The inhibition of CETP: From simply raising HDL-c to promoting cholesterol efflux and lowering of atherogenic lipoproteins

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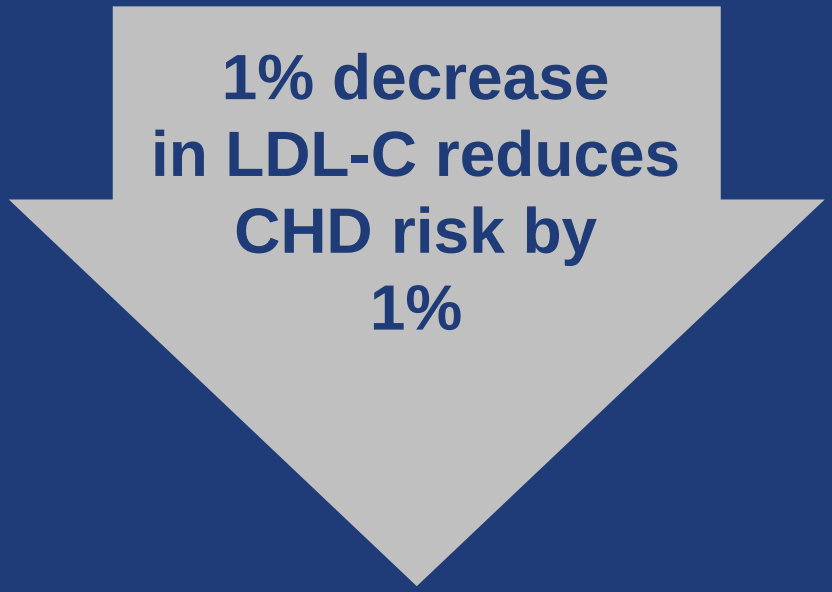
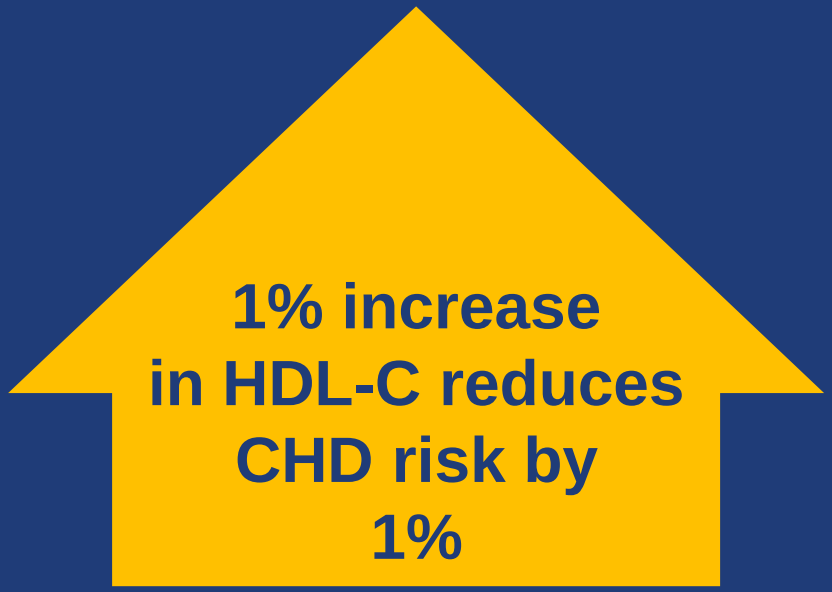
CETP inhibition results

Confusing?

Relationship between changes in LDL-C and HDL-C levels and CHD risk





National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation 2002;106:3143–42
Barter P. Eur Heart J Suppl 2004;6:A19–A22

What is the impact of HDL on CVD in large trials?

- How does HDL protect?
- How can we increase HDL?

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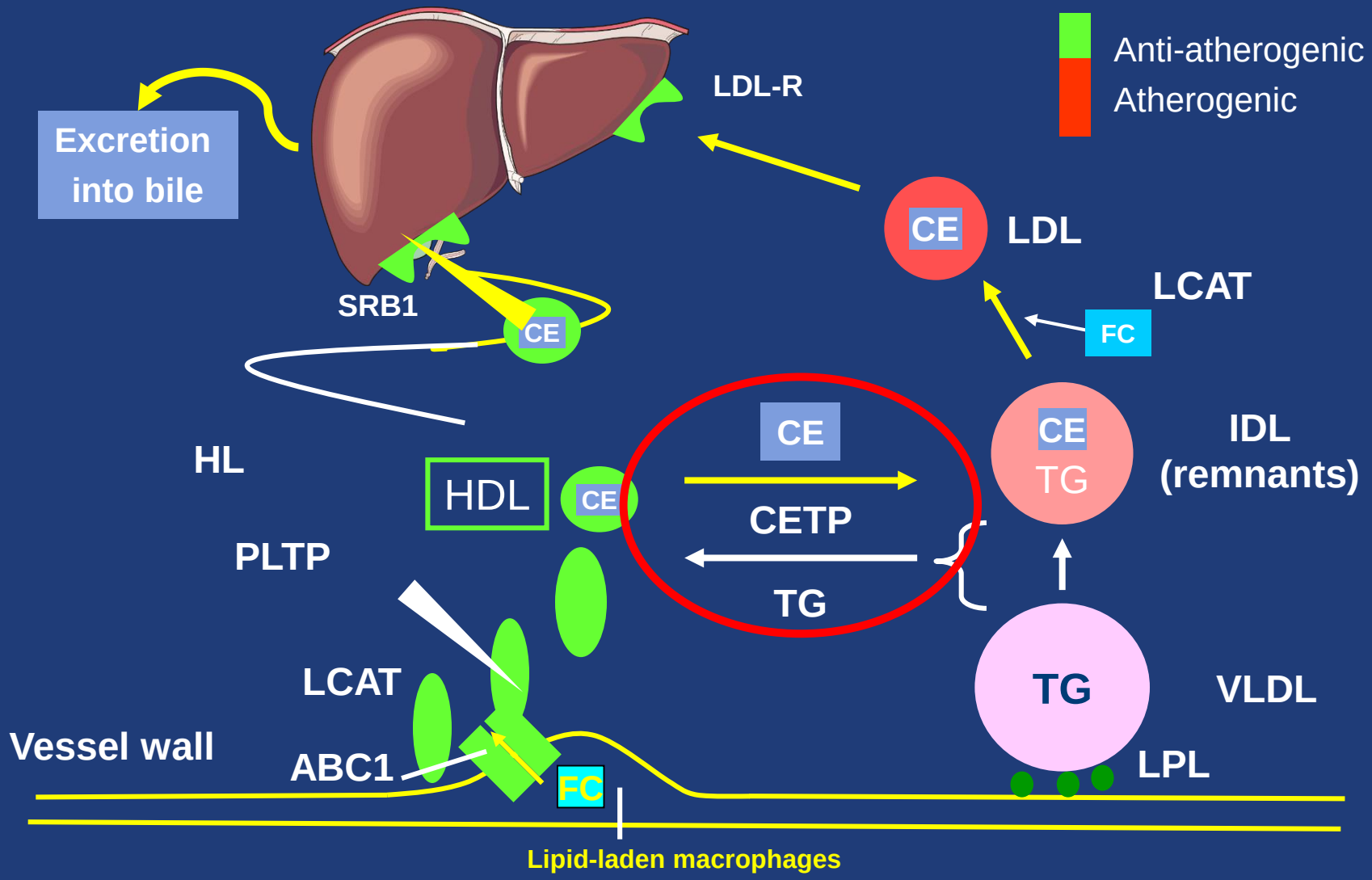
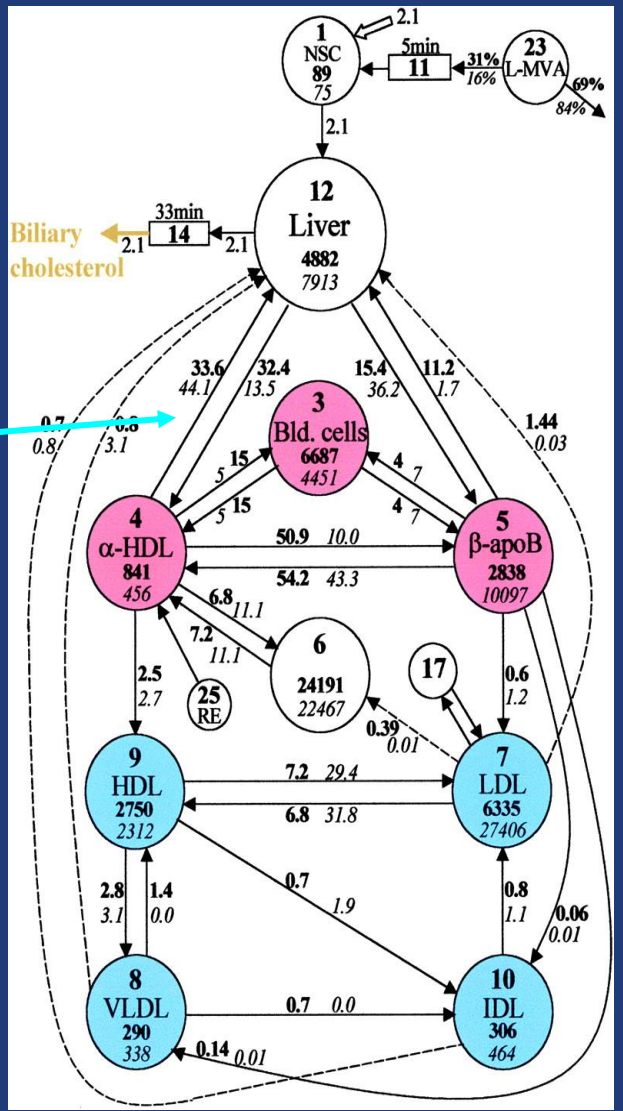
Reverse cholesterol transport: focus on CETP



