

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

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

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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
- Dalcatrapib 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

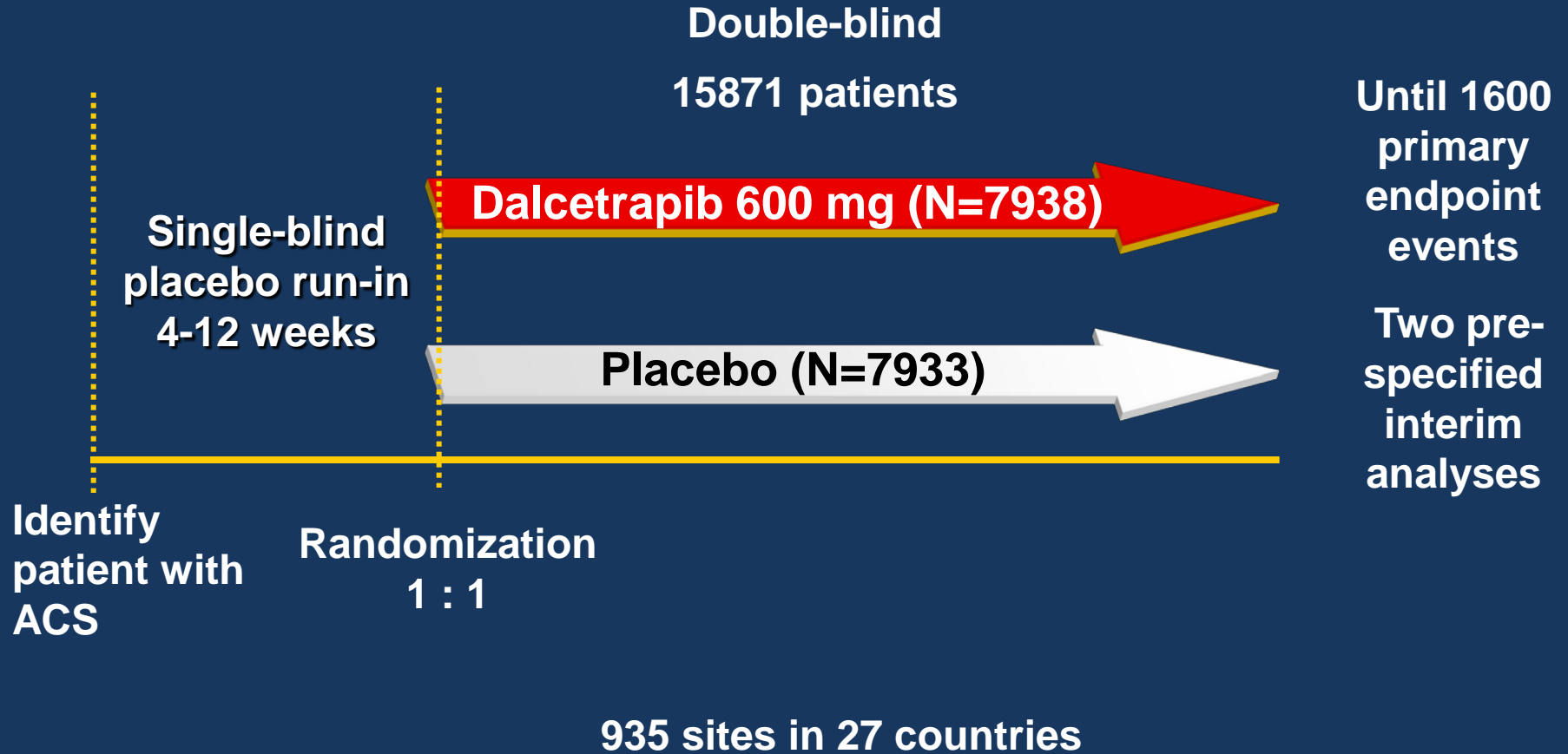
- To compare the effects of dalcetrapib with placebo, added to evidence-based background therapy, on cardiovascular risk in patients with recent acute coronary syndrome



