Effects of the Cholesteryl Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome

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On behalf of the **dal-OUTCOMES*** investigators

* Funded by F. Hoffmann-La Roche, Ltd.

Background

- In observational analyses, higher levels of HDL-C are associated with lower cardiovascular risk
- However, it is uncertain whether raising HDL-C therapeutically reduces cardiovascular risk
- Inhibition of cholesteryl ester transfer protein (CETP) raises HDL-C and therefore might reduce cardiovascular risk
- Dalcetrapib is a CETP inhibitor that raised HDL-C by approximately 30% in Phase 2 trials, without effect on blood pressure or neurohormones.

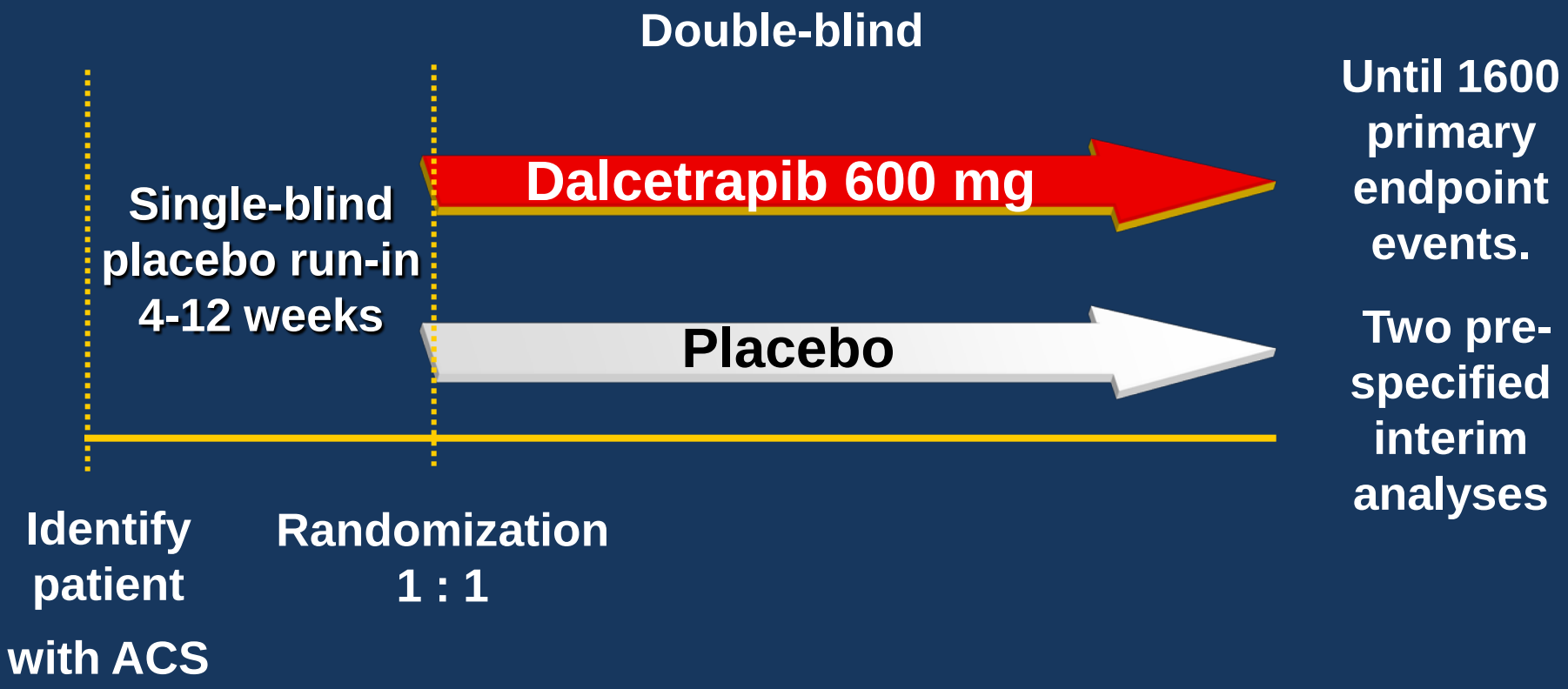
Objective of the dal-OUTCOMES trial

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

Entry criteria

- Age ≥45 years
- Acute coronary syndrome
- Evidence-based management of LDL-C
- No restriction on entry level of HDL-C
- Key exclusions: Triglycerides >400 mg/dl; treatment with niacin, fibrates, or bile acid sequestrants.