Barter PJ, et al. Arterioscler Thromb Vasc Biol 2003;23:160–7

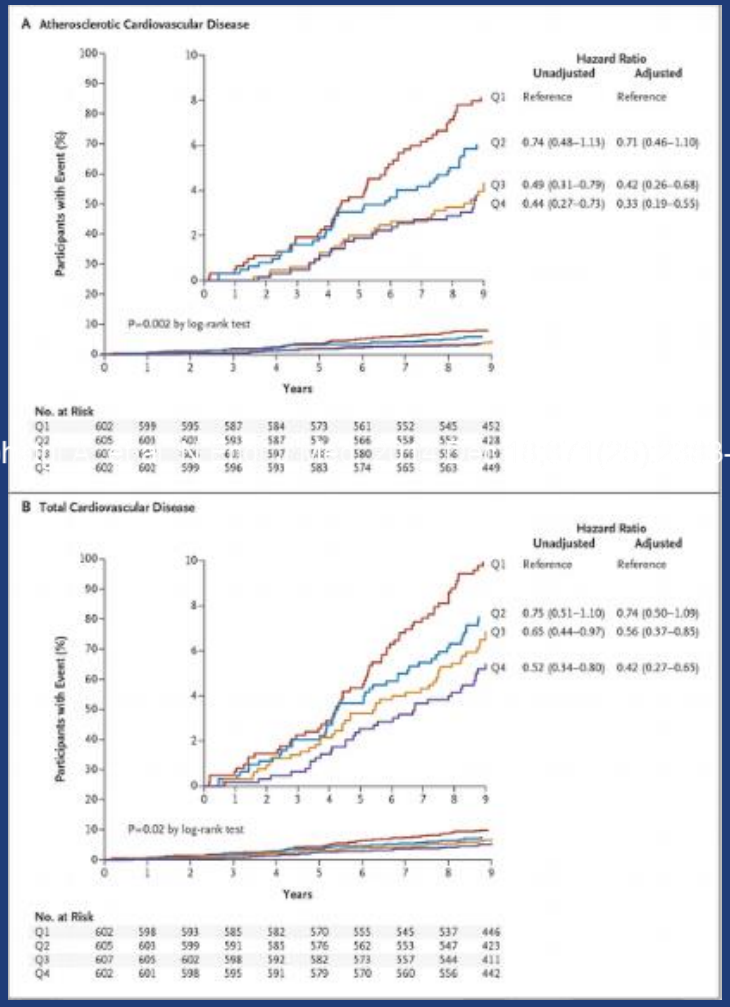
It is difficult to measure (meaningfully) increased cholesterol efflux via RCT in vivo!

Absence of ApoAI-mediated output of CE to liver



Schwartz *et al.*, JLR, 2004

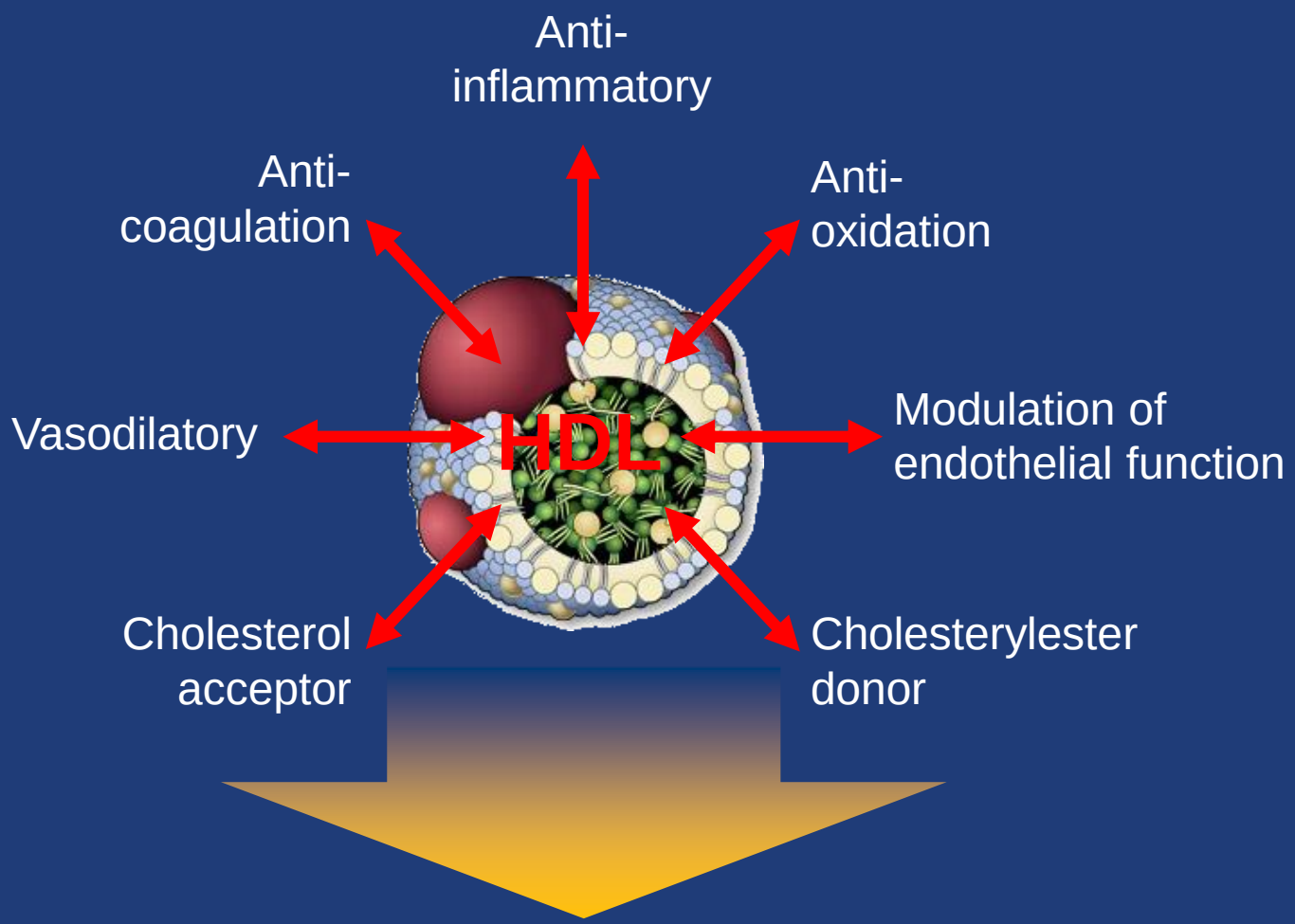
Cholesterol efflux capacity, a new biomarker that characterizes a key step in reverse cholesterol transport, was inversely associated with the incidence of cardiovascular events in a population-based cohort (Dallas Heart Study).



Rohatgi A. et al.

New Engl J Med 2014 Dec 18;371(25):2383-93.