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





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%

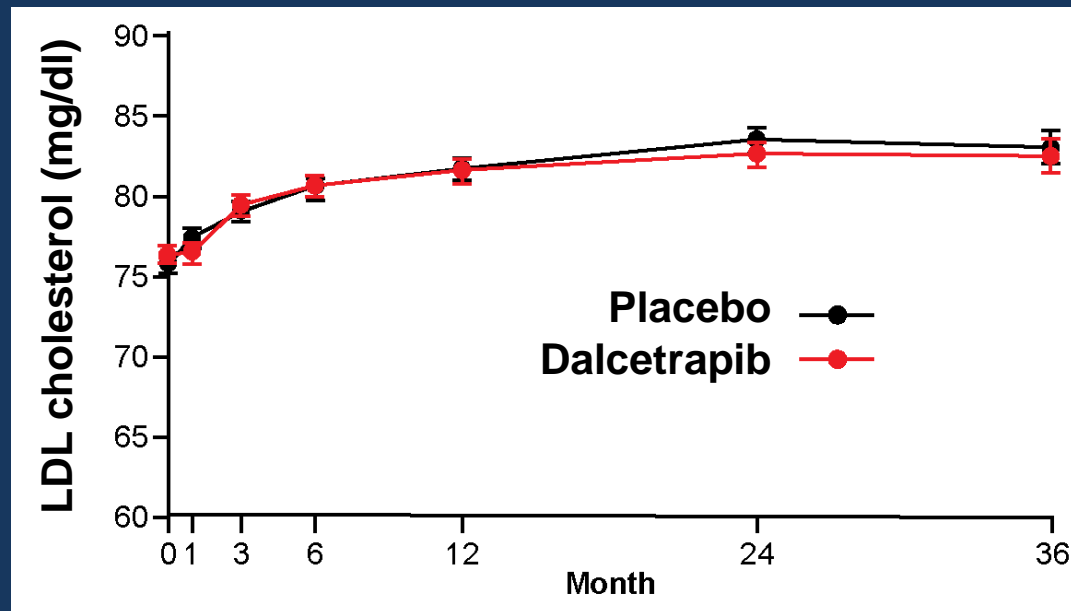
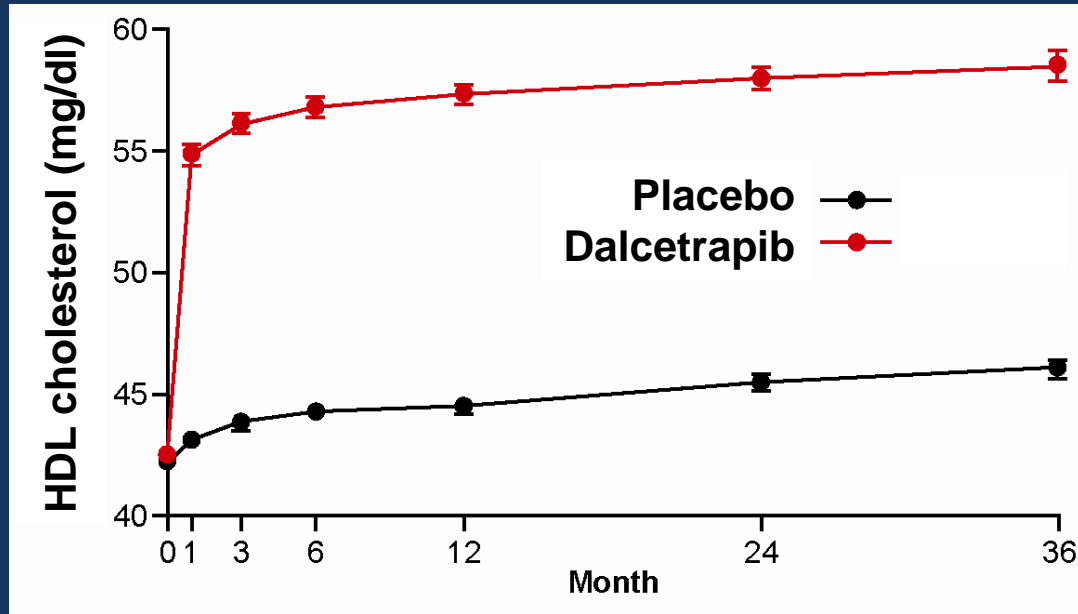