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.

Baseline characteristics

(all balanced between treatment groups)

Mean age (years)	60
Female	19%
Caucasian	88%
Region	
Europe or Israel	50%
North America	32%
Cardiovascular risk factors	
Hypertension	68%
Metabolic syndrome	63%
Diabetes	24%
Current smoker	21%
Cardiac biomarker-positive qualifying (index) event	87%
Time from index event to randomization (days)	61

Concurrent treatments

(all balanced between treatment groups)

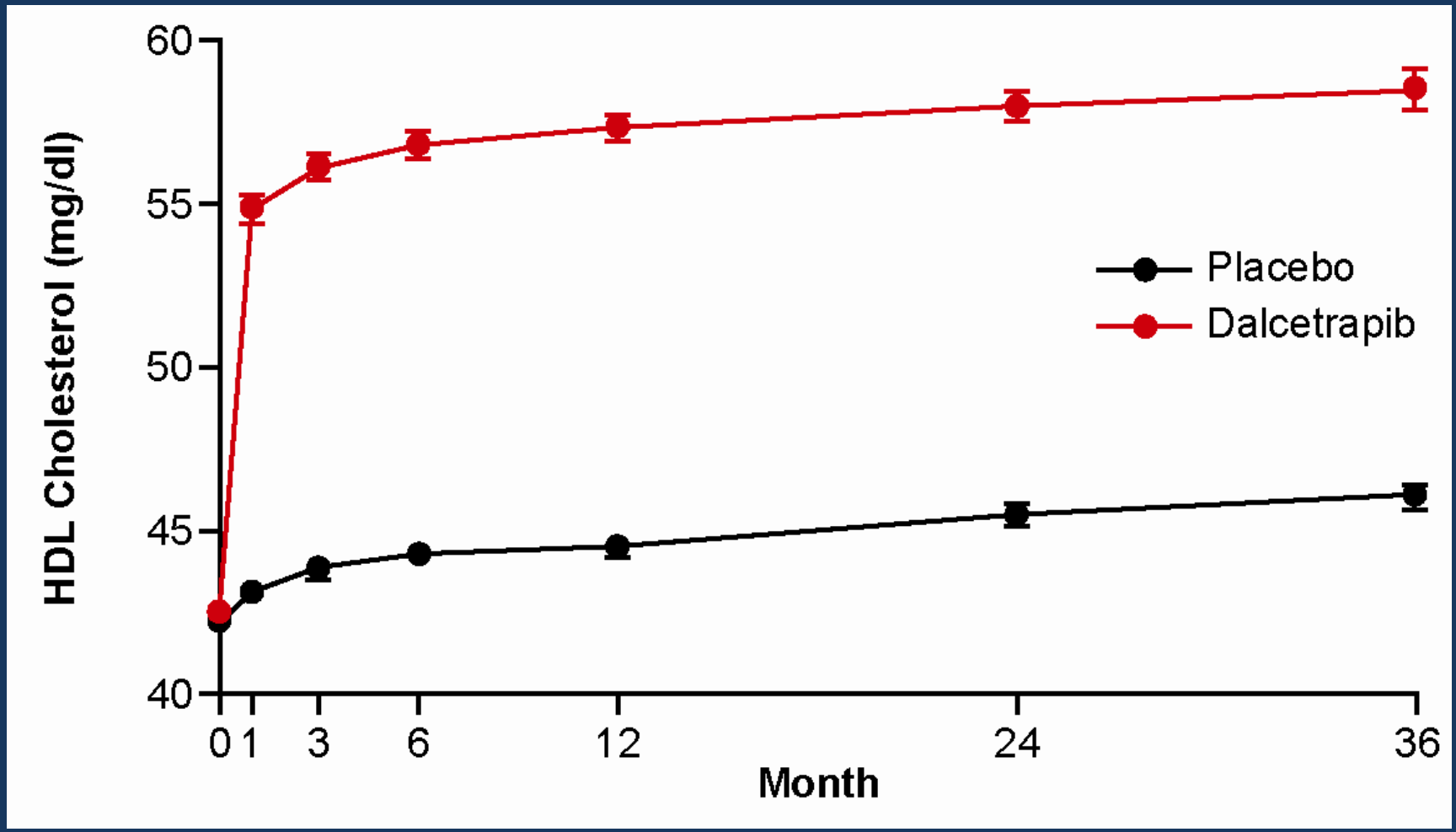
PCI or CABG for index event (before randomization)	**91%**
Statin	**97%**
Aspirin	**97%**
Clopidogrel, ticlopidine or prasugrel	**89%**
Beta blocker	**88%**
ACE inhibitor or ARB	**79%**

