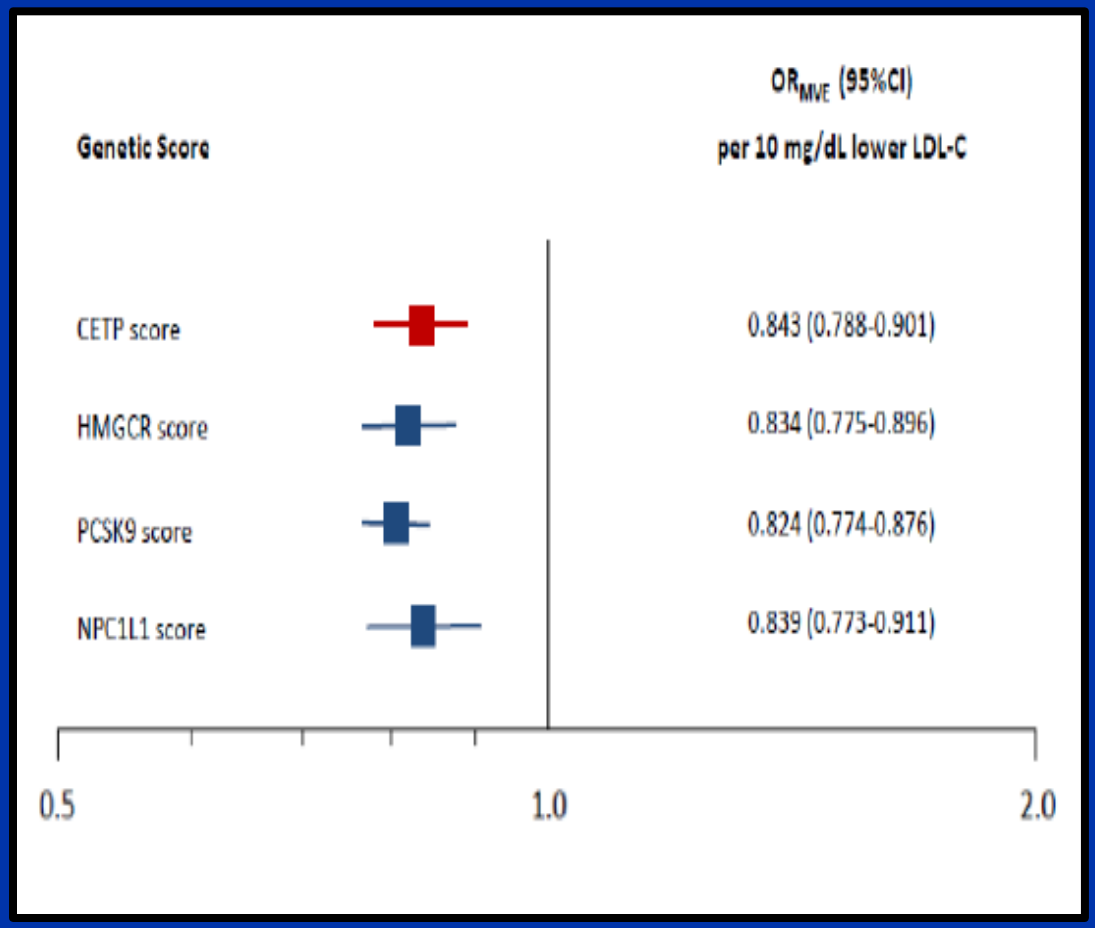
Analysis	No. participants (n)	No. cases (%)	Δ HDL-C (95% CI)	Δ LDL-C (95% CI)	Δ apoB (95% CI)	OR_{MVE} (95%CI)
Primary Analysis						
CETP score ≥ median	53 402	7048 (13.2)	4.62 (3.84, 5.40)	-2.15 (-3.33, -0.97)	-1.47 (-2.54, -0.40)	0.964 (0.955-0.983)
CETP score < median	49 435	6773 (13.7)	Reference	reference	reference	reference
Dose Response						
CETP score quartile 4	25 925	3371 (13.0)	7.12 (5.47, 8.77)	-3.29 (-5.52, -1.06)	-2.14 (-4.20, -0.08)	0.934 (0.889-0.979)
CETP score quartile 3	26 048	3459 (13.3)	4.98 (3.39, 6.57)	-2.32 (-4.27, -0.37)	-1.38 (-3.52, 0.75)	0.953 (0.910-0.998)
CETP score quartile 2	25 011	3415 (13.7)	2.37 (1.14, 3.60)	-0.95 (-3.09, -1.19)	-0.69 (-2.65, 1.27)	0.985 (0.929-1.041)
CETP score quartile 1	25 853	3576 (13.8)	reference	reference	reference	reference



