REVEAL:
Randomized placebo-controlled trial of anacetrapib in 30,449 patients with atherosclerotic vascular disease

Martin Landray and Louise Bowman

on behalf of the HPS 3 / TIMI 55 - REVEAL Collaborative Group

Funded by MSD, British Heart Foundation, Medical Research Council

Designed, conducted and analysed independently of the funders

University of Oxford is the trial sponsor

HPS 3 / TIMI 55 - REVEAL Collaborative Group

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With many thanks to the more than 30,000 patients and hundreds of clinicians & researchers who made this trial possible.

Background

- Anacetrapib is a potent inhibitor of Cholesteryl Ester Transfer Protein (CETP) which doubles HDL-cholesterol and lowers LDL-cholesterol
- Previous trials of other CETP inhibitors have been stopped after around 2 years of follow-up due to unexpected cardiovascular hazards (torcetrapib) or apparent lack of efficacy (dalcetrapib, evacetrapib)
- The REVEAL trial assessed the efficacy and safety of adding anacetrapib vs. placebo to effective doses of atorvastatin among patients with established occlusive vascular disease

Effects of adding anacetrapib to intensive statin therapy

- Significant 9% proportional reduction in major coronary events (effect appears to be greater in later years of treatment)
- Small reduction in risk of new-onset diabetes mellitus
- No excess of symptomatic side-effects with anacetrapib (levels in adipose tissue rise with continued treatment)
- No excess of mortality, cancer or other serious adverse events (small increase in BP and small reduction in kidney function)
- Post-trial follow-up of all consenting participants (off-drug) to assess longer-term efficacy and safety of anacetrapib

Simultaneous publication in www.nejm.org

REVEAL trial design

Eligibility: 30,000 patients aged over 50 years with occlusive vascular disease

Background statin: Atorvastatin 20 or 80 mg daily (China: 10 or 20 mg)

⇨ Mean LDL-cholesterol 61 mg/dL (1.6 mmol/L)

Randomized: Anacetrapib 100 mg daily vs. matching placebo

Follow-up: ≥4 years and ≥1900 primary outcomes

Primary outcome: Major Coronary Event

(i.e. Coronary death, myocardial infarction, or coronary revascularization)