Baseline lipids (mean)

(all balanced between treatment groups)

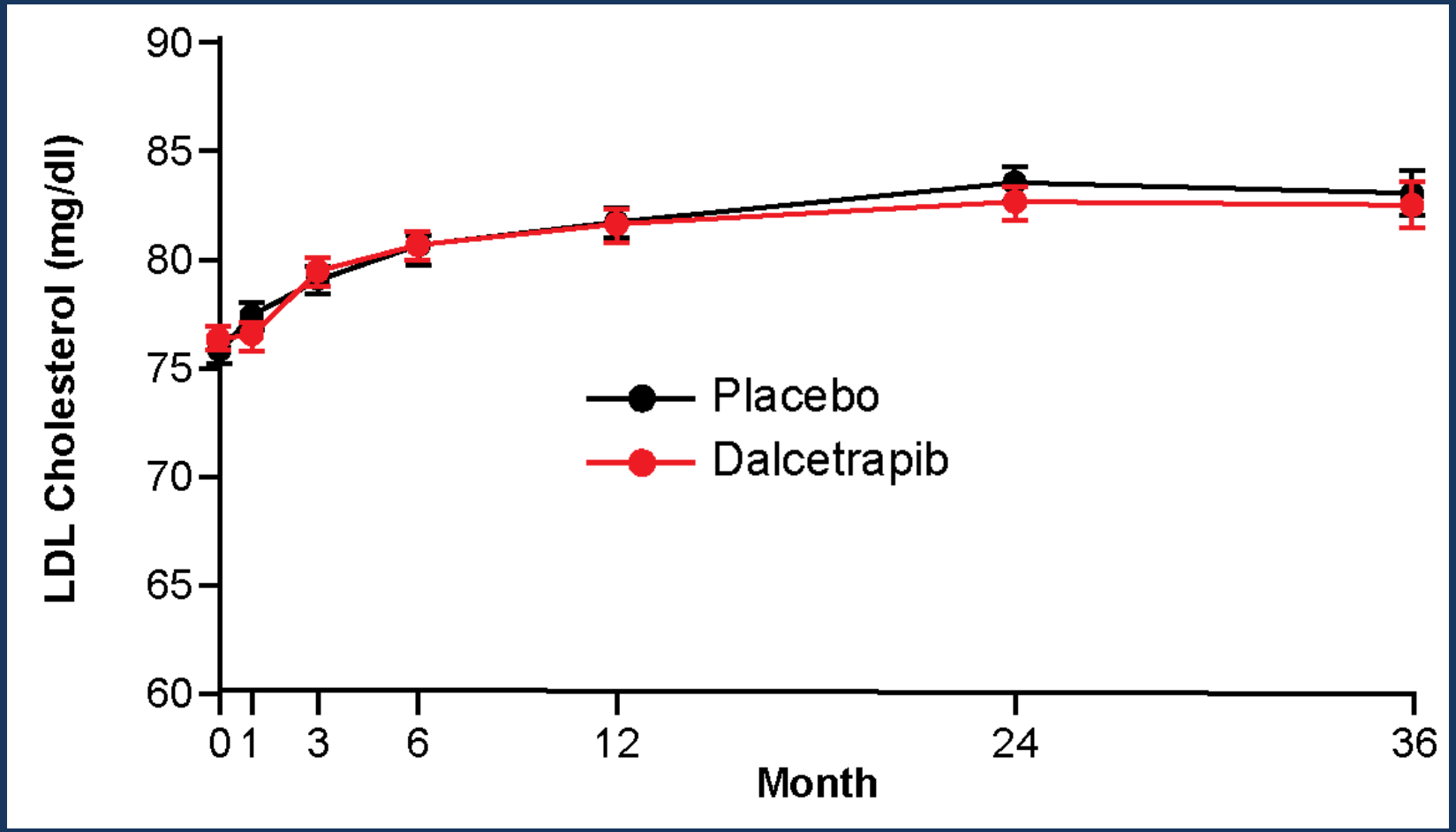
	mg/dl	mmol/L
LDL cholesterol	76	1.96
HDL cholesterol	42	1.09
Triglycerides	134	1.51