Baseline lipids (mean)

(all balanced between treatment groups)

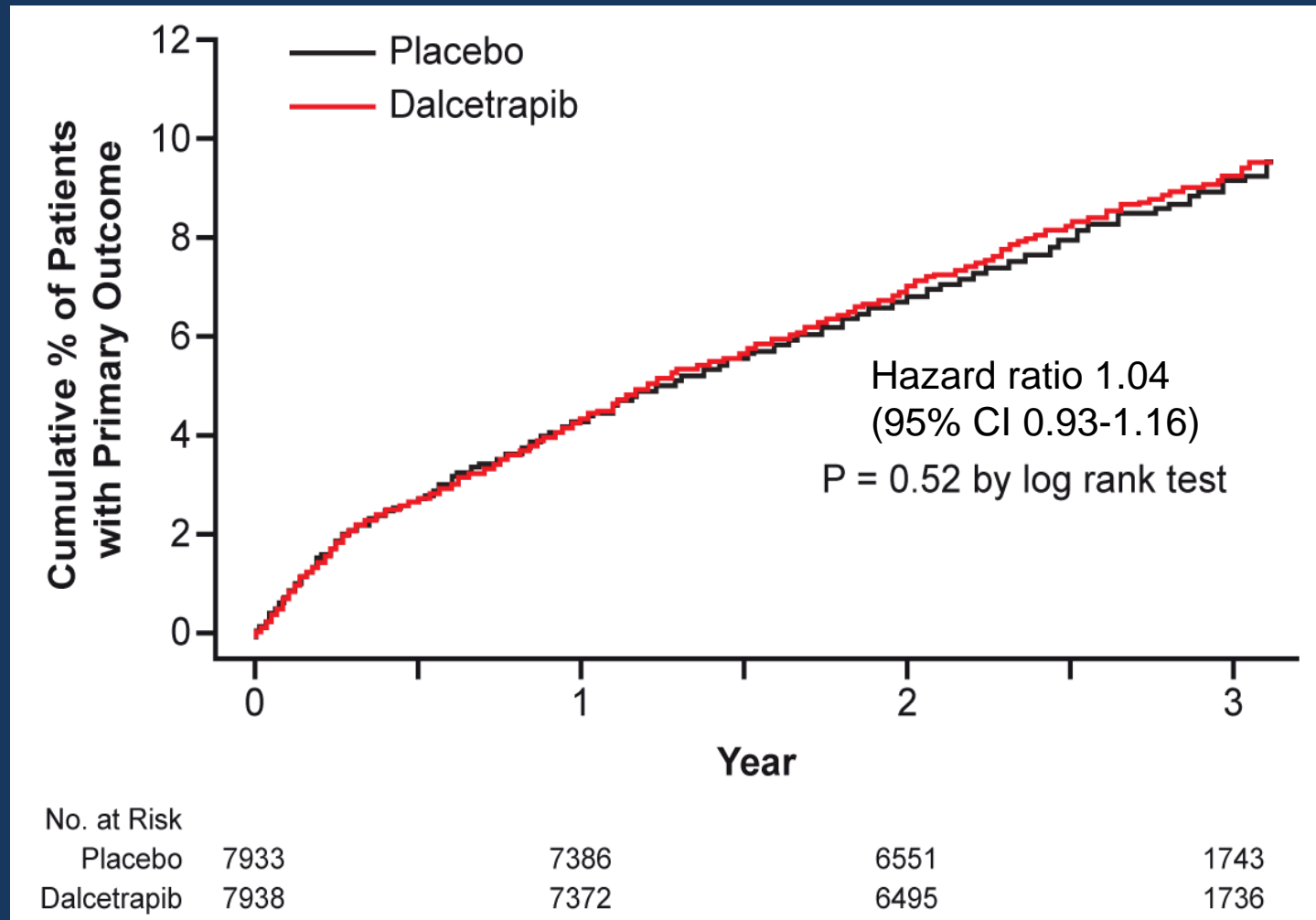
	mg/dl	mmol/L
LDL cholesterol	76	1.96
HDL cholesterol	42	1.09
Triglycerides	134	1.51

