Vascular Effects and Safety of Dalcetrapib in Patients with, or at Risk of CHD: the dal-VESSEL Randomised Clinical Trial

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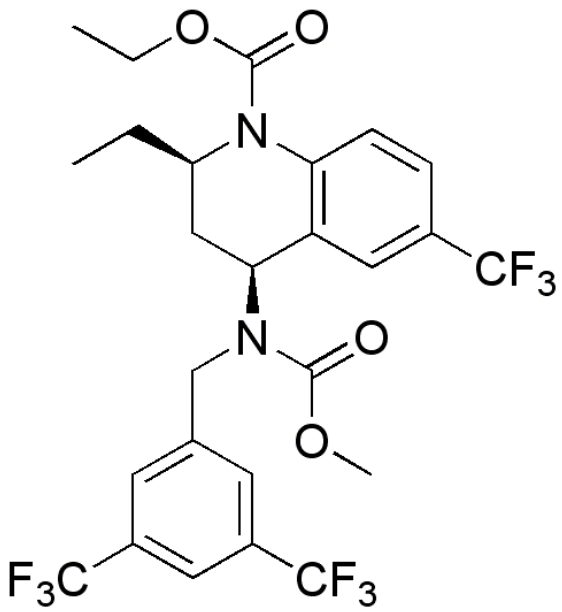
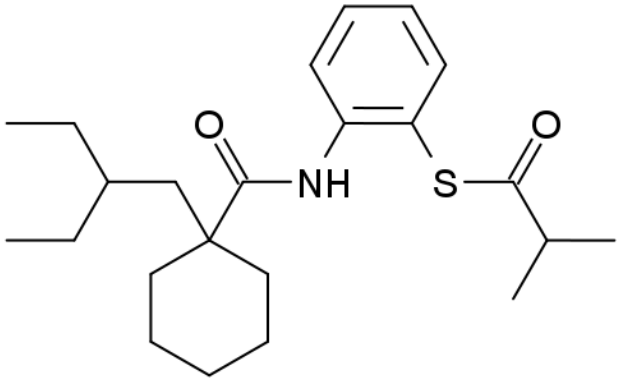
No conflicts with respect to any aspect of this presentation

Cholesterol Ester Transport Inhibitors

cholesteryl ester transfer protein (CETP), normally transfers cholesterol from HDL cholesterol to very low density or low density lipoproteins (VLDL or LDL).



Torcetrapib



dalcetrapib

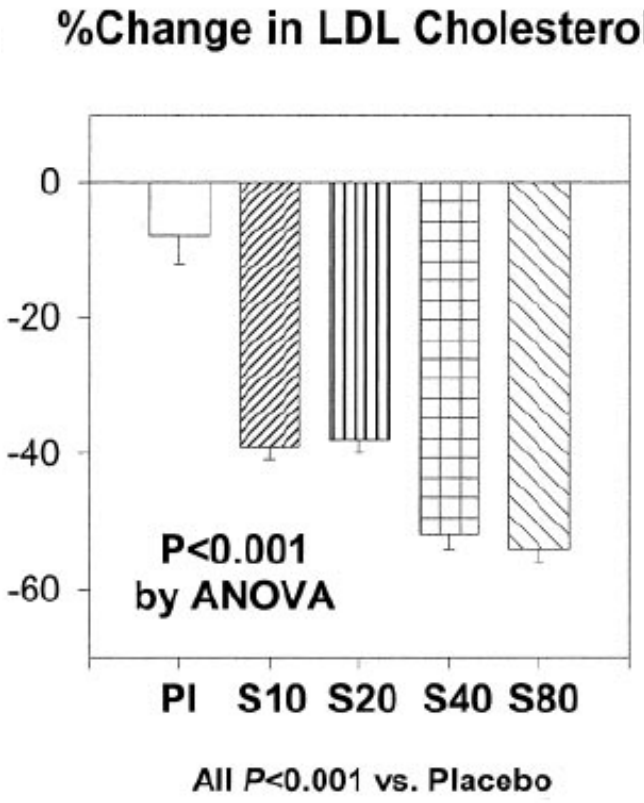
- 61% increase in HDL cholesterol, 20% decrease in LDL cholesterol. ***4.6mm increase in blood pressure***, IVUS: no significant decrease in the progression of coronary atherosclerosis. NEJM 2007; 356:1304-1316