HDL-C by treatment group



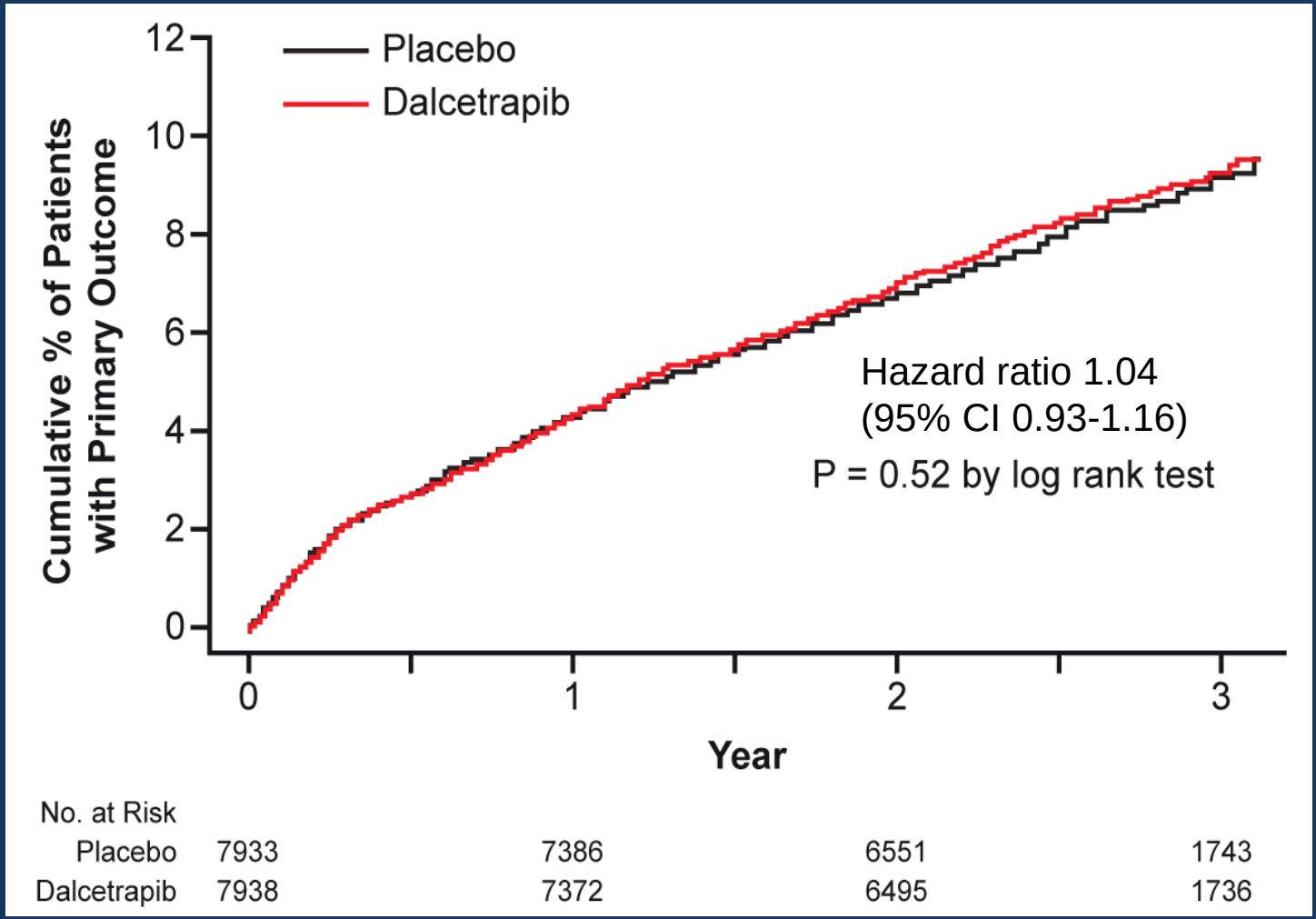
Data are mean ± 95% CI

LDL-C by treatment group



Data are mean ± 95% CI

