Beyond Statins: CETP inhibition—failed promise or the dawn of a new therapeutic arena?

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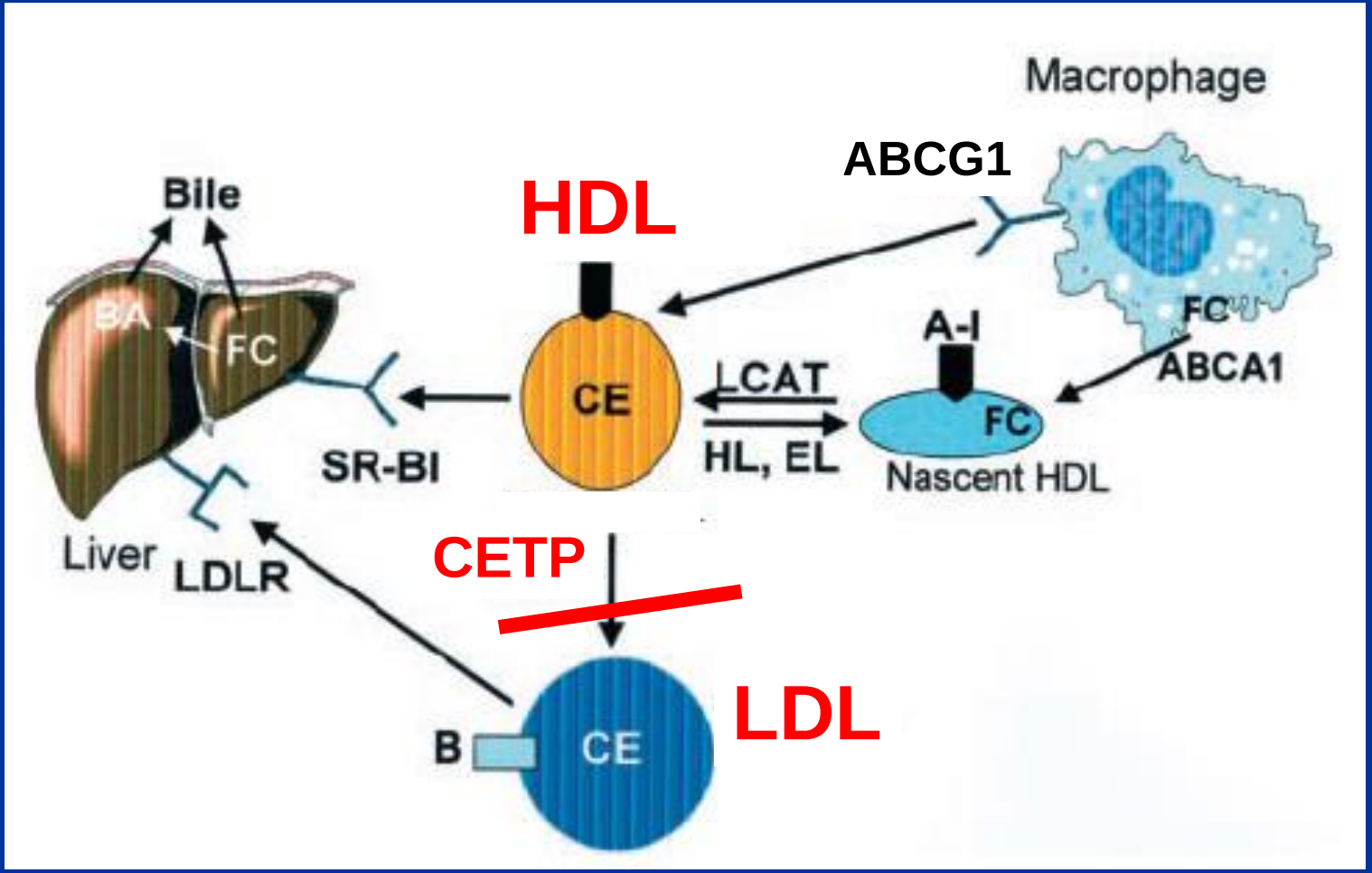
Disclosure

- I have received consulting fees for serving on the events committee for Dal-Outcomes, sponsored by Roche
- I have received consulting fees, research support, and/or speaker's honoraria from Abbott, AstraZeneca, Merck, and Pfizer

Presentation outline

- The role of CETP in lipid metabolism and CV risk
- Clinical trials
  - ILLUMINATE—torcetrapib
  - Dal-OUTCOMES—dalcetrapib
  - REVEAL—anacetrapib
  - In development—evacetrapib
- The future of CETP inhibition

CETP transfers cholesterol from HDL to LDL



Does inhibiting reduce cardiovascular risk?

What do we know about the relationship between CETP and atherosclerosis?

CETP in animal studies (Mice)

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

CETP in humans

A majority, but not all epidemiologic data, suggest that lower CETP activity is associated with lower cardiovascular risk

Meta-analysis of CETP genotypes and CHD

- 46 studies had data on 27,196 coronary cases and 55,338 controls
- CETP polymorphisms conveying lower CETP mass and activity were associated with higher HDL-C and significantly reduced coronary risk

Thompson et al, *JAMA* 2008;299:2777-88

Women's Genome Health Study: CETP genotypes and CHD

- A prospective cohort of 18,245 initially healthy American women
- Polymorphisms of the CETP gene conveying decreased CETP activity were associated with higher HDL cholesterol concentration and lower risk of myocardial infarction

Ridker et al, *Circ Cardiovasc Genet* 2009

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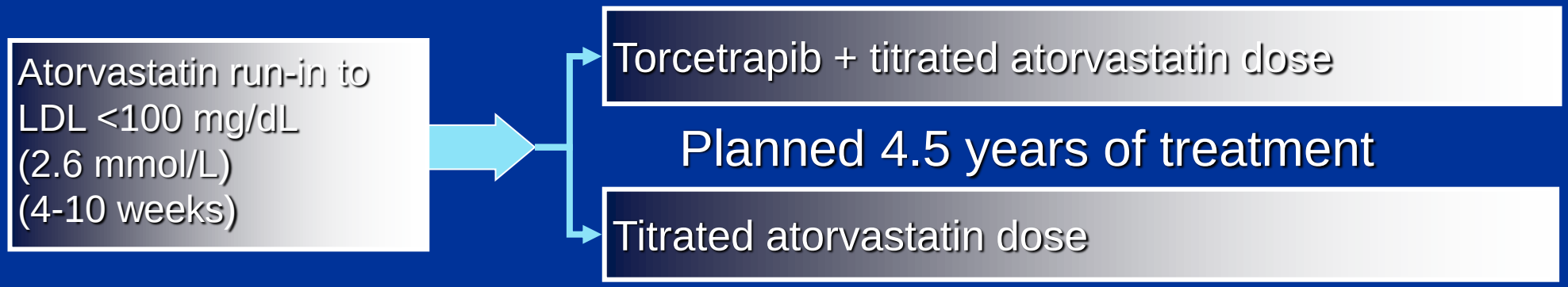
ILLUMINATE: Long-term Outcomes in Patients With CHD or CHD Risk Equivalence