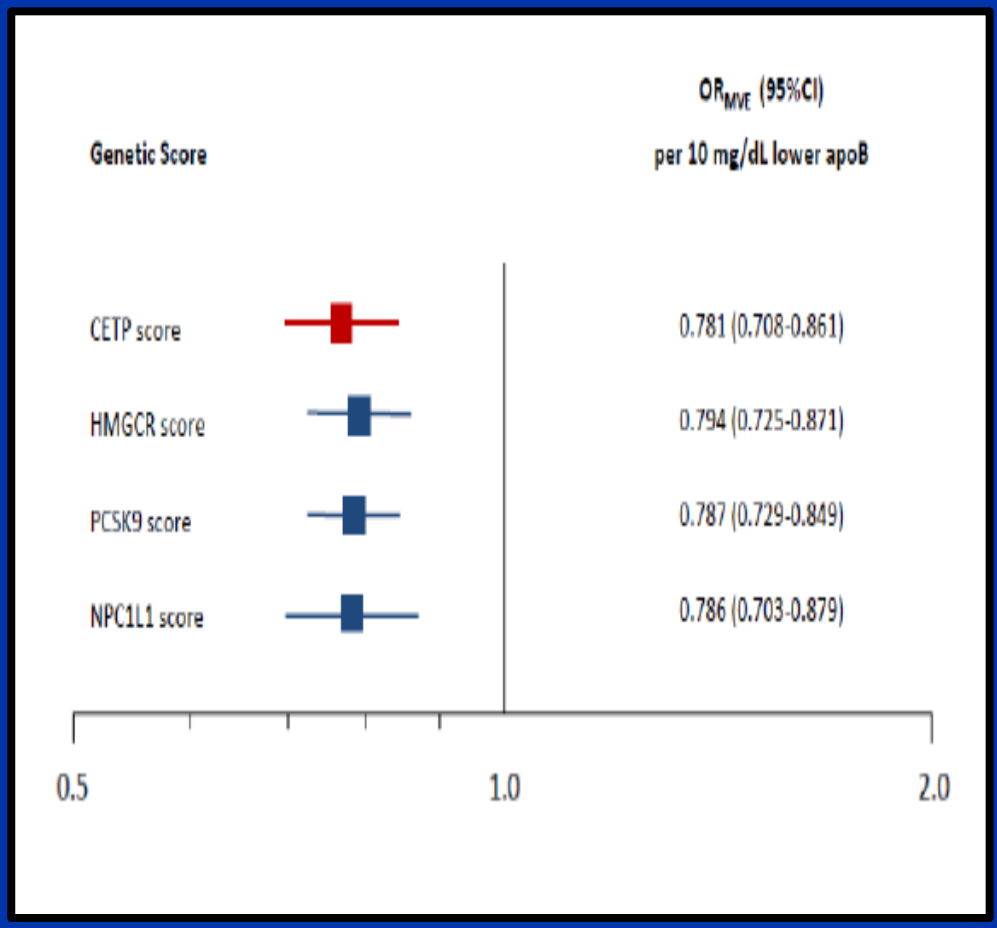
Ference, Ray, Nicholls et al JAMA. 2017

Lipid Variants, LDL-C, ApoB and CV Risk

LDL-C



ApoB



Ference, Ray, Nicholls et al JAMA. 2017

Summary

- Prior clinical trials of CETP inhibitors have informed the development path moving forward
- The greatest CV potential of CETP inhibition lies in their ability to lower LDL-C levels
- We must design trials of CETP inhibitors that lower LDL-C in patients with high LDL-C levels