Primary outcome* by treatment group



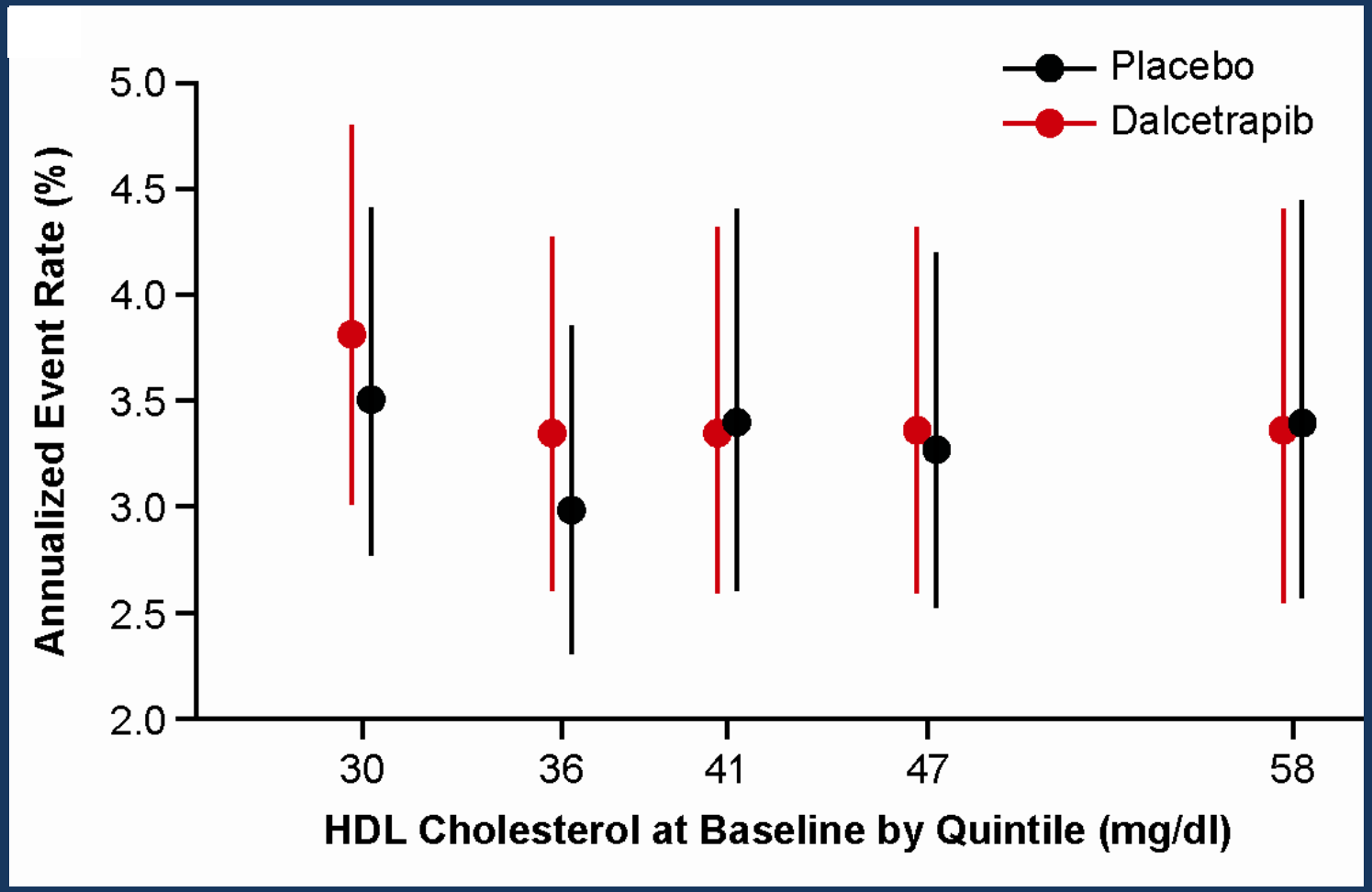
* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