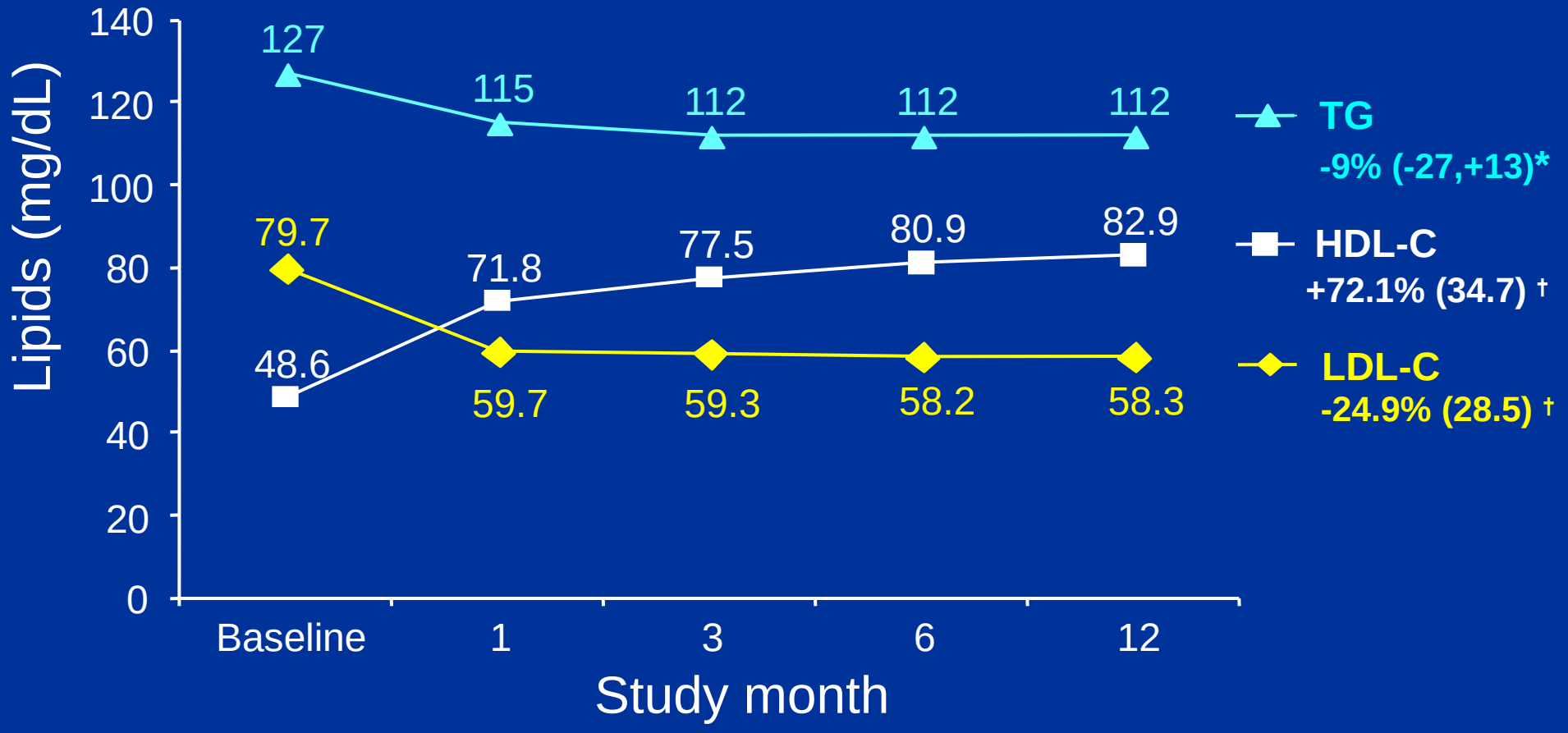
Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events



Patient Population	Subjects	Primary End Point
• Men or postmenopausal women • Statin eligible • Any HDL-C level • CHD or risk equivalent (type 2 DM)	• 15,067 • 7 countries	• Major cardiovascular events • Power=0.9 for 21% reduction

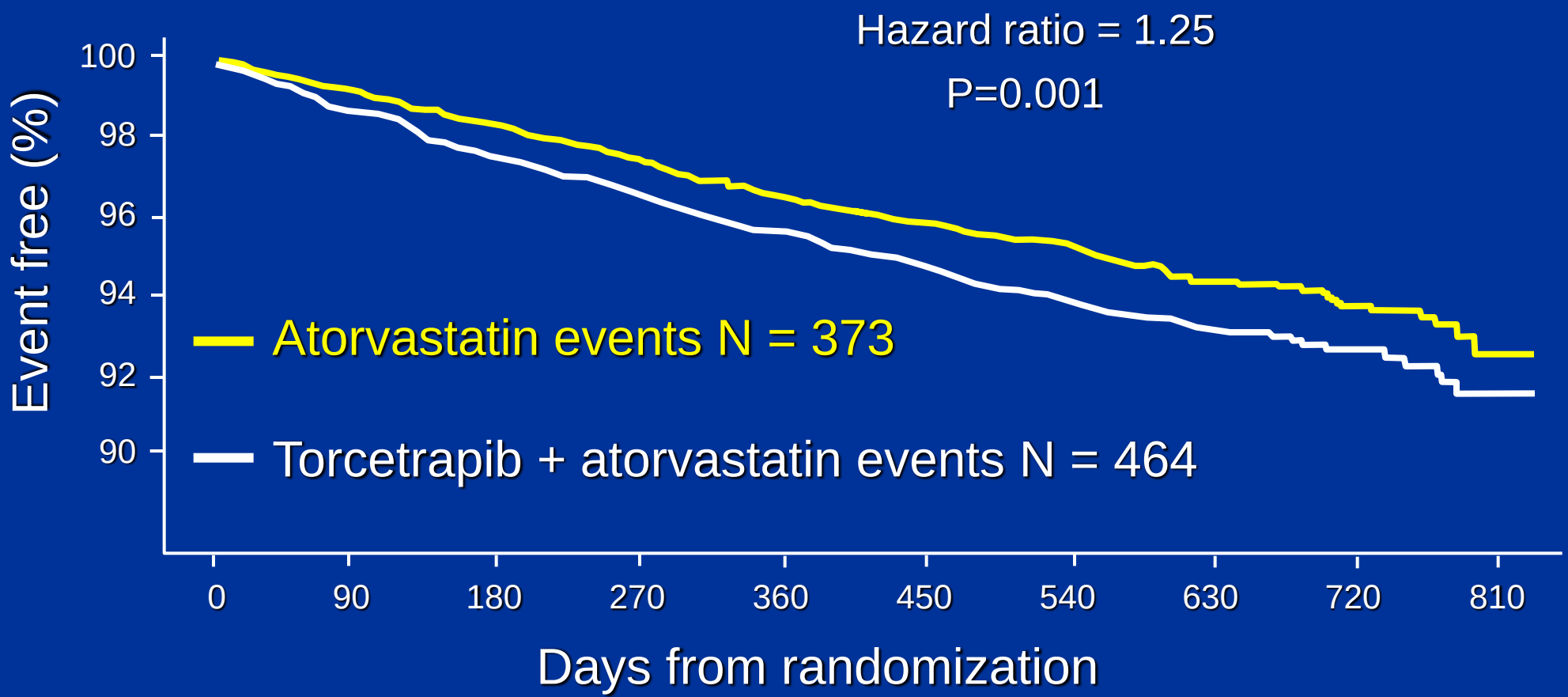
Barter et al, NEJM 2007;357:2109-2122

ILLUMINATE: On-trial lipid levels with torcetrapib added to background atorvastatin



