



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

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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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Data Monitoring Committee

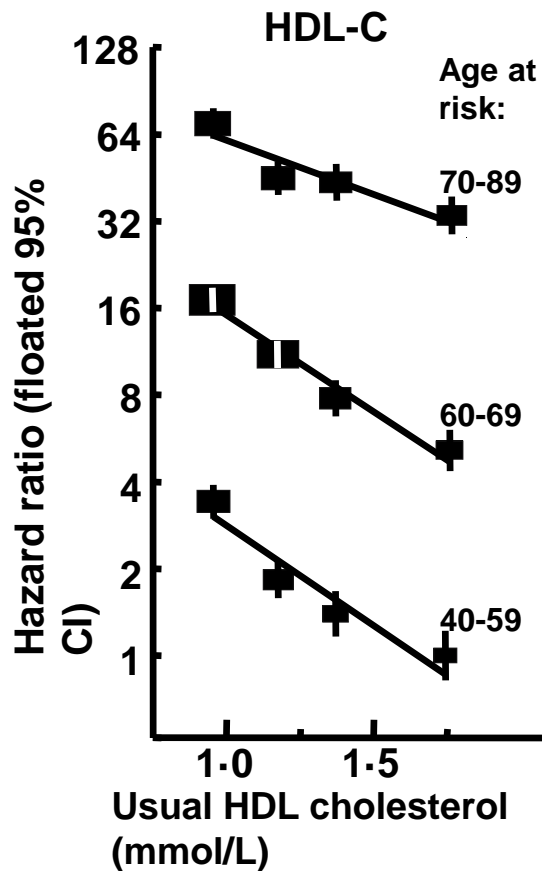
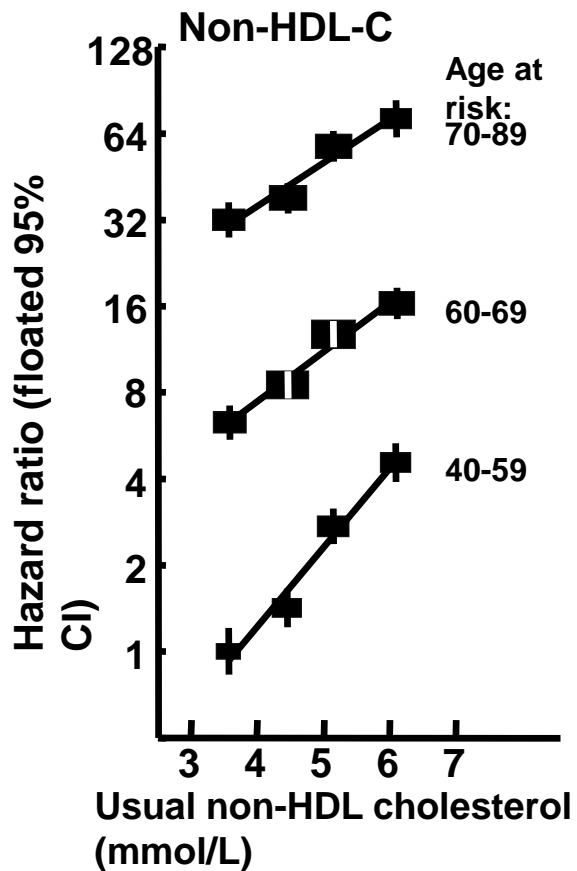
Peter Sandercock (*Chair*) , David DeMets, Andrew Tonkin, John Kjekshus, James Neuberger, Jonathan Emberson (*non-voting*)

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

Is a low HDL Cholesterol associated with an increased risk of vascular disease?

CHD mortality ratios vs usual lipid levels, by age at risk (adj. for age [40-89], sex and cohort)

3020 deaths



Is a low HDL Cholesterol associated with an increased risk of vascular disease?

YES...But...

Do HDL raising drugs prevent MI and Stroke?

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

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)

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)

Baseline demographics

Characteristic		Total
		(30449)
Age (years)	Mean	67
Gender	Male	25534 (84%)
	Female	4915 (16%)
Region	Europe	15738 (52%)
	North America	6082 (20%)
	China	8629 (28%)

Prior disease & blood lipids at randomization

(after 8-12 weeks' treatment with atorvastatin)

Characteristic		Total (30449)	
Prior disease	Coronary heart disease	26679	(88%)
	Cerebrovascular disease	6781	(22%)
	Peripheral arterial disease	2435	(8%)
	Diabetes mellitus	11320	(37%)
Lipids	HDL cholesterol	40 mg/dL	(1.0 mmol/L)
	LDL cholesterol	61 mg/dL	(1.6 mmol/L)
	Non-HDL cholesterol	92 mg/dL	(2.4 mmol/L)