Risk of primary and secondary outcomes

Event	Dalcetrapib (% at 3 years)	Placebo (% at 3 years)	Hazard Ratio (95% CI) P-value
Primary composite	9.2	9.1	**1.04** (0.93-1.16) 0.52
CHD death	1.6	1.8	**0.94** (0.73-1.21) 0.66
Non-fatal MI	5.9	6.0	**1.02** (0.89-1.17) 0.80
Unstable angina	1.3	1.3	**0.91** (0.68-1.22) 0.54
Resuscitated cardiac arrest	0.2	0.1	**1.41** (0.63-3.18) 0.40
Ischemic Stroke	1.4	1.0	**1.25** (0.92-1.70) 0.16
All cause mortality	3.1	3.4	**0.99** (0.82-1.19) 0.90
Coronary revascularization	9.5	9.6	**1.00** (0.87-1.11) 0.97

Why did dalcetrapib fail to reduce risk?

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

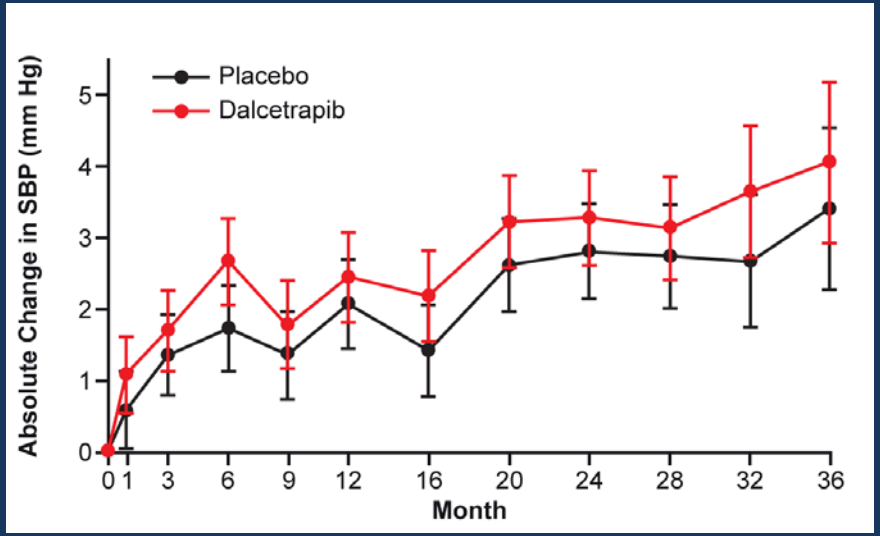


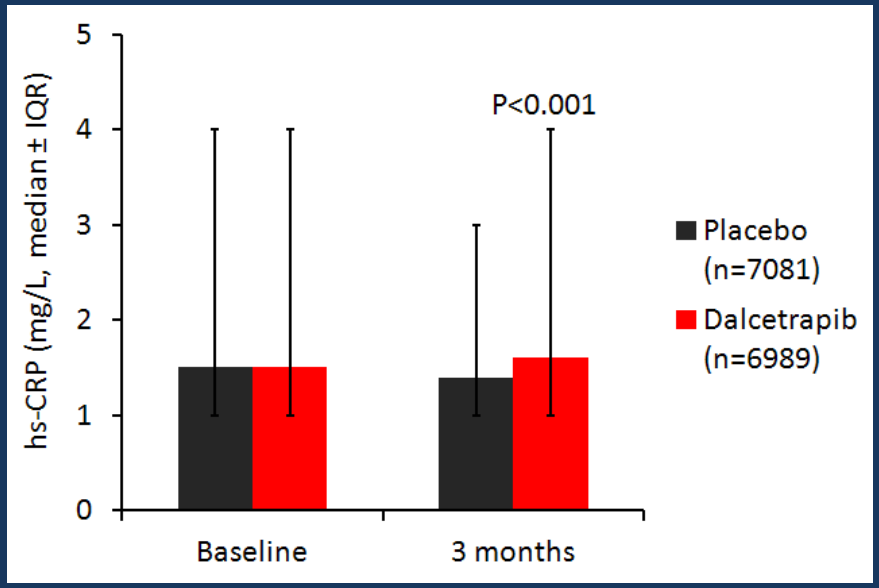
Systolic blood pressure and hs-CRP were slightly higher with dalcetrapib than placebo

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

- 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 mark an adverse effect of inhibiting CETP.

Study Organization

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- Bernard Chaitman (ex officio)
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ORIGINAL ARTICLE

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