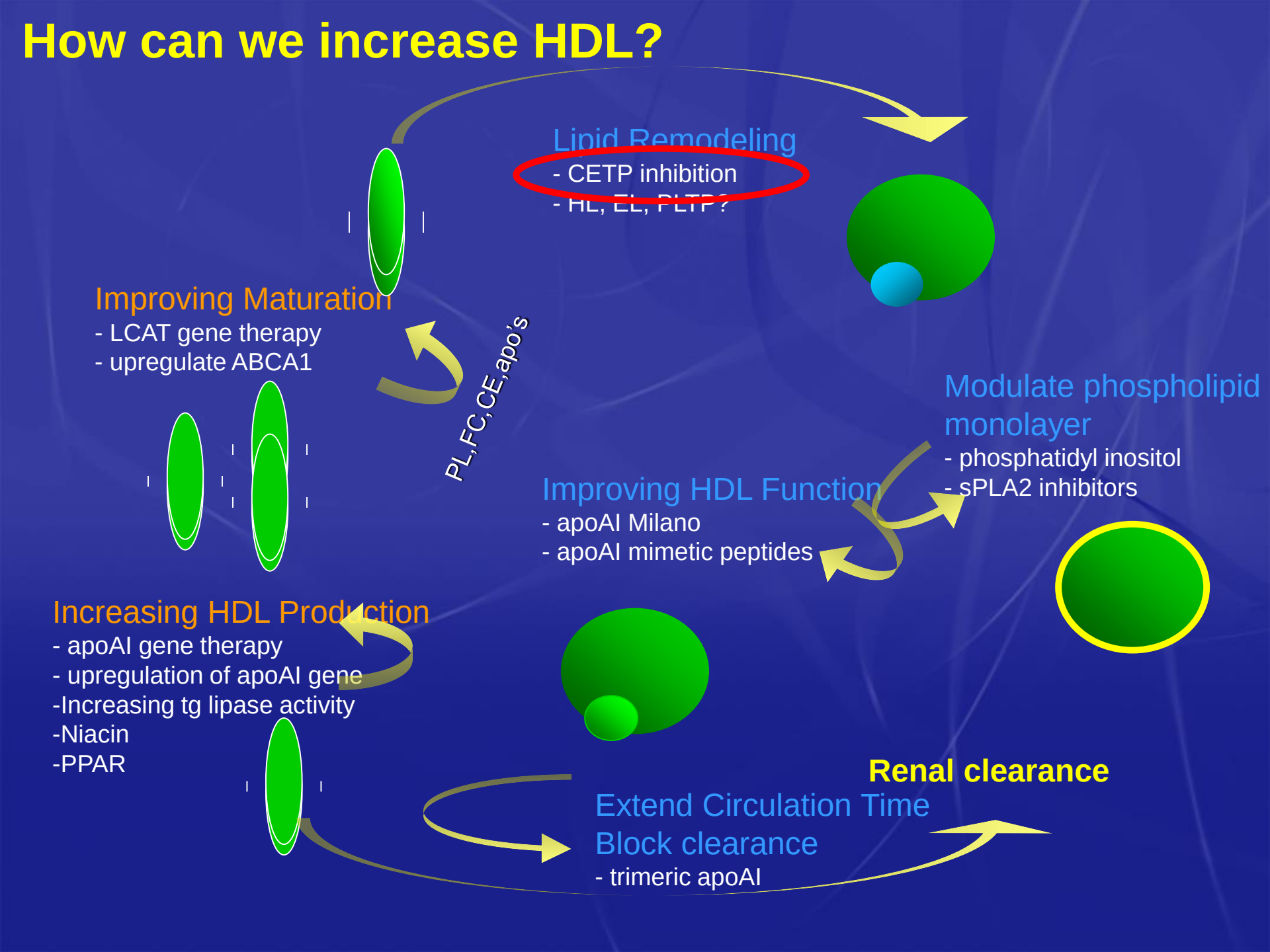
Other mechanisms contributing to vascular protection



What is the impact of HDL on CVD in large trials?

- How does HDL protect?
- How can we increase HDL?

How can we increase HDL?



Focus on CETP inhibitors

Our hope to raise HDL-C (and sometimes lower LDL-C) in order to lower clinical events?

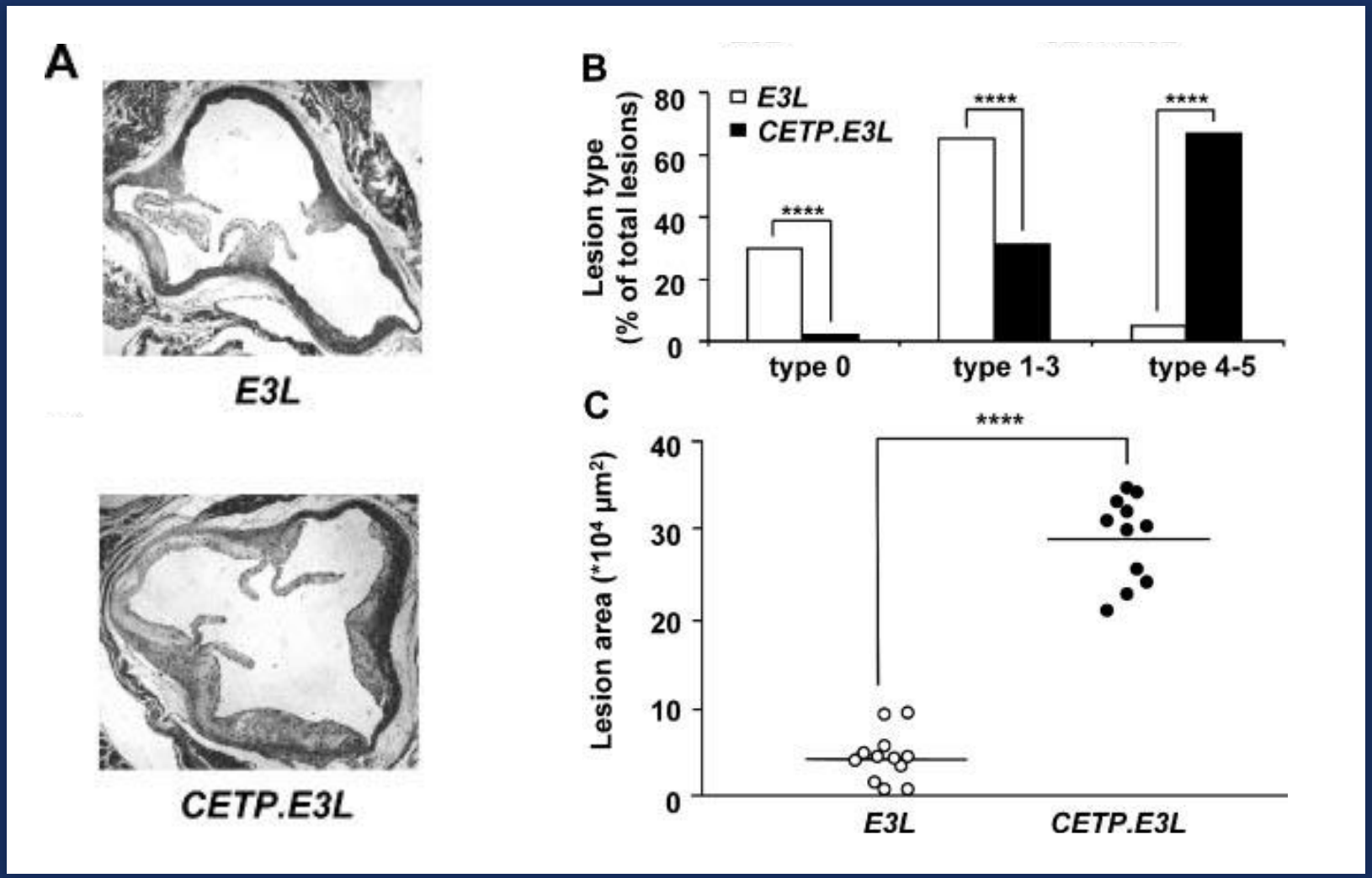
Relationship between CETP and atherosclerosis

Animal studies (rodents)

- Rodents are naturally deficient in CETP
- Rodents are naturally resistant to the development of atherosclerosis
- Expression of CETP in transgenic mice and rats increases atherosclerosis in most (but not all) models

Barter PJ, et al. Arterioscler Thromb Vasc Biol 2003;23:160–7

Cholesteryl Ester Transfer Protein decreases HDL and severely aggravates atherosclerosis in APO*E*3-Leiden* mice