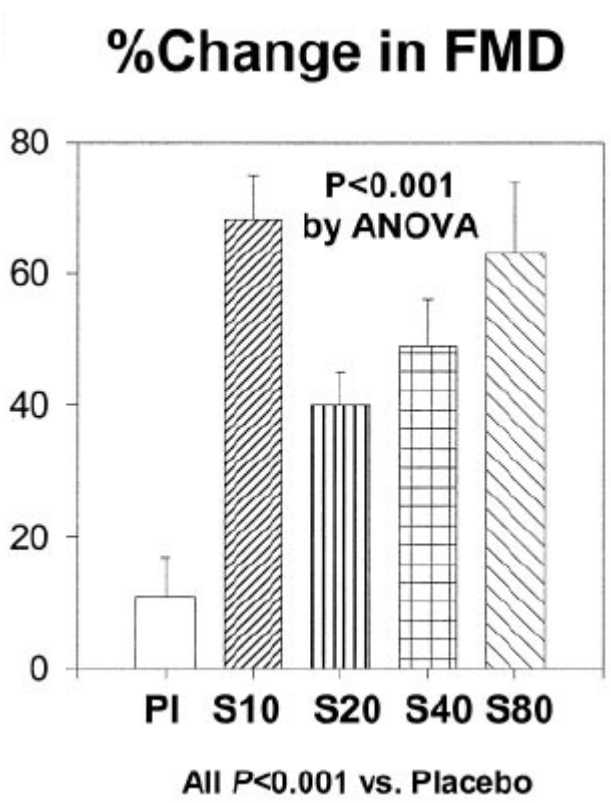
- Phase 3 trial stopped: increase in deaths among patients taking torcetrapib and atorvastatin versus taking atorvastatin alone

dal -VESSEL (phase IIb trial)

- dal-VESSEL randomised, double-blind, placebo-controlled study in patients with CHD or CHD risk equivalents.
- 476 patients with HDL-C levels <50 mg/dL: dalcetrapib 600 mg/day or placebo in addition to their existing treatments.
  - Primary efficacy endpoint is change in brachial flow mediated dilatation after 12 weeks.
  - Primary safety endpoint was 24-hour ambulatory blood pressure.
- Flow Mediated Dilatation is a marker of endothelial dysfunction and associated with atherosclerosis.

Flow mediated dilatation: What changes are seen with statins?