REVEAL Collaborative Group. Am Heart J 2017;187:182-90

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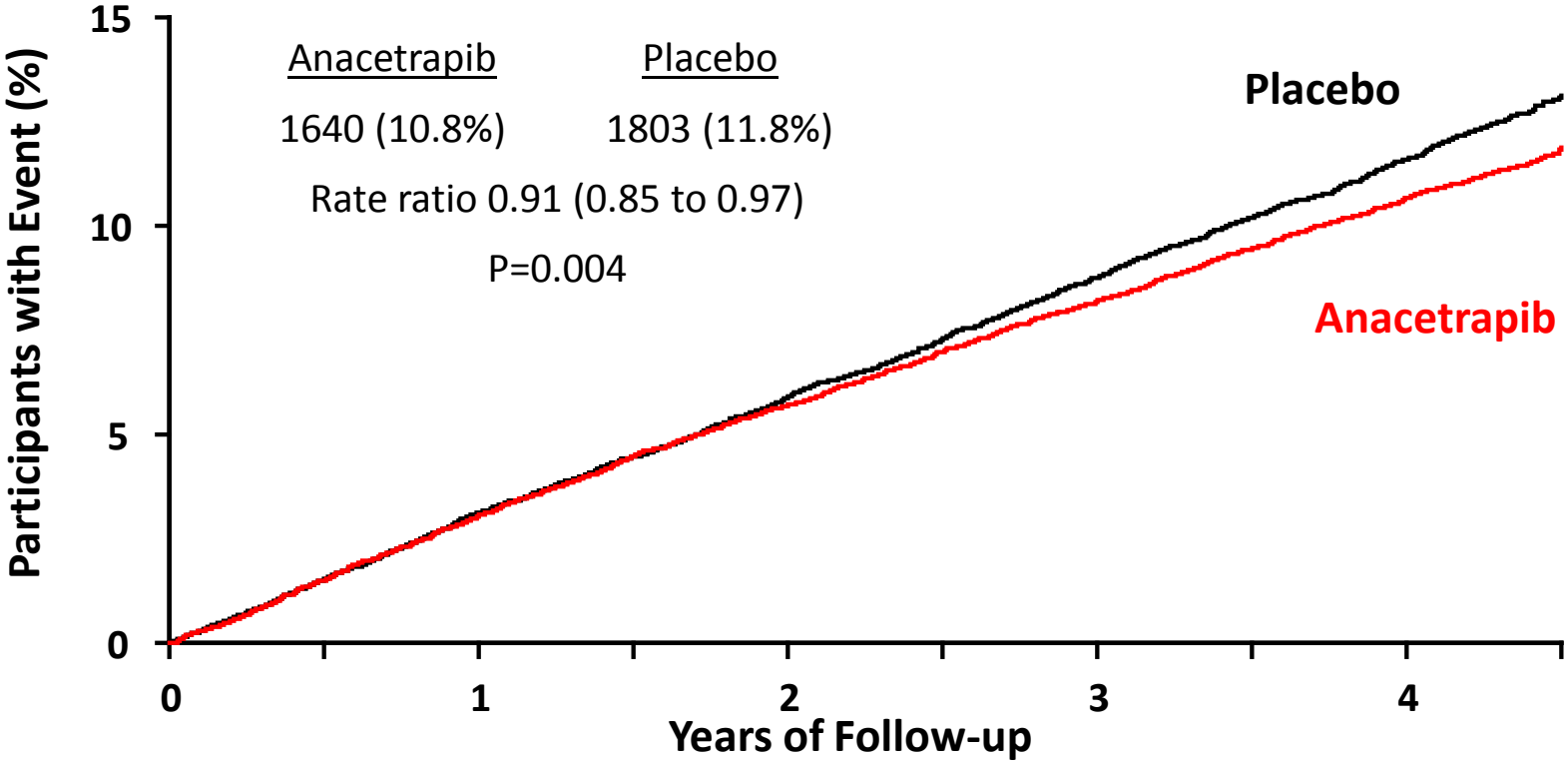
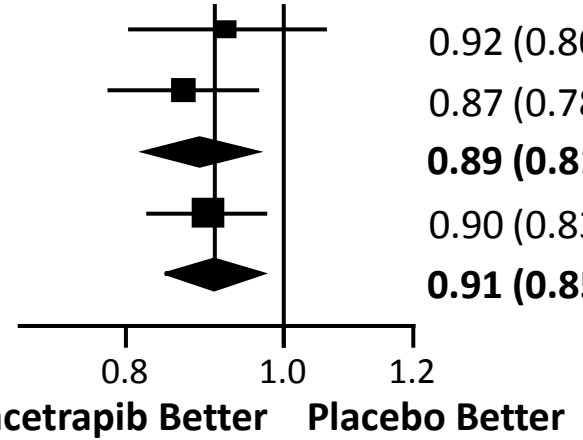


Components of the primary outcome

Type of Event	Anacetrapib (N=15225) no. of participants with events	(%)	Placebo (N=15224) no. of participants with events	(%)	Rate Ratio (95% CI)	P Value
Coronary death	388	(2.5)	420	(2.8)	0.92 (0.80–1.06)	0.25
Myocardial infarction	669	(4.4)	769	(5.1)	0.87 (0.78–0.96)	0.007
Coronary death or MI	**934**	**(6.1)**	**1048**	**(6.9)**	**0.89 (0.81–0.97)**	**0.008**
Coronary revascularization	1081	(7.1)	1201	(7.9)	0.90 (0.83–0.97)	0.01
Major coronary event	**1640**	**(10.8)**	**1803**	**(11.8)**	**0.91 (0.85–0.97)**	**0.004**