Westerterp M, et al. Arterioscler Thromb Vasc Biol 2006;26:2552–9

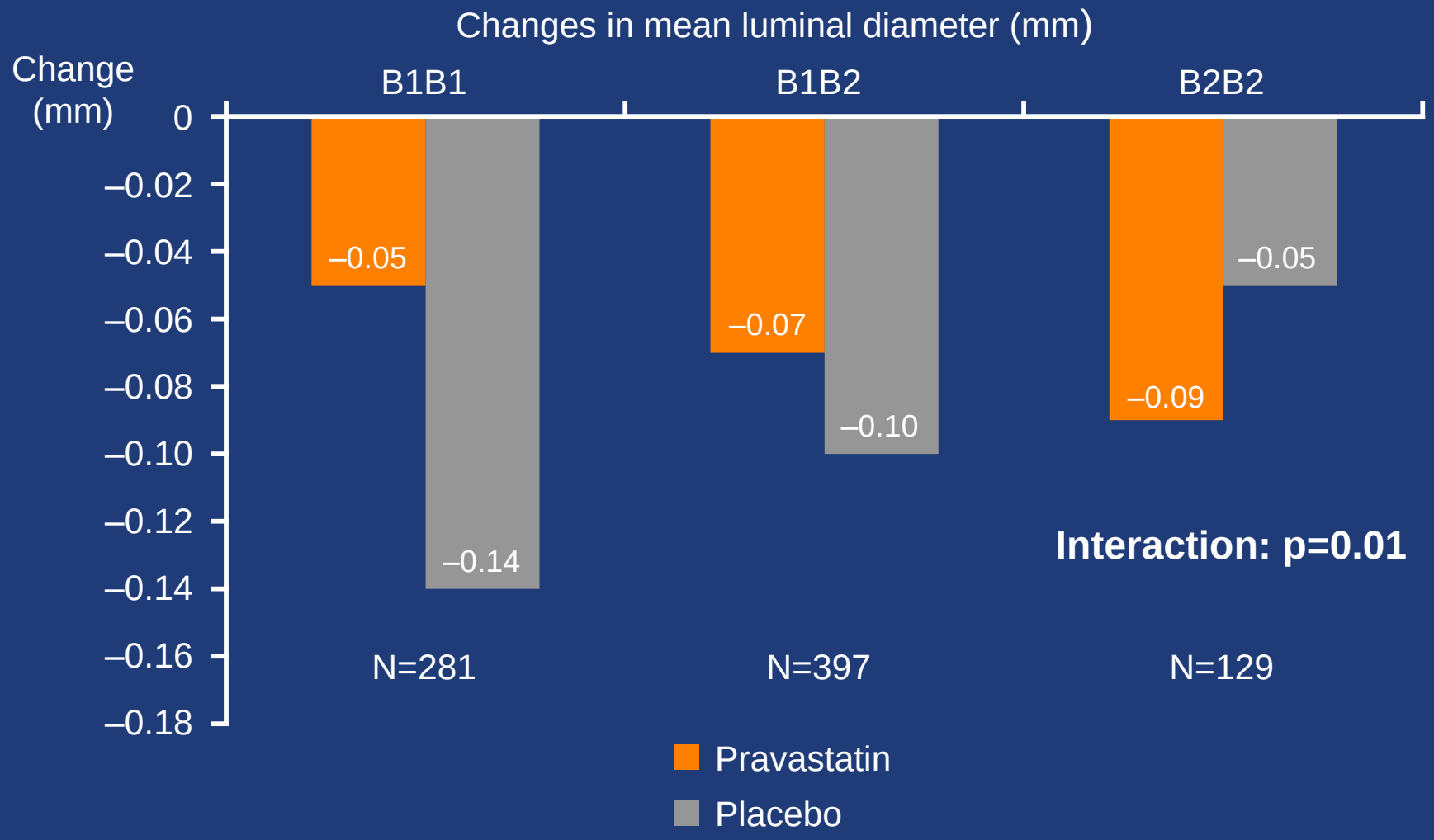
REGRESS: baseline lipids, lipoproteins and CETP concentrations according to CETP-TaqIB genotype

Lipids	B1B1 (n=281)	B1B2 (n=397)	B2B2 (n=129)	P
Total cholesterol (mmol.L-1)	6.04	6.01	6.14	0.35
HDL cholesterol (mmol.L-1)	0.89	0.92	1.02	<0.0001
LDL cholesterol (mmol.L-1)	4.31	4.29	4.36	0.66
Triglycerides (mmol.L-1)	1.70	1.62	1.32	0.04
CETP concentration (ug.mL-1)	2.29	2.01	1.76	<0.0001

Adapted from: Kuivenhoven JA, Jukema JW, et al. N Engl J Med 1998;338:86–93

Interaction between CETP genotype and statin therapy with regard to progression of coronary atherosclerosis

CETP gene polymorphisms



Kuivenhoven JA, Jukema JW, et al. N Engl J Med 1998;338:86–93

Relationship between CETP and atherosclerosis
Human studies

- Torcetrapib inhibits CETP and raises HDL-C by about 60% and lowers LDL-C by up to 20%

Barter PJ, et al. N Engl J Med 2007;357:2109–22

ILLUMINATE: long-term outcomes in patients with CHD or CHD risk equivalence

Patient population

- Men or postmenopausal women
- Statin eligible
- Any HDL-C level
- CHD or risk equivalent (type 2 DM)