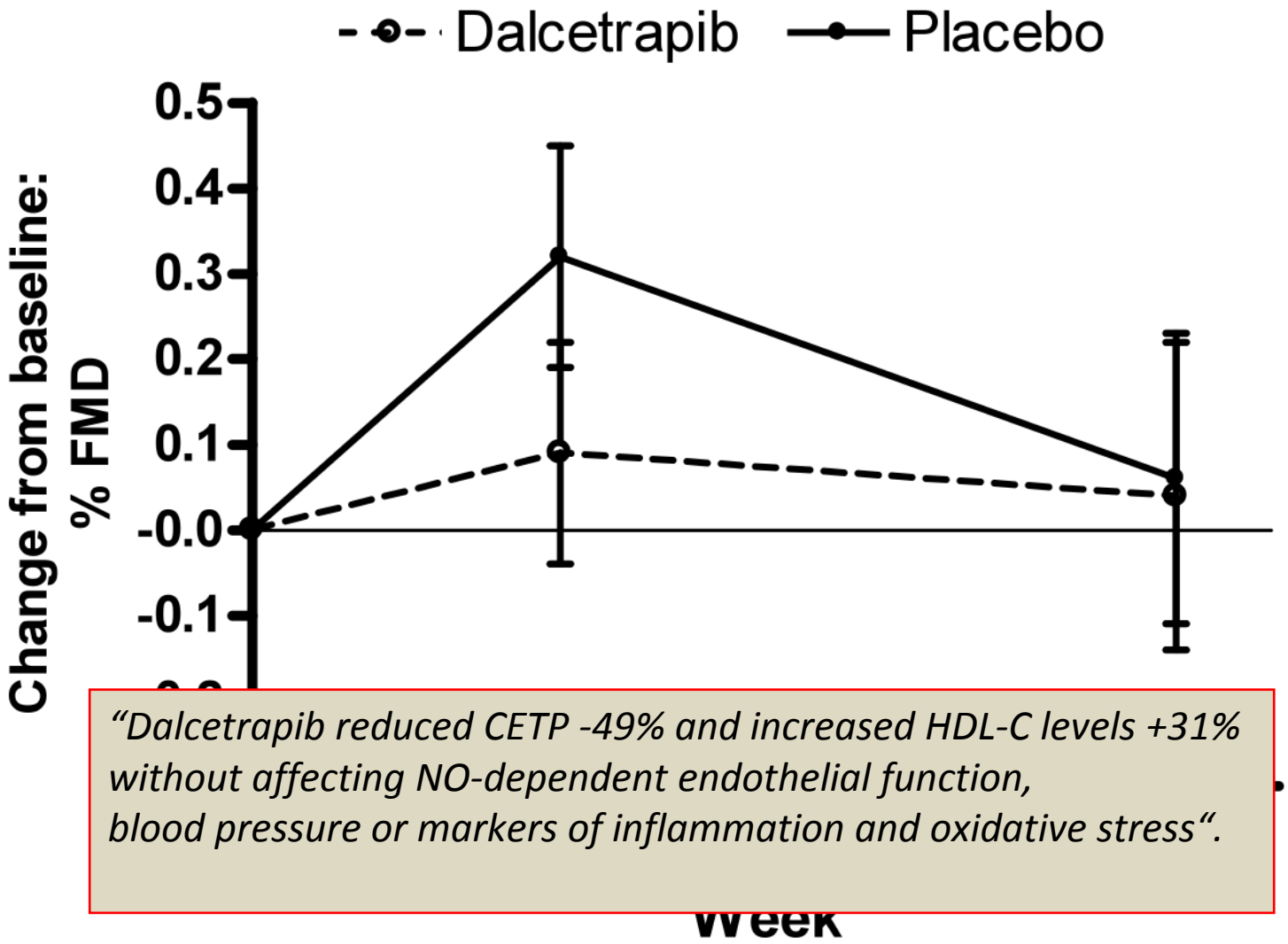




Simvastatin 10mg, 20mg, 40mg, 80mg

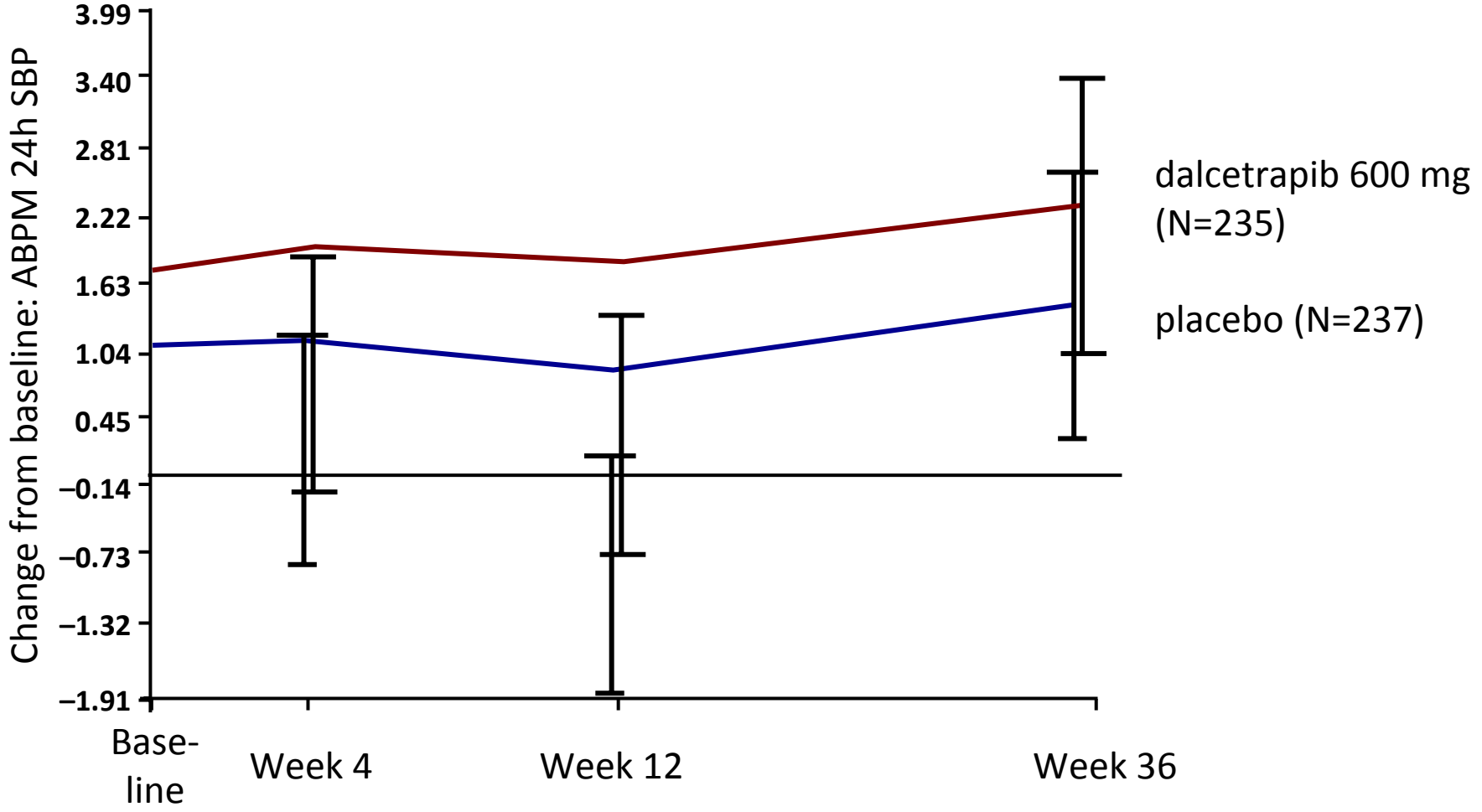
Koh et al Diabetes Care 31:776–782, 2008

dal-Vessel-Trial – Flow-mediated Dilation



"Dalcetrapib reduced CETP -49% and increased HDL-C levels +31% without affecting NO-dependent endothelial function, blood pressure or markers of inflammation and oxidative stress".

Systolic Blood Pressure – Change from Baseline



Blood pressure changes at 4 weeks

- Mean SBP dalcetrapib (128 mmHg) placebo (125 mmHg).
- Difference *vs* placebo 0.65 mmHg, 95% CI –0.68, 1.99; *P*=0.337).
- *"The primary safety endpoint was therefore met with respect to SBP".*
- At 12 weeks (difference *vs* placebo 1.21 mmHg, 95% CI –0.15, 2.58; *P*=0.081)
- At 36 weeks (difference *vs* placebo 0.90 mmHg, 95% CI –0.65, 2.45; *P*=0.253).

dal-Vessel-Trial

- The first multicentre trial demonstrating the feasibility of using FMD to evaluate risk markers using novel CV compounds.
- Dalcetrapib reduced CETP activity by 49% and increased HDL-C levels by 31%.
- No significant effect on NO-dependent endothelial function, blood pressure or markers of inflammation and oxidative stress.
- The dal-OUTCOMES trial (NCT00658515) will show whether dalcetrapib improves outcomes.