Barter et al, *NEJM* 2007;357:2109-22

ILLUMINATE: Primary endpoint: Time to first MACE*



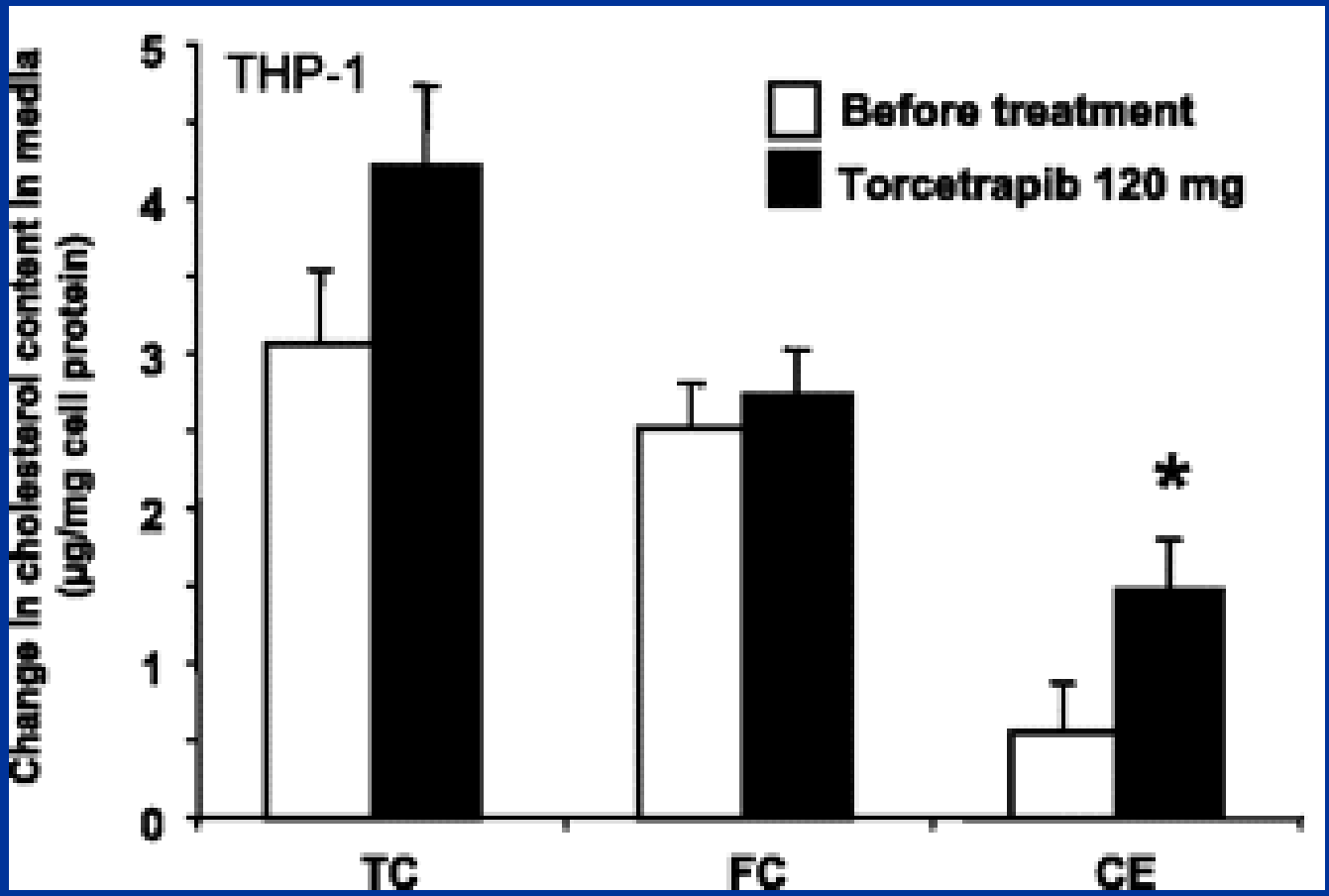
*MACE: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

Barter et al, *NEJM* 2007;357:2109-22

What was the reason for the adverse outcome with torcetrapib?

- Inhibiting CETP is pro-atherogenic
- Inhibiting CETP generates dysfunctional HDL
- Torcetrapib has adverse off-target pharmacology unrelated to CETP