Subjects

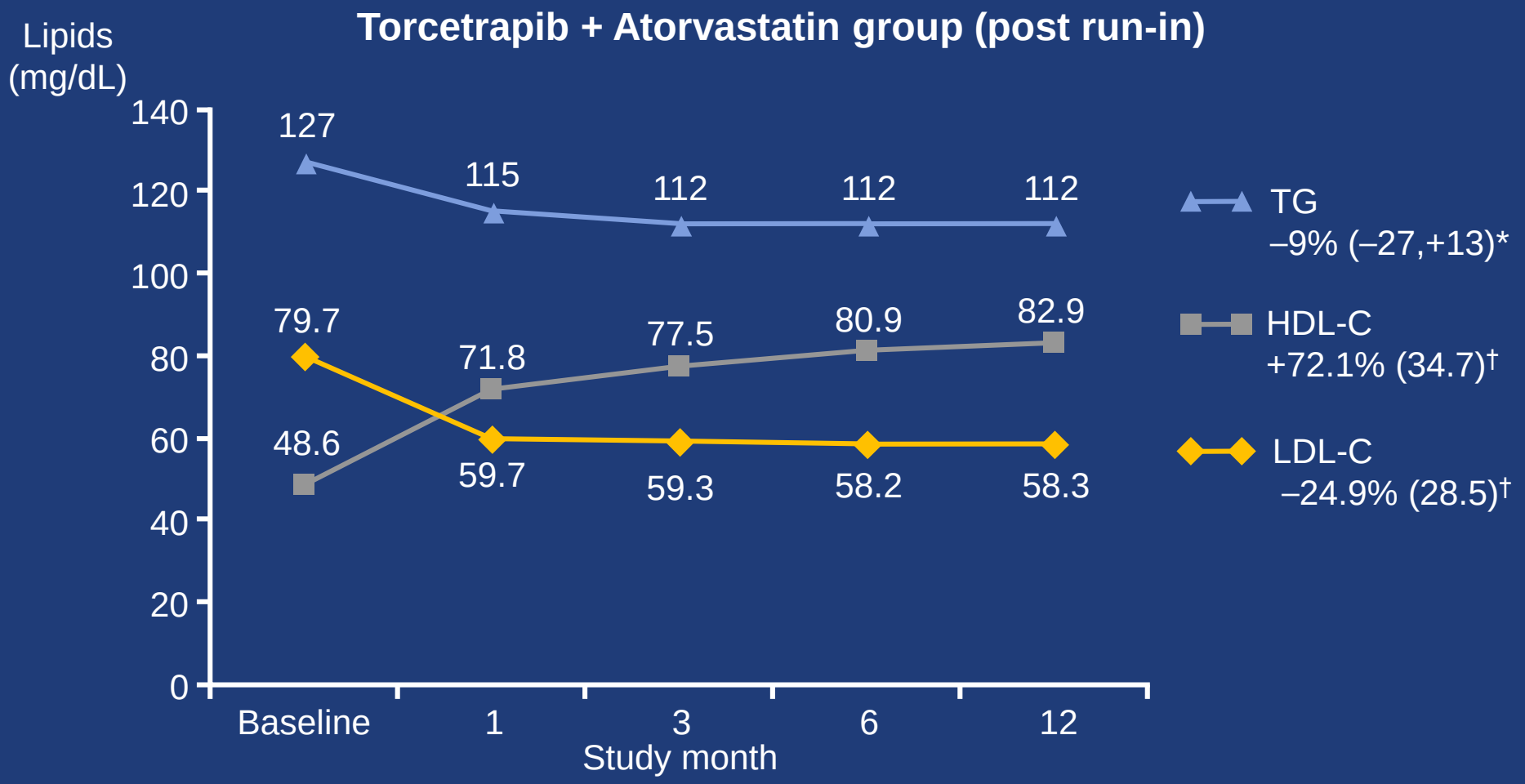
- 15,067
- 7 countries

Primary endpoint

- Major cardiovascular events
- Power = 0.9 for 21% reduction

Barter PJ, et al. N Engl J Med 2007;357:2109–22

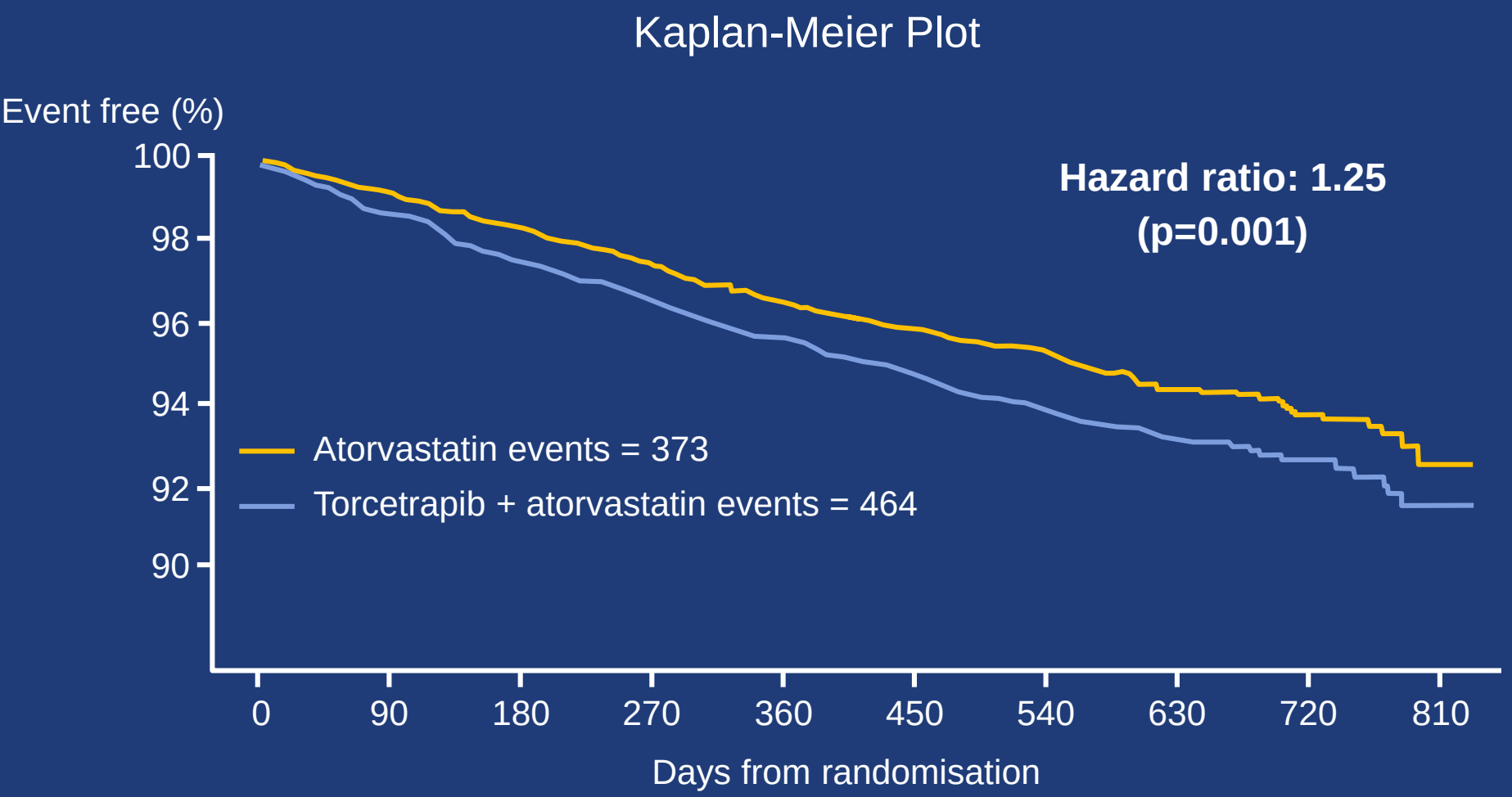
On-trial lipid levels by study month



*Median % change (IQR) at Month 12; p<0.001 vs atorvastatin group
†Mean % change (±SD) at Month 12; p<0.001 vs atorvastatin group

Barter PJ, et al. N Engl J Med 2007;357:2109–22

Time to first major cardiovascular event* (primary endpoint)



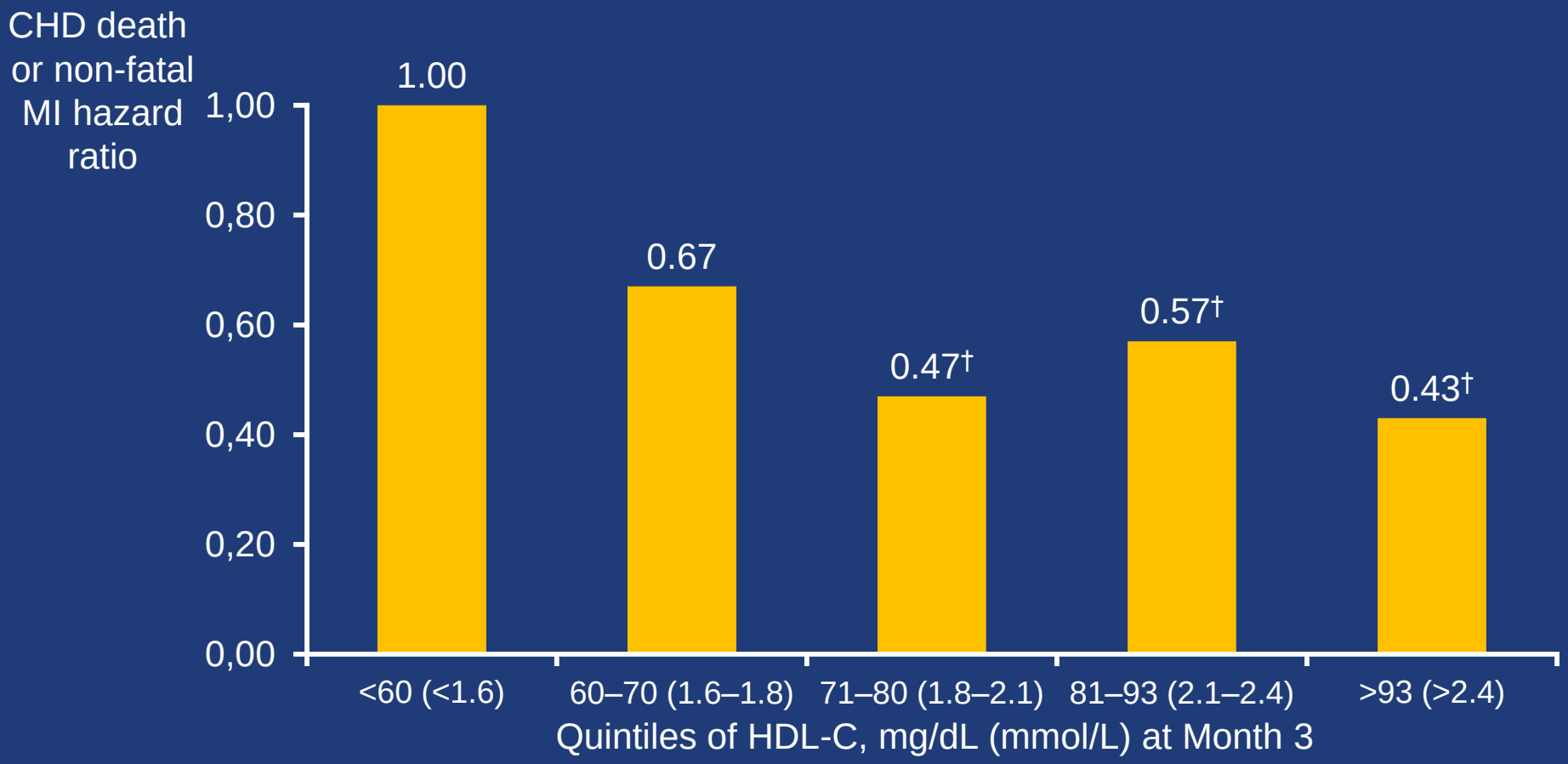
*Coronary heart disease death, non-fatal myocardial infarction, stroke or hospitalization for unstable angina

Barter PJ, et al. N Engl J Med 2007;357:2109–22

What went wrong?