HDL-C and LDL-C by treatment group



Data are
mean \pm 95% CI

Primary outcome* by treatment group



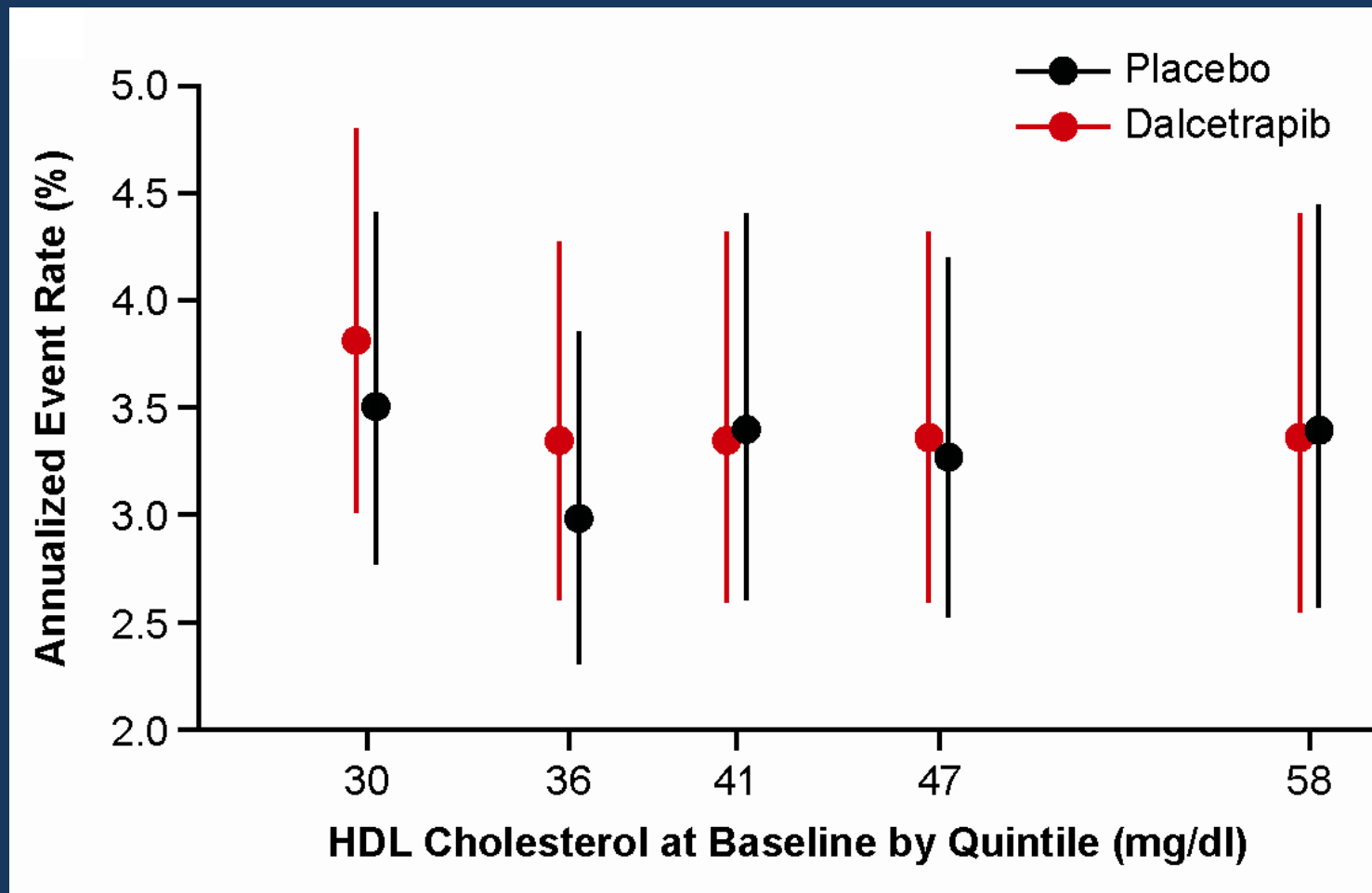
* Coronary heart disease death, non-fatal MI, ischemic stroke, hospitalization for unstable angina, resuscitated cardiac arrest

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?