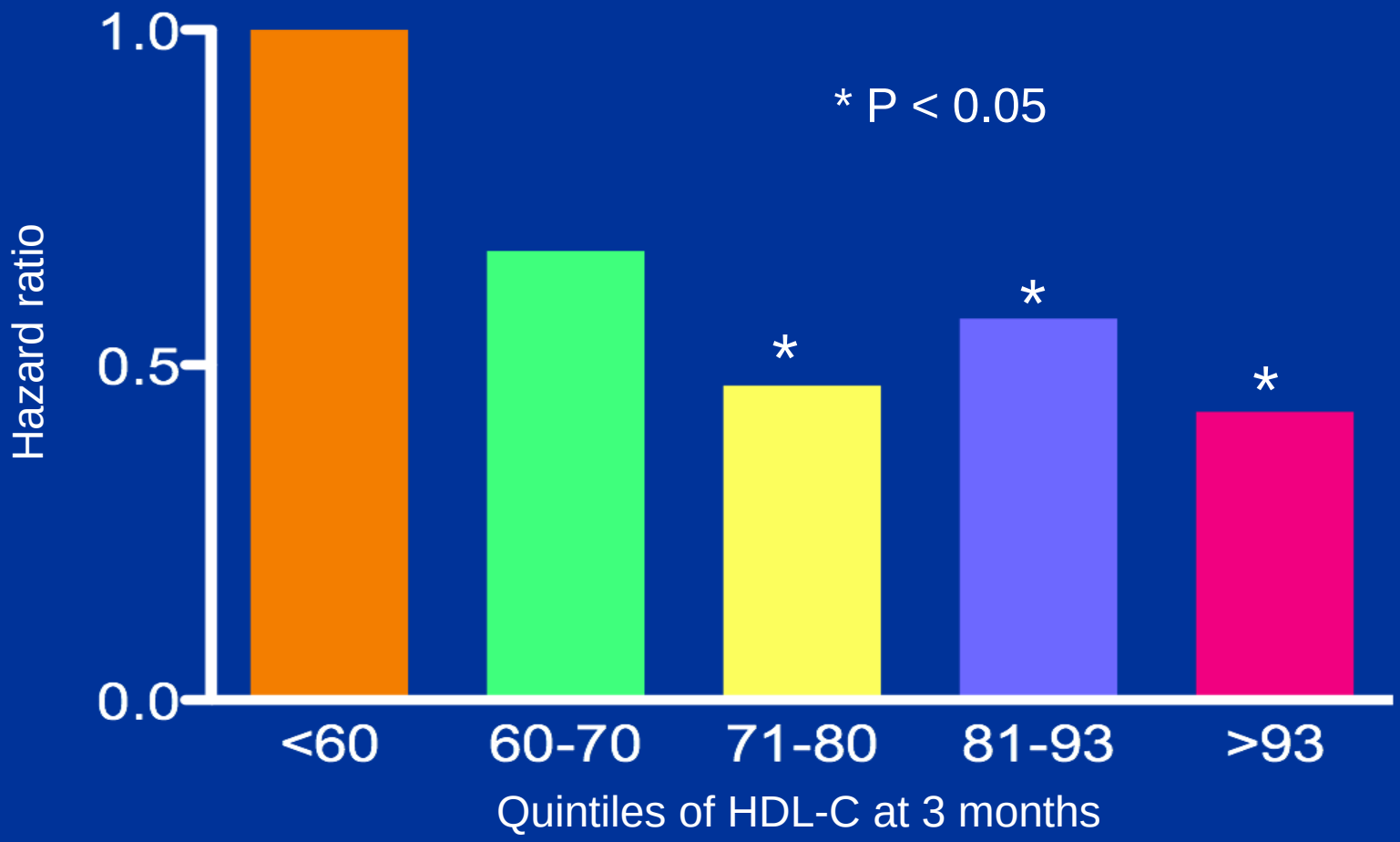
HDL-C from torceptrapib-treated patients increased efflux of cholesterol from macrophages



Laurent Yvan-Charvet et al,
ATVB 2007;27:1132

ILLUMINATE: In the torcetrapib group, higher achieved HDL-C was associated with lower event rate

Hazard ratio for CHD death or non-fatal MI according to achieved level of HDL-C



Barter et al, *AHA* 2007

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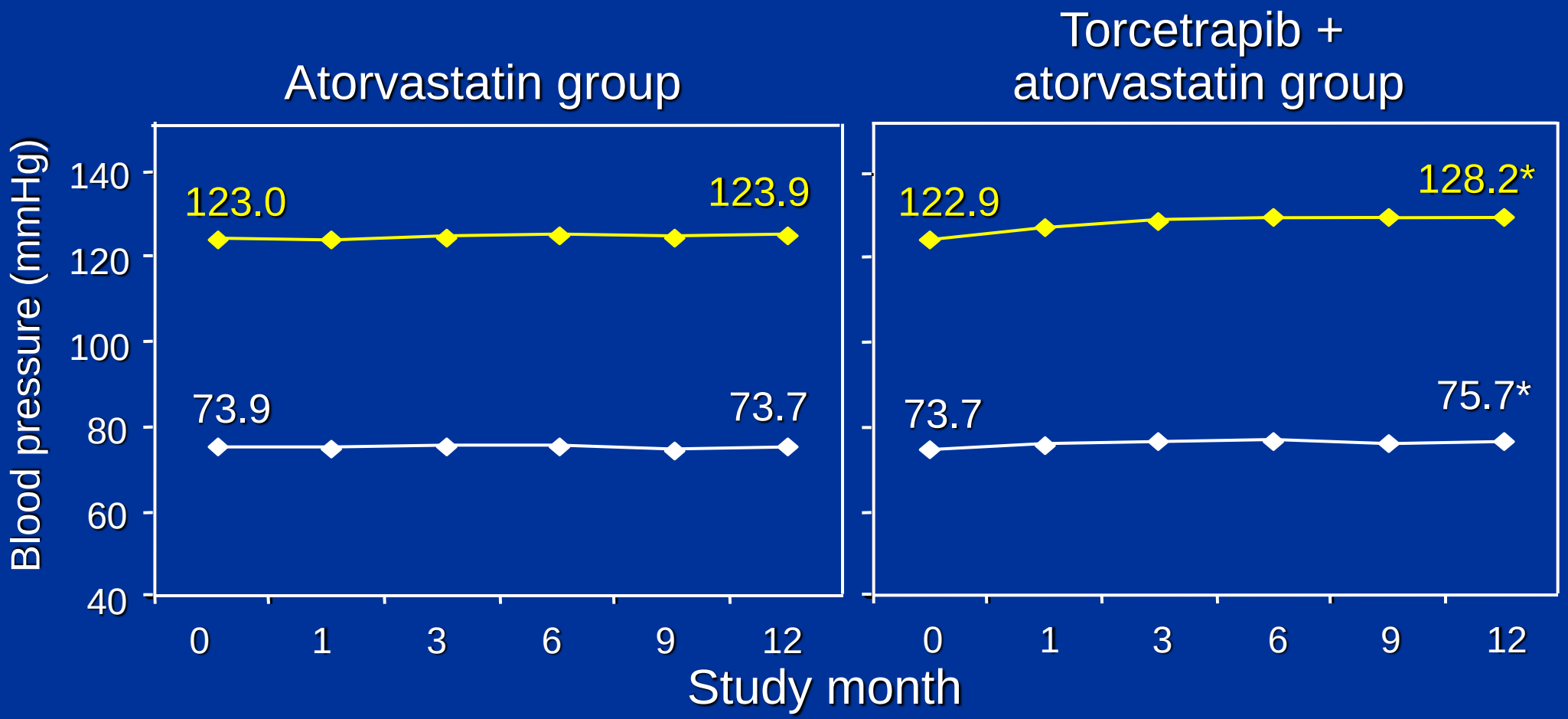
On-trial blood pressure by study month