ILLUMINATE trial: higher achieved HDL-C in torcetrapib-treated patients, lower event rate*

Hazard ratios for CHD death or non-fatal MI by quintile of on-trial HDL-C (reference group: HDL-C <60 mg/dL [1.55 mmol/L] stratum)

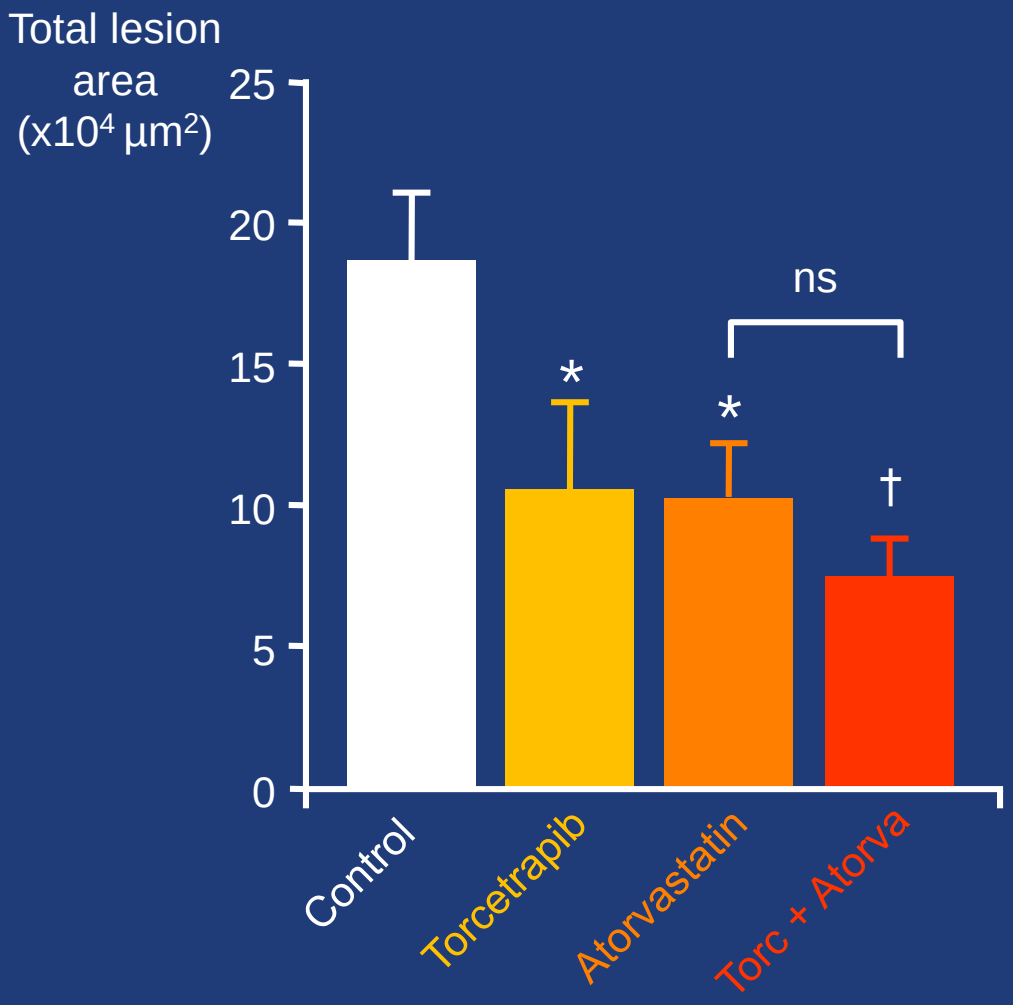


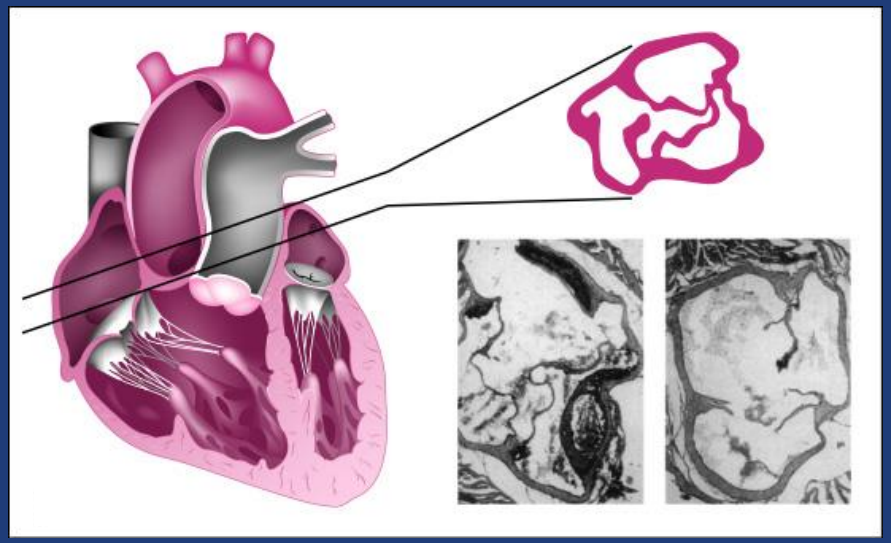
*Cox proportional hazard model adjusted for age, gender, and baseline HDL-C. Excludes 265 patients with missing Month-3 HDL-C values

†p<0.05 vs reference group

Barter PJ, et al. American Heart Association Scientific Sessions. 2007

Torcetrapib reduces atherosclerotic lesion area, but does not add to the effect of atorvastatin