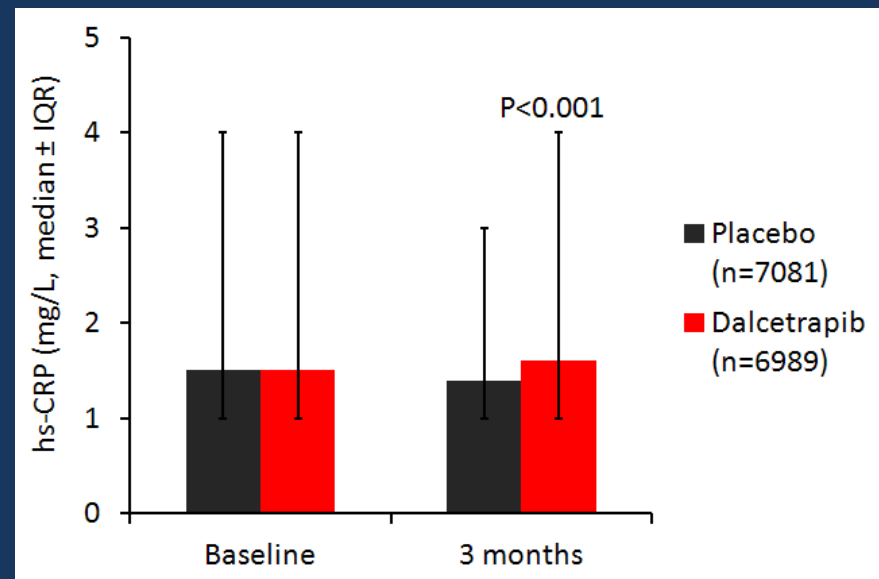
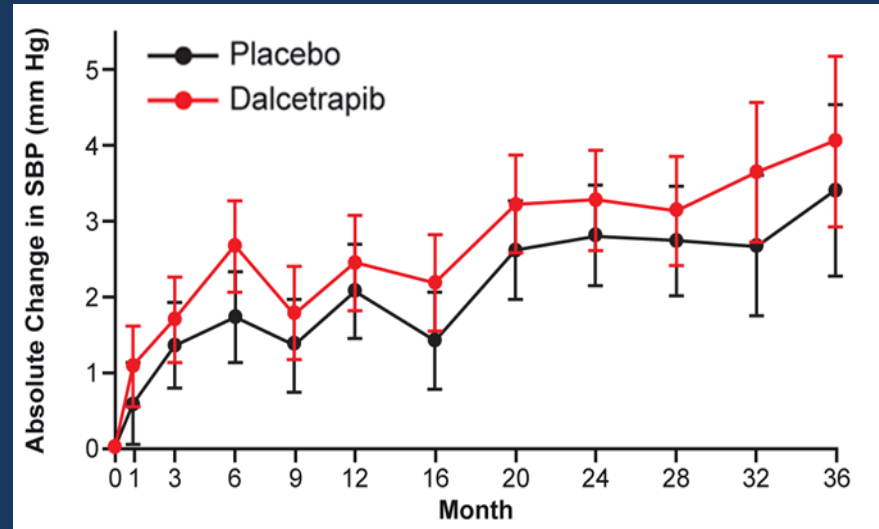
No association between baseline HDL-C (by quintiles) and risk of primary endpoint



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 reflect an adverse effect of inhibiting CETP.

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ORIGINAL ARTICLE

Effects of Dalcatrapib in Patients with a Recent Acute Coronary Syndrome

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