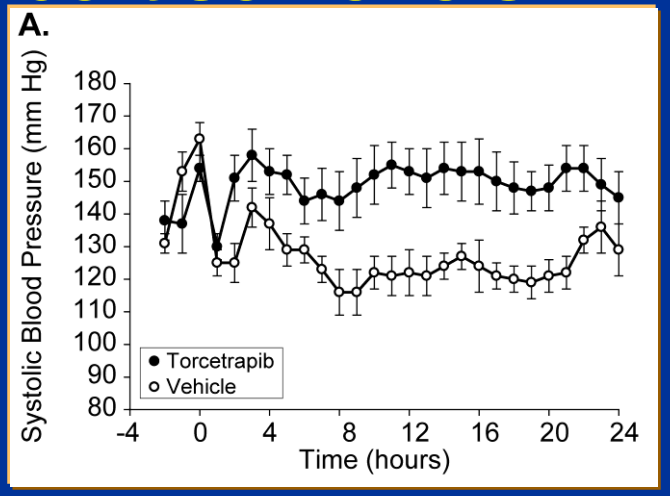
* P < 0.001 vs atorvastatin at month 12

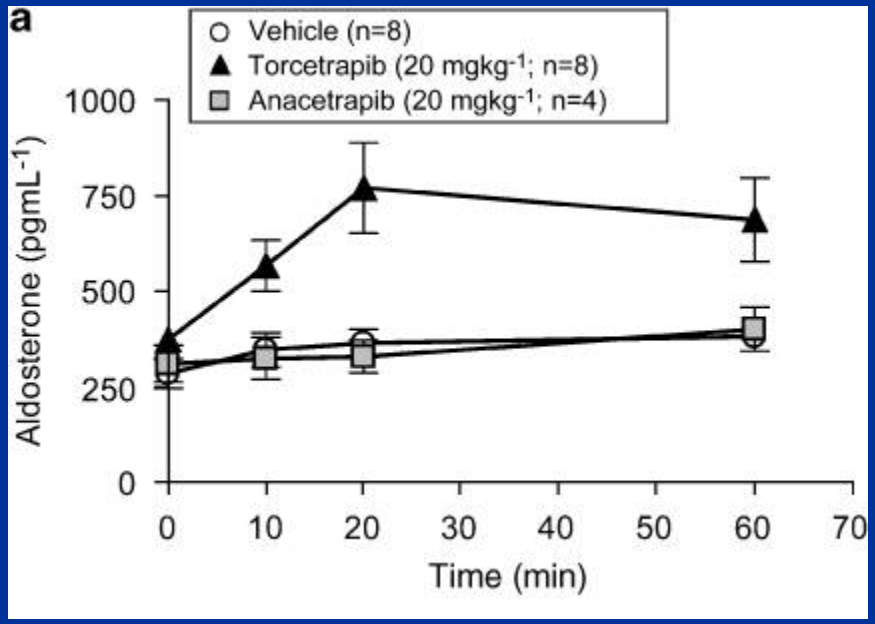
Barter et al, *NEJM* 2007;357:2109-22

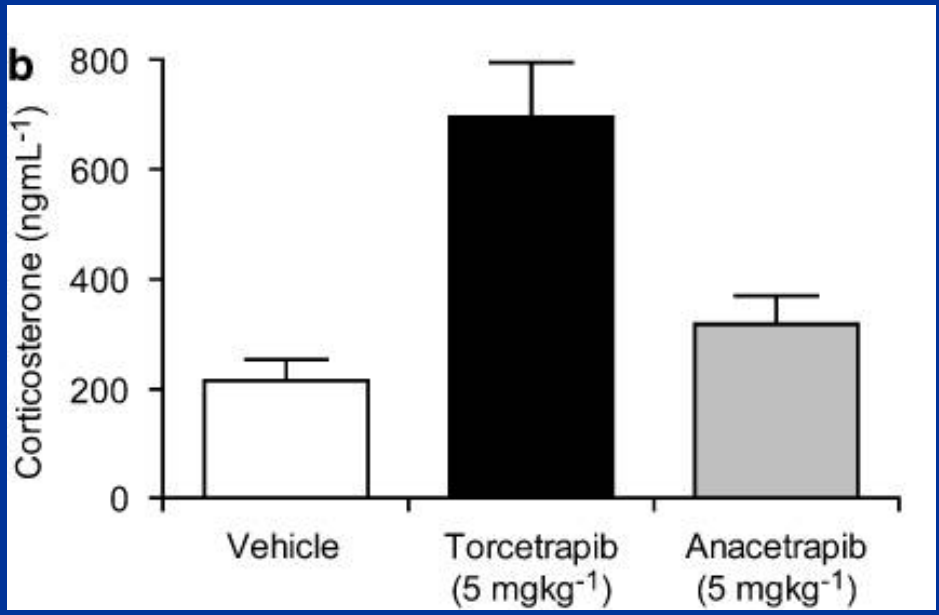
Off-target pharmacological effects of torcetrapib unrelated to CETP inhibition

- In patients receiving torcetrapib in the ILLUMINATE trial there was a significant:
  - Increase in blood pressure
  - Decrease in serum potassium
  - Increases in serum aldosterone and cortisol
- In human adrenal cell culture, torcetrapib induces aldosterone and cortisol release and induces expression of CYP11B2 and CYP11B1, the enzymes catalyzing the last step of aldosterone and cortisol biosynthesis, respectively.

Torcetrapib increases BP, aldosterone, and cortisol levels in rats





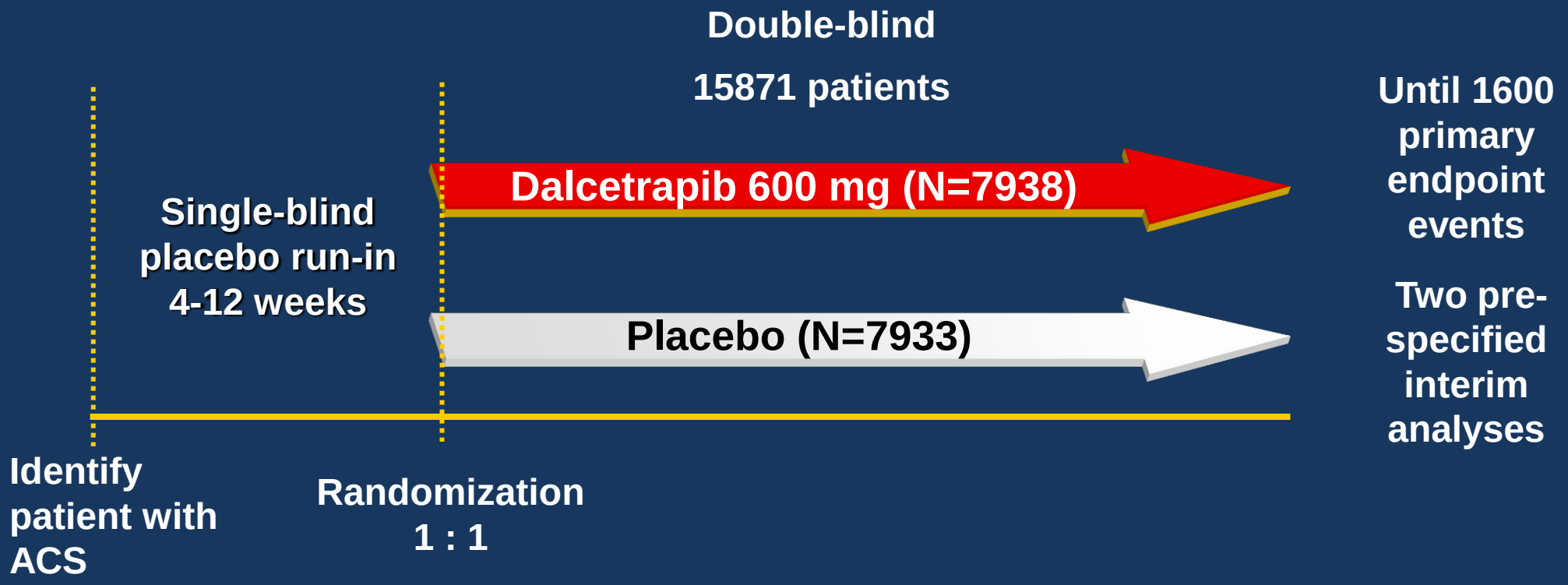


Forrest et al., *Br J Pharmacol*. 2008;154:1465–1473.