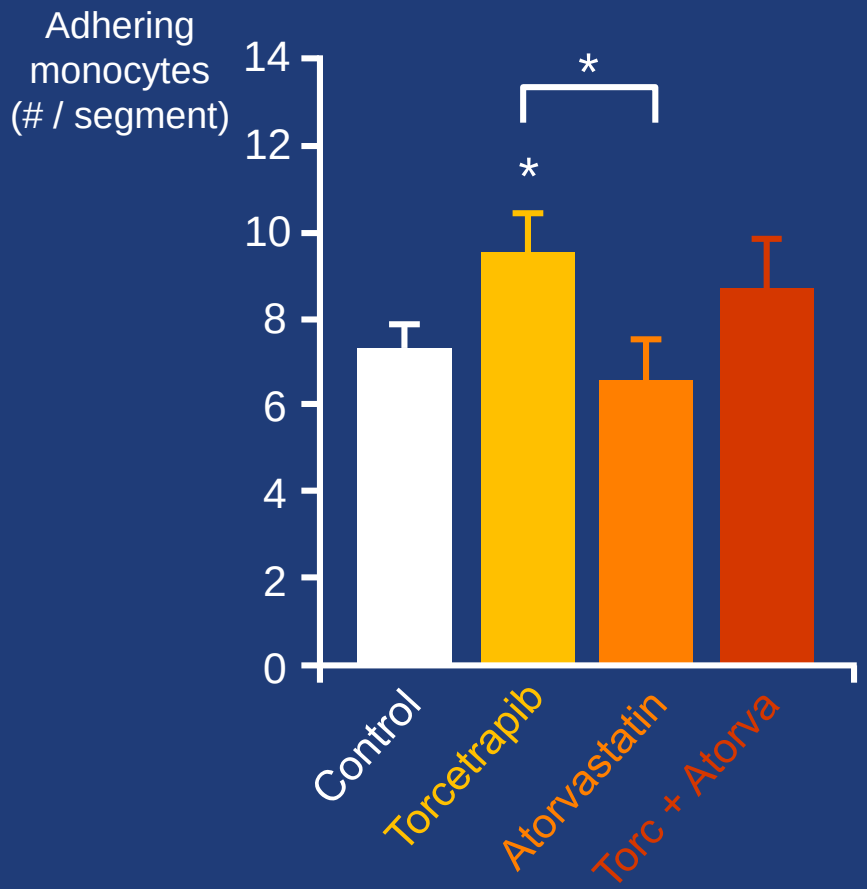




*p<0.05 vs control
†p<0.01 vs control

de Haan W, et al. Circulation 2008;117:2515–22

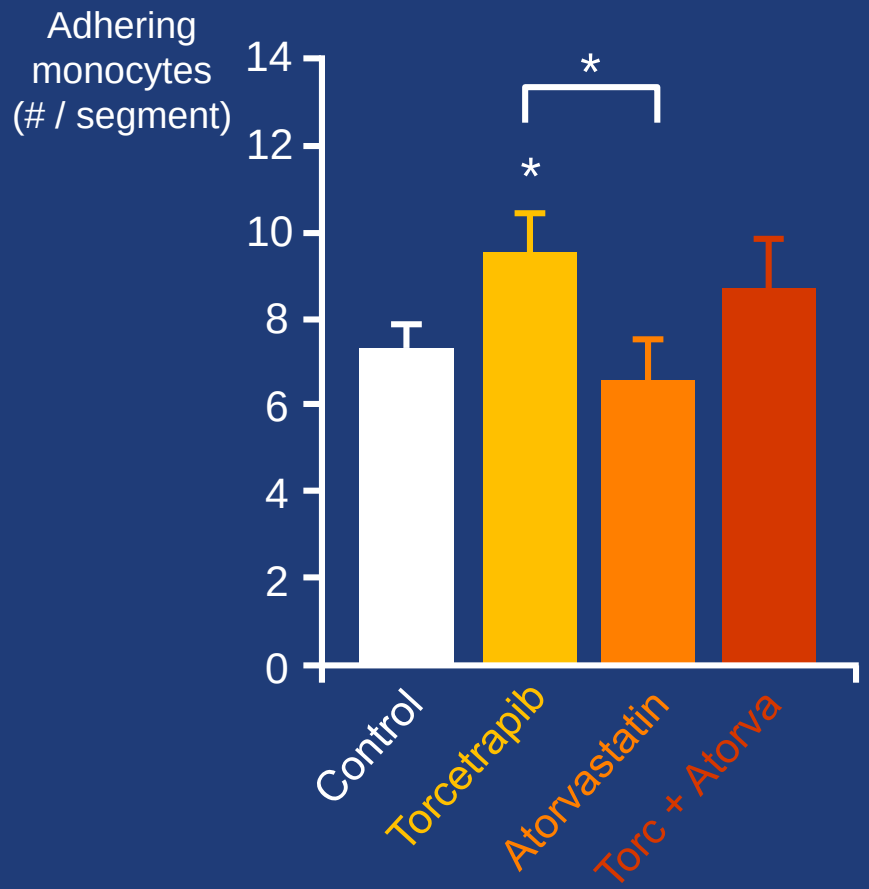
Torcetrapib increases monocyte adherence and macrophage content of the plaque

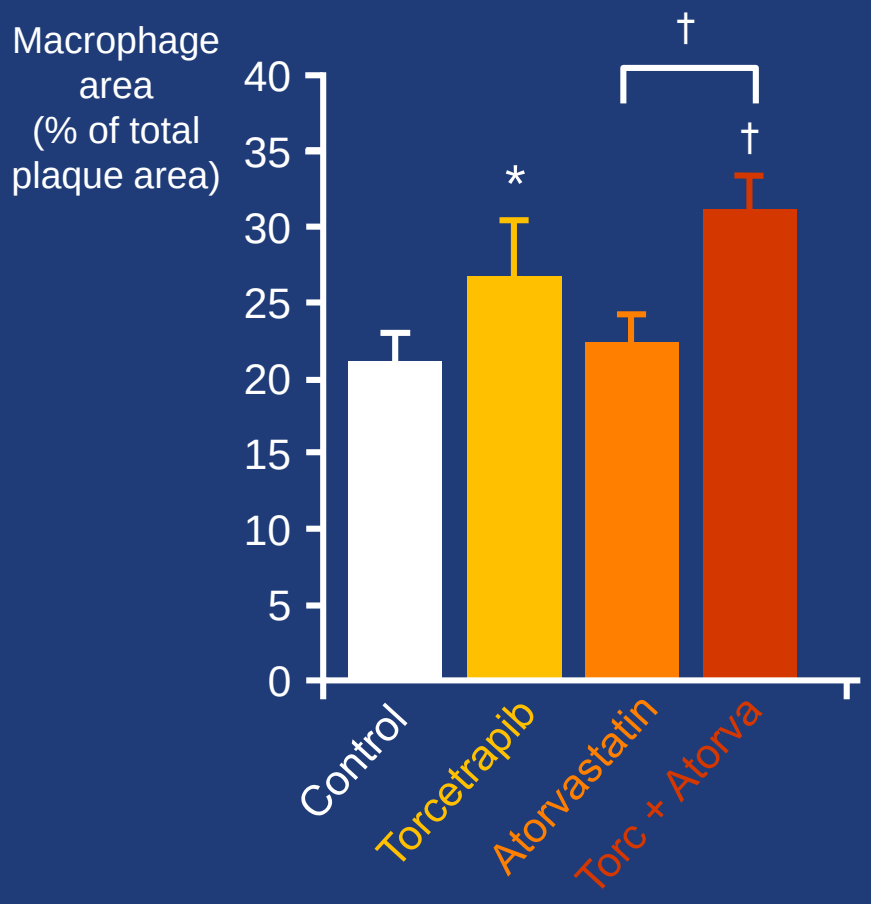


*p<0.05 vs control / comparator

de Haan W, et al. Circulation 2008;117:2515–22

Torcetrapib increases monocyte adherence and macrophage content of the plaque





*p<0.05 vs control / comparator
†p<0.01 vs control / comparator

de Haan W, et al. Circulation 2008;117:2515–22

Off-target pharmacological effects of torcetrapib

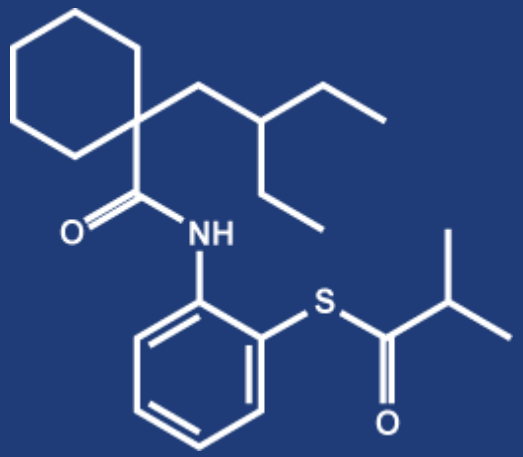
- Torcetrapib has off-target (non-CETP inhibitor) effects
- In patients receiving torcetrapib in ILLUMINATE there was a significant
  - increase in systolic blood pressure
    - of 5.4 mmHg at 12 months in the torcetrapib group compared with 0.9 mmHg in the atorvastatin-only group ($p<0.001$)
    - of >15 mmHg at 12 months in 9.4% of the atorvastatin-only group and in 19.5% of the torcetrapib group ($p<0.001$)
  - decrease in serum potassium
  - increase in serum bicarbonate
  - increase in serum sodium
  - increase in serum aldosterone
- The adverse outcome in ILLUMINATE trial MAY thus have been the consequence of off-target actions of torcetrapib and MAY not be related to CETP inhibition

Barter PJ, et al. N Engl J Med 2007;357:2109–22

Dalcetrapib

- Dalcetrapib acts on CETP activity, increasing HDL-C by up to 36%[1,2]
- To date, dalcetrapib has not exhibited any of the off-target effects associated with the CETP inhibitor torcetrapib[2–4]

Dalcetrapib
Molecular weight: 389.60
Lipophilicity: cLogP ~7



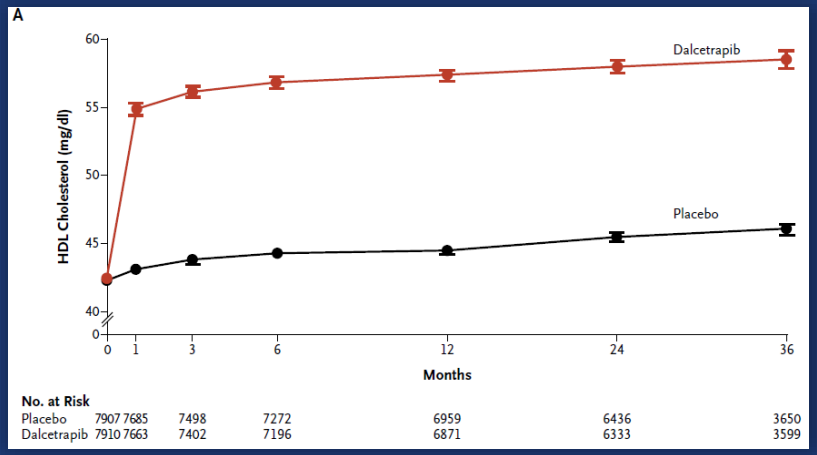
1. Niesor EJ, et al. J Lipid Res 2010;51:3443–54
2. Stein EA, et al. Am J Cardiol 2009;104:82–91
3. Stroes ES, et al. Br J Pharmacol 2009;158:1763–70
4. Stein EA, et al. Eur Heart J 2010;31:480–48