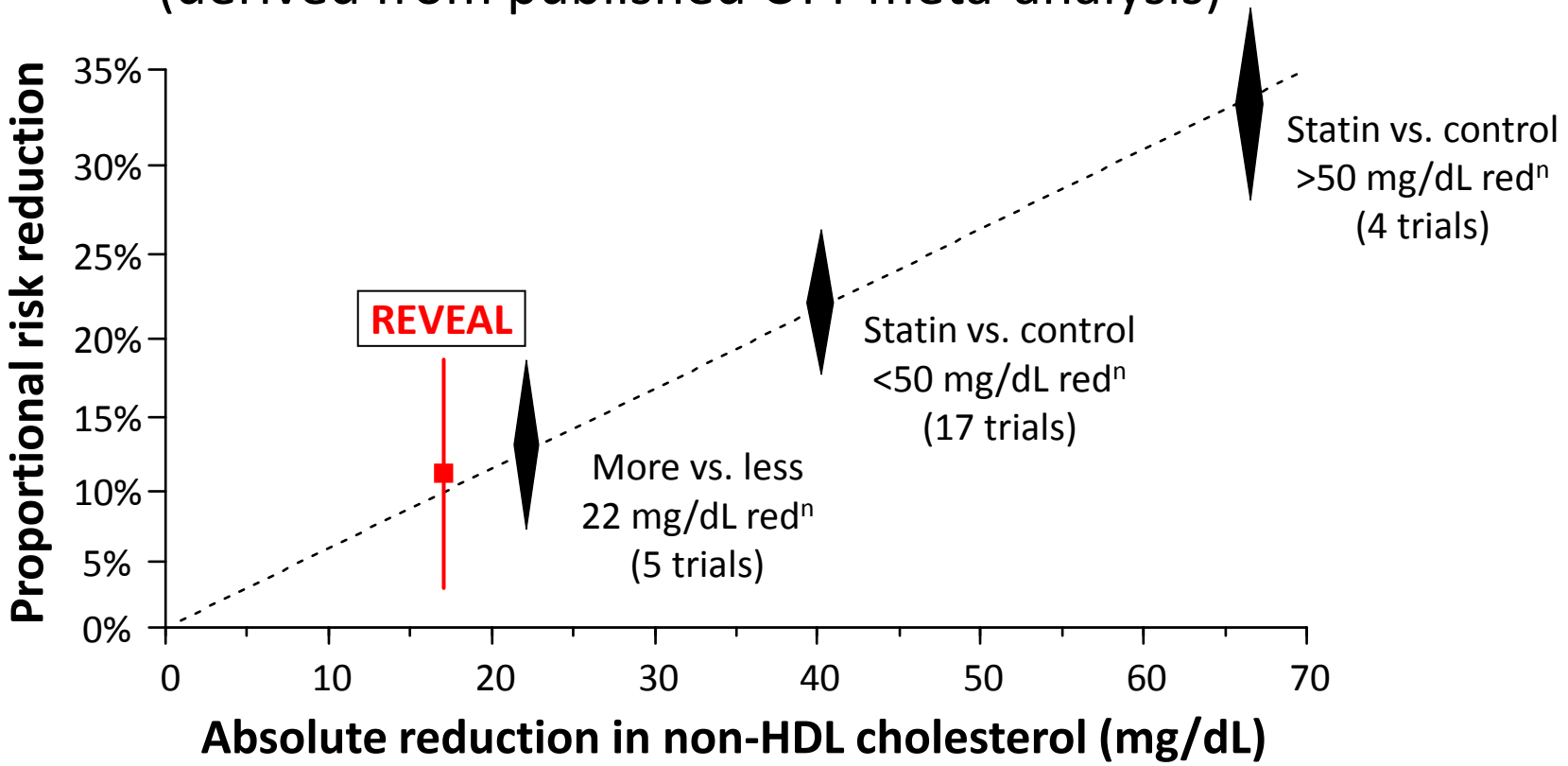


Major coronary event: Coronary death, MI or coronary revascularization

No significant evidence of differential proportional effects among 23 pre-specified subgroup categories

Proportional reduction in Coronary death or MI vs. absolute reduction in non-HDL cholesterol

(derived from published CTT meta-analysis)



Other clinical assessments

Assessment	Anacetrapib	Placebo	Difference	P
New-onset diabetes mellitus	510 (5.3%)	571 (6.0%)	-0.6%	0.05
Blood pressure				
Systolic (mmHg)	132.4	131.7	+0.7	0.002
Diastolic (mmHg)	77.6	77.4	+0.3	0.04
Hypertensive serious adverse events	151 (1.0%)	141 (0.9%)	+0.1%	0.56
Kidney disease				
New-onset eGFR <60 mL/min/1.73m^2	1344 (11.5%)	1236 (10.6%)	+0.84%	0.04
Renal failure serious adverse events	169 (1.1%)	146 (1.0%)	+0.15%	0.20

No effect on vascular, non-vascular, or all-cause mortality

No effect on cancer, liver, muscle, cognitive function, or other adverse events

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