Objective of the dal-OUTCOMES trial

- To compare the effects of dalcetrapib with placebo, added to evidence-based background therapy, on cardiovascular risk in patients with recent acute coronary syndrome

Dal-OUTCOMES study design



935 sites in 27 countries

Outcome measures

- **Primary outcome composite (time to first occurrence):**
  - Coronary heart disease death
  - Non-fatal MI
  - Ischemic stroke
  - Hospitalization for unstable angina (with objective evidence of acute myocardial ischemia)
  - Cardiac arrest with resuscitation
- **Secondary outcome measures:**
  - All cause mortality
  - Coronary revascularization

Flow of patients in the trial

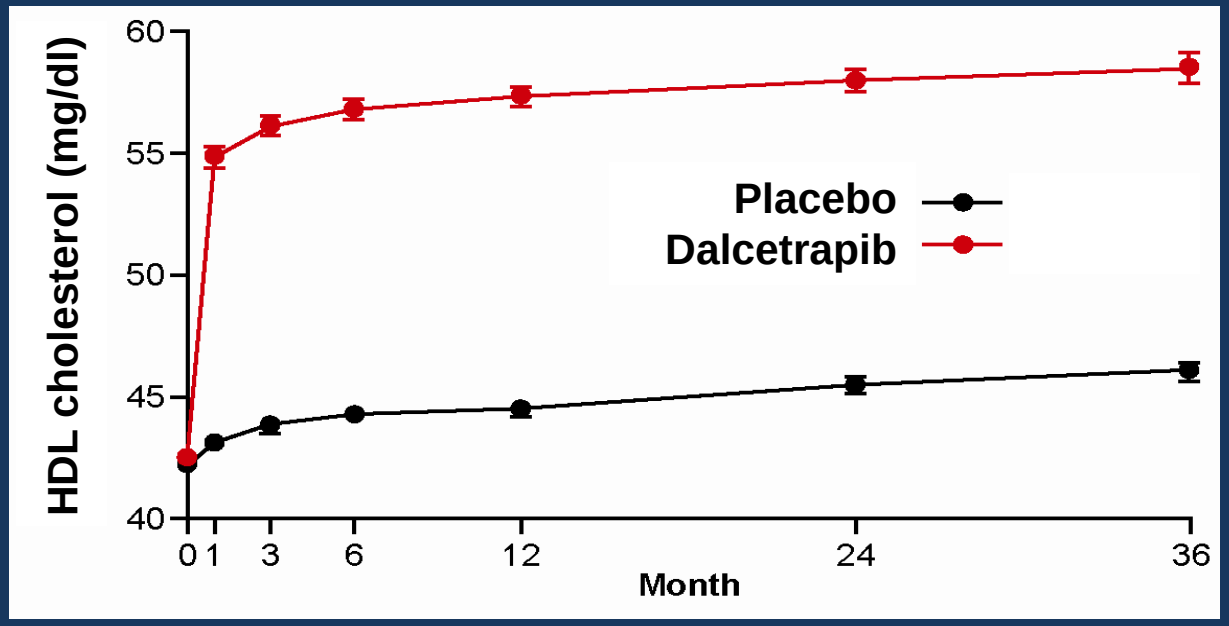
- 19,005 entered single blind run-in
- 15,871 patients randomized
- Withdrawal of consent or loss to follow-up: dalcetrapib 3.9%, placebo 3.3%
- At the 2nd pre-specified interim analysis, including 1135 (71% of projected) primary endpoint events, the DSMB recommended termination of the trial for futility.
- At termination, median follow-up 31 mo.

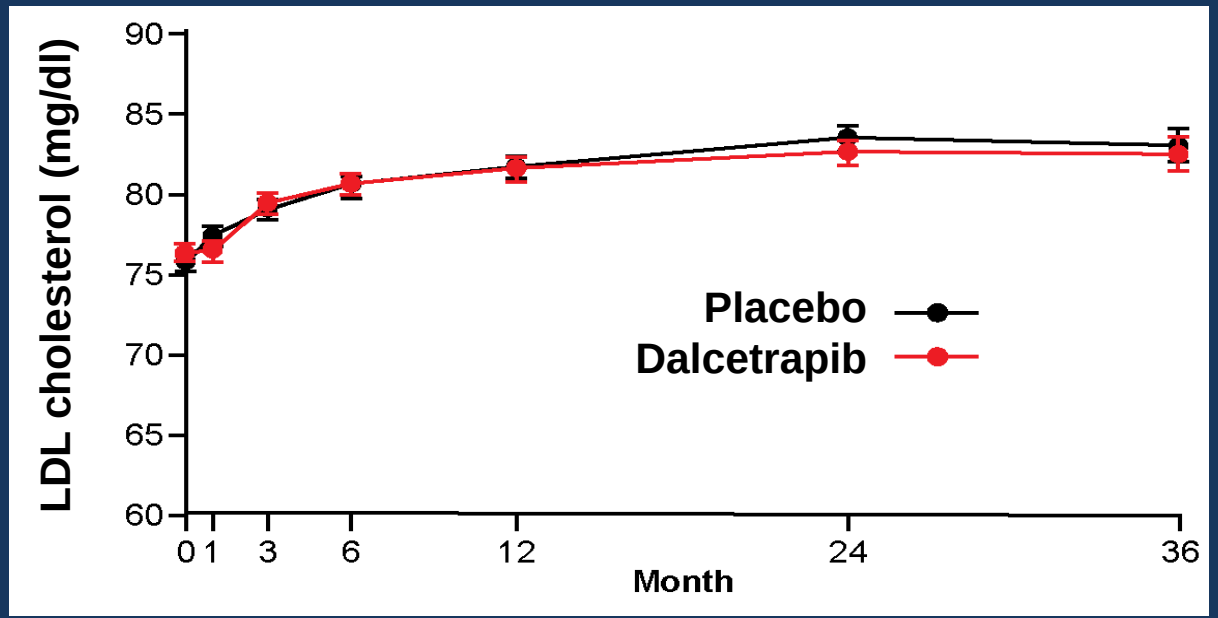
Concurrent treatments

(all balanced between treatment groups)