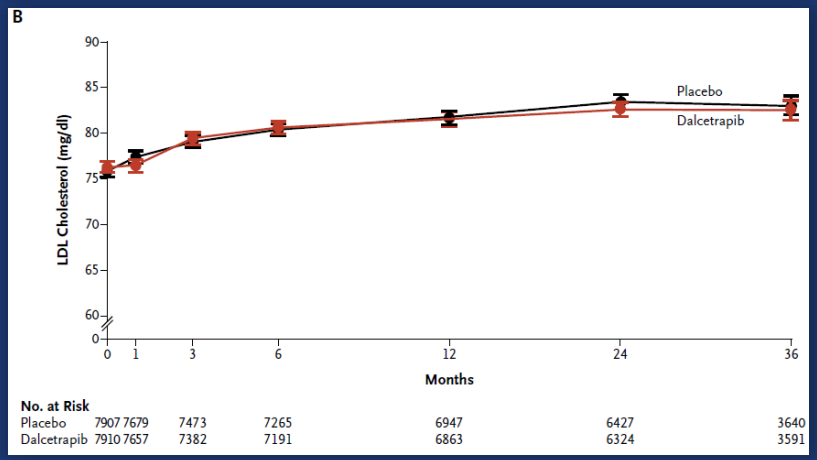
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D.,





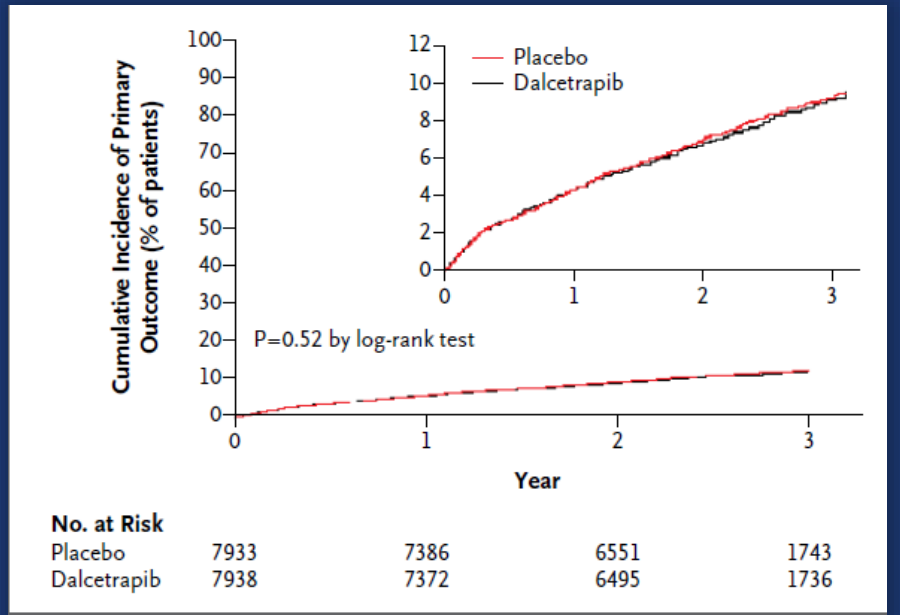


Figure 2. Incidence of the Primary Efficacy End Point.

Shown is the cumulative incidence in the two study groups of the composite primary end point of death from coronary heart disease, a major nonfatal coronary event (myocardial infarction, hospitalization for unstable angina with objective evidence of acute myocardial ischemia, or resuscitation after cardiac arrest), or stroke of presumed atherothrombotic cause. The inset shows the same data on an enlarged y axis.

Schwartz GG, et al. N Engl J Med 2012;367:2089–99

HDL-C elevation (with additional LDL-C lowering) by CETP inhibition: is it dead?

Or should it not be buried yet: it may well still be alive and kicking!

Circulation
Cardiovascular Quality and Outcomes

American Heart Association.

Journey Through Cholesteryl Ester Transfer Protein Inhibition: From Bench to Bedside

Ioannis Karalis, Patrick C.N. Rensen and J. Wouter Jukema

Circ Cardiovasc Qual Outcomes. 2013;6:360-366; originally published online May 14, 2013;

Table. Comparison of the Characteristics of the 4 CETP Inhibitors That Have Been and Are Currently Being Tested in Large Randomized Clinical Trials

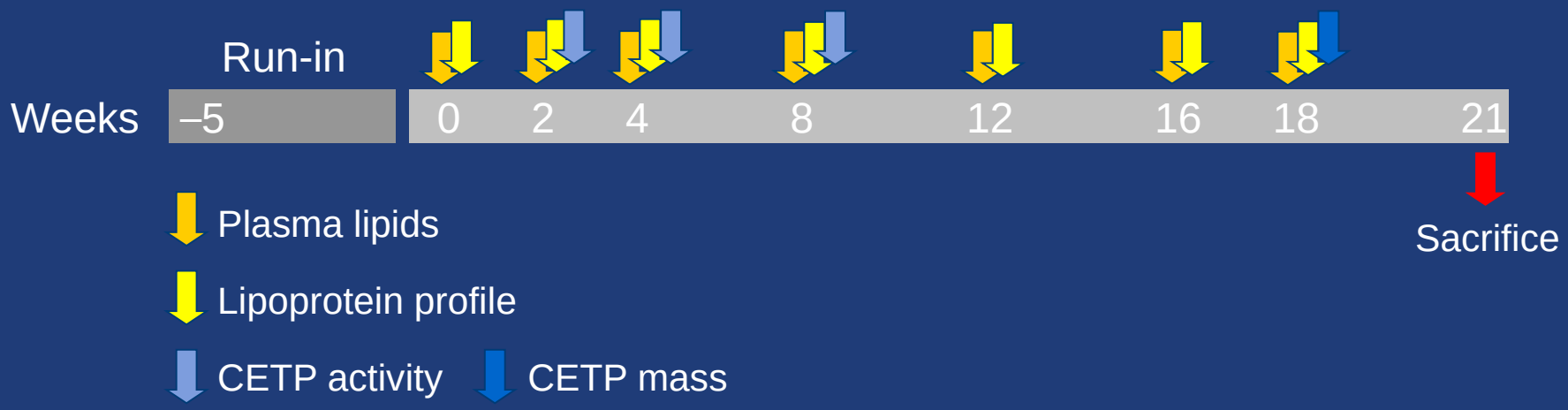
CETP Inhibitor	Effect on HDL-C Increase	Effect on LDL-C Decrease	Off-Target Effects	Randomized Clinical Trial (Number of Patients Included)	Year of Publication (or Expected Completion Date)
Torcetrapib	++	+	++	ILLUMINATE (15 067)	2007
Dalcetrapib	+	None	+	DAL-OUTCOMES (15 871) DAL-OUTCOMES 2 (stopped)	2012
Anacetrapib	+++	++	Not documented	REVEAL (aiming 30 000)	2017
Evacetrapib	+++	++	Not documented	ACCELERATE (aiming 11 000)	2015

12.000 • 2016

ACCELERATE indicates Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High-Risk for Vascular Outcomes; ILLUMINATE, Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events; DAL-OUTCOMES, Effect of Dalcetrapib on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome; and REVEAL, randomized evaluation of the effects of anacetrapib through lipid.

Karalis I, et al. Circ Cardiovasc Qual Outcomes 2013;6:360–6

Experimental study design: female APOE*3-Leiden.hCETP mice



- Female APOE*3-Leiden.hCETP mice
  - control (Western-type diet + 0.1% cholesterol)
  - low anacetrapib (0.03 mg/kg/d)
  - moderate anacetrapib (0.3 mg/kg/d)
  - moderate / high anacetrapib (3 mg/kg/d)
  - high anacetrapib (30 mg/kg/d)
  - atorvastatin (2.4 mg/kg/d)
  - combination (0.3 mg/kg/d anacetrapib + 2.4 mg/kg/d atorvastatin)

Kühnast S, et al. Eur Heart J 2015;36:39–50