PCI or CABG for index event (before randomization)	**91%**
Statin	**97%**
Aspirin	**97%**
Clopidogrel, ticlopidine or prasugrel	**89%**
Beta blocker	**88%**
ACE inhibitor or ARB	**79%**

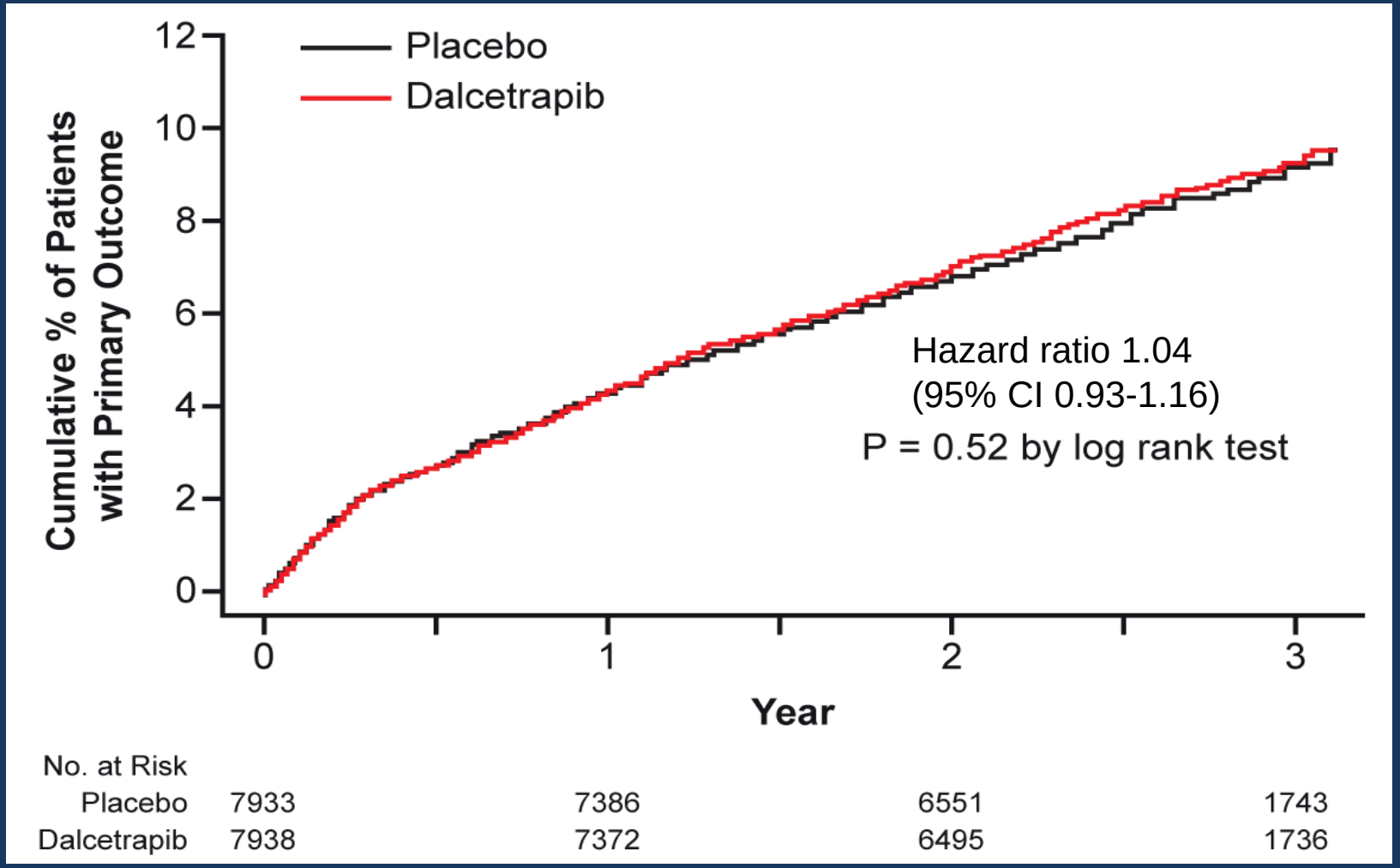
HDL-C and LDL-C by treatment group





Data are
mean ± 95% CI

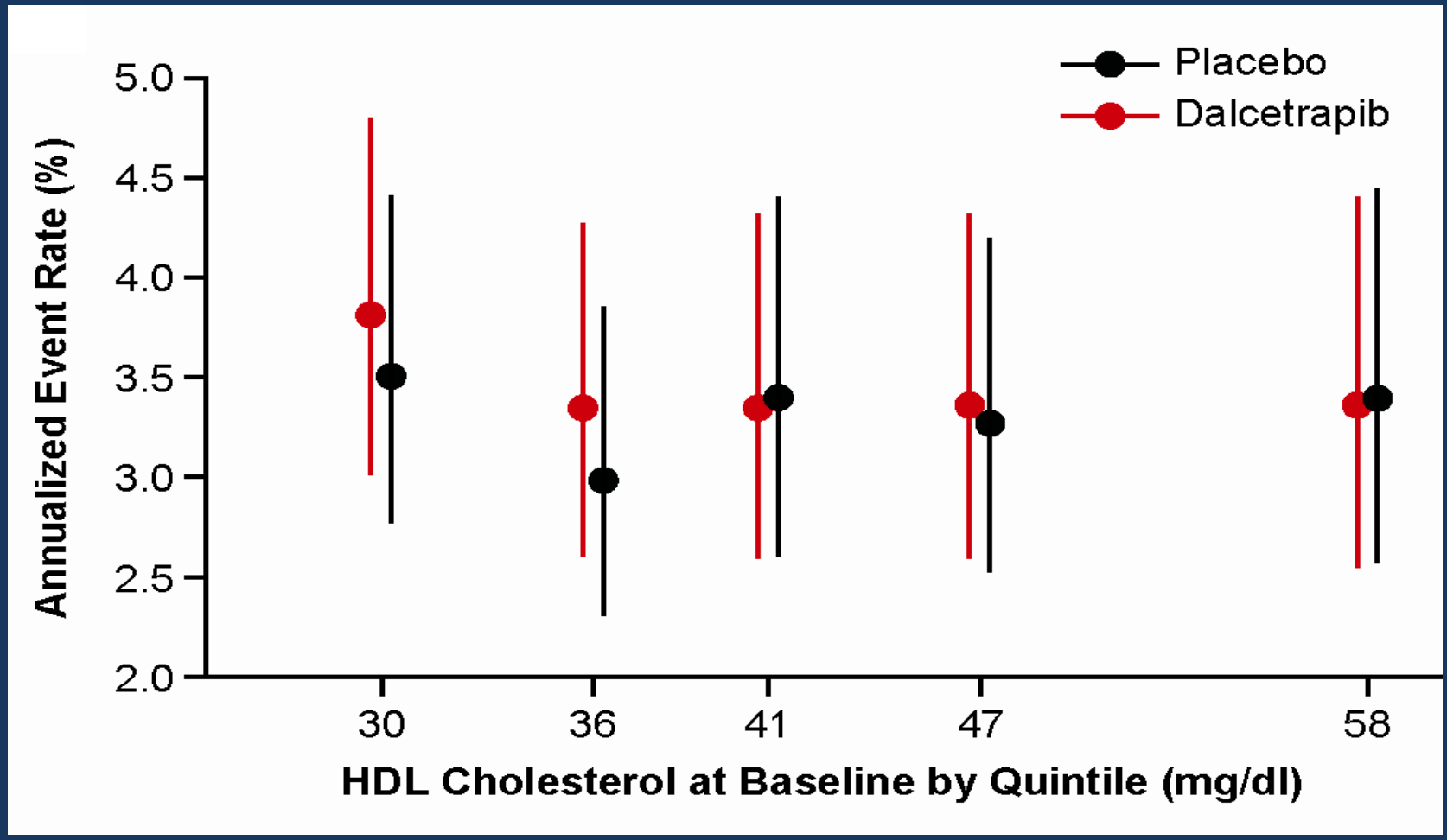
Primary outcome* by treatment group



* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

Why did dalcetrapib fail to reduce risk?

No association between baseline HDL-C (by quintiles) and risk of primary endpoint

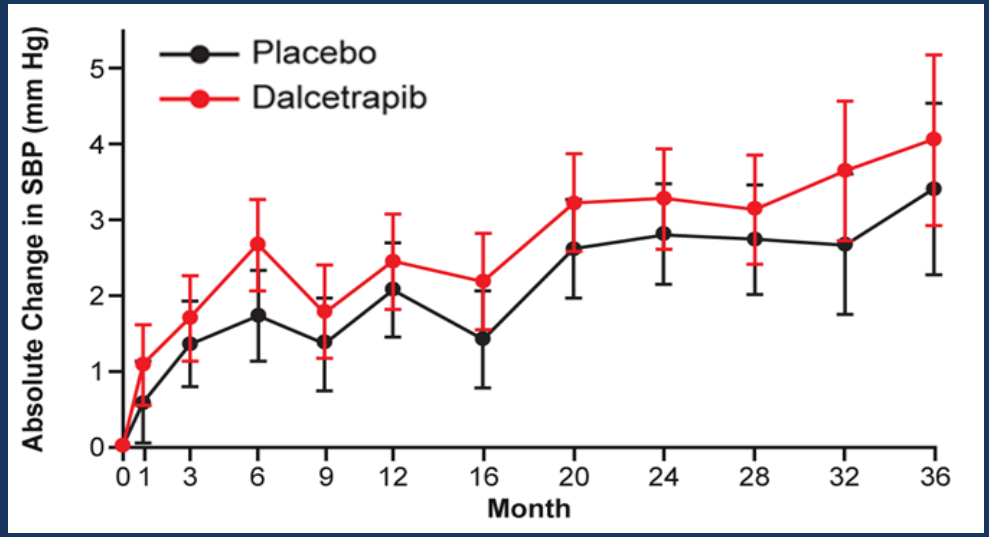


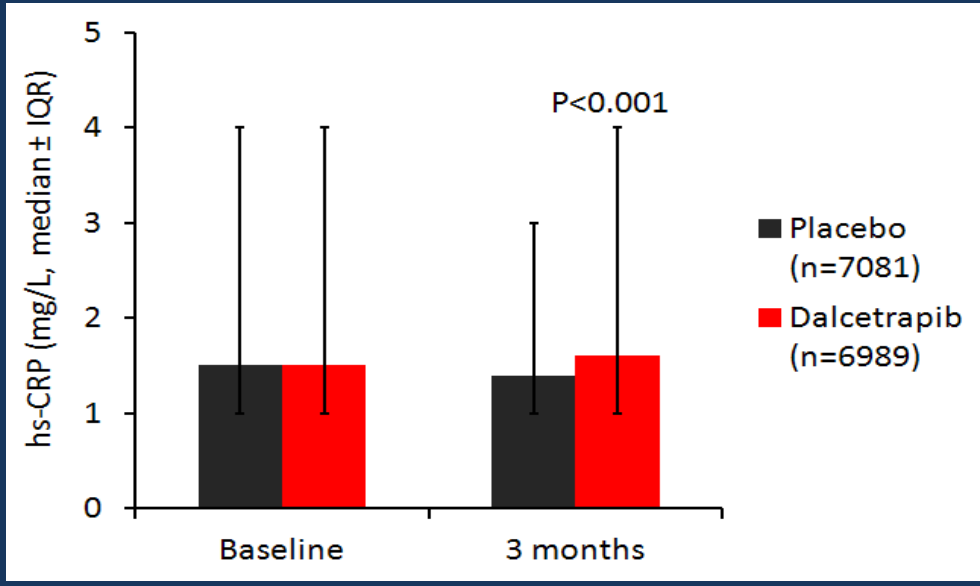
Systolic blood pressure and hs-CRP were slightly higher with dalcetrapib than placebo

With dalcetrapib, compared with placebo:

- Mean ***systolic blood pressure*** was 0.6 mm Hg higher (P<0.001)
- No effect on plasma aldosterone, bicarbonate, or potassium
- No difference in number of anti-hypertensive medications

- At 3 months of assigned treatment, median ***hs-CRP*** was 0.2 mg/L higher (P<0.001, based on ANOVA after log transformation)





Conclusions: dal-OUTCOMES

- In patients with recent ACS, the CETP inhibitor dalcetrapib raised HDL-C by ~30% with minimal effect on LDL-C and had no effect on the risk of major cardiovascular events.
- HDL-C concentration did not predict risk in this study population.
- Slightly higher systolic blood pressure and C-reactive protein with dalcetrapib might reflect an adverse effect of inhibiting CETP.

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There are several possible explanations for why these four trials failed to meet their primary endpoints.

1. The inverse relationship between the concentration of HDL-C and CV risk observed in population studies is an epiphenomenon rather than reflecting an ability of HDL to protect. This proposition is not supported by the animal studies in which increasing HDL is demonstrably anti-atherogenic.

2. Effects on the development of atherosclerosis in animals (or humans) do not necessarily translate into effects on clinical events in humans

3. Interventions that increase the concentration of HDL-C may not be accompanied by an increase in the protective properties of HDL

4. Increasing the level of HDL may be of little value when the concentration of LDL-C is very low.

5. The agents used had adverse effects that off-set the potential benefits of the HDL raising. While this may have been the case with torcetrapib, it is not likely with the other agents.

6. A reduction in clinical CV events may require a much greater increase in HDL than has been achieved in the trials with niacin and dalcetrapib.

The Future is Bleak for CETP Inhibitors!

- But let's at least hold out optimism that the trials with anacetrapib and evacetrapib demonstrate some benefit, BUT UNLIKELY!
- Other promising therapeutic approaches to modify lipids: Anti-PCSK9 (monoclonal antibody to PCSK9), mipomersen (antisense oligonucleotide for apoB-just FDA approved for FH)