Follow-up and adherence to treatment

Follow-up	Median duration	4.1 years	
	Complete	99.8%	
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		Anacetrapib	Placebo
Adherence at midpoint	Randomized treatment*	89.9%	89.7%
	Study atorvastatin	90.3%	89.7%
	Any statin	94.6%	94.7%

* No difference in any reason for stopping allocated treatment

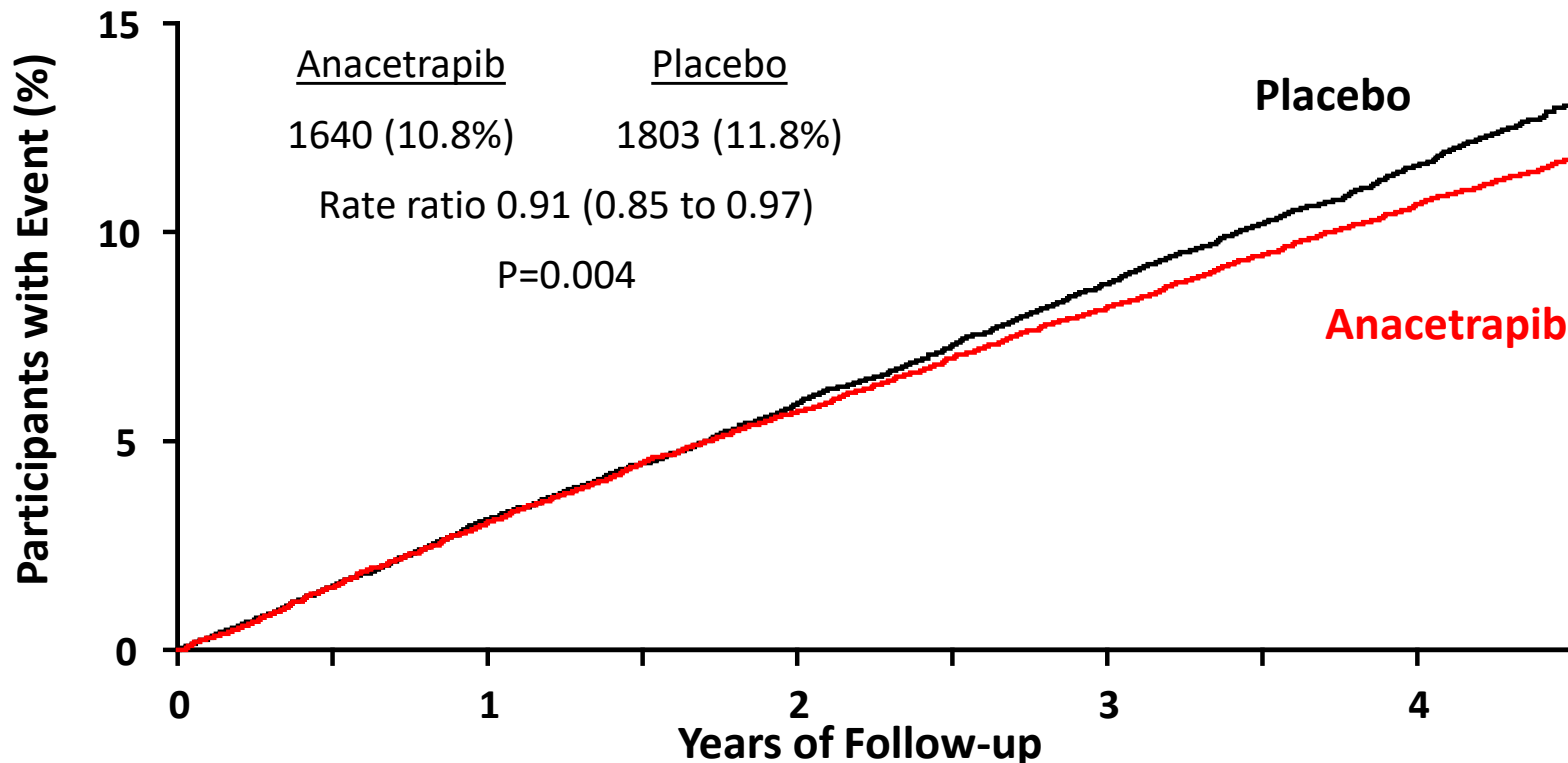
Effects of anacetrapib on lipids at trial midpoint

Measurement	Absolute difference		Proportional difference
	mg/dL	SI units	
HDL cholesterol	+43	+1.1 mmol/L	104%
Apolipoprotein AI	+42	+0.4 g/L	36%
LDL cholesterol			
- Direct (Genzyme)	-26	-0.7 mmol/L	-41%
- Beta-quantification*	-11	-0.3 mmol/L	-17%
Apolipoprotein B	-12	-0.1 g/L	-18%
Non-HDL cholesterol	-17	-0.4 mmol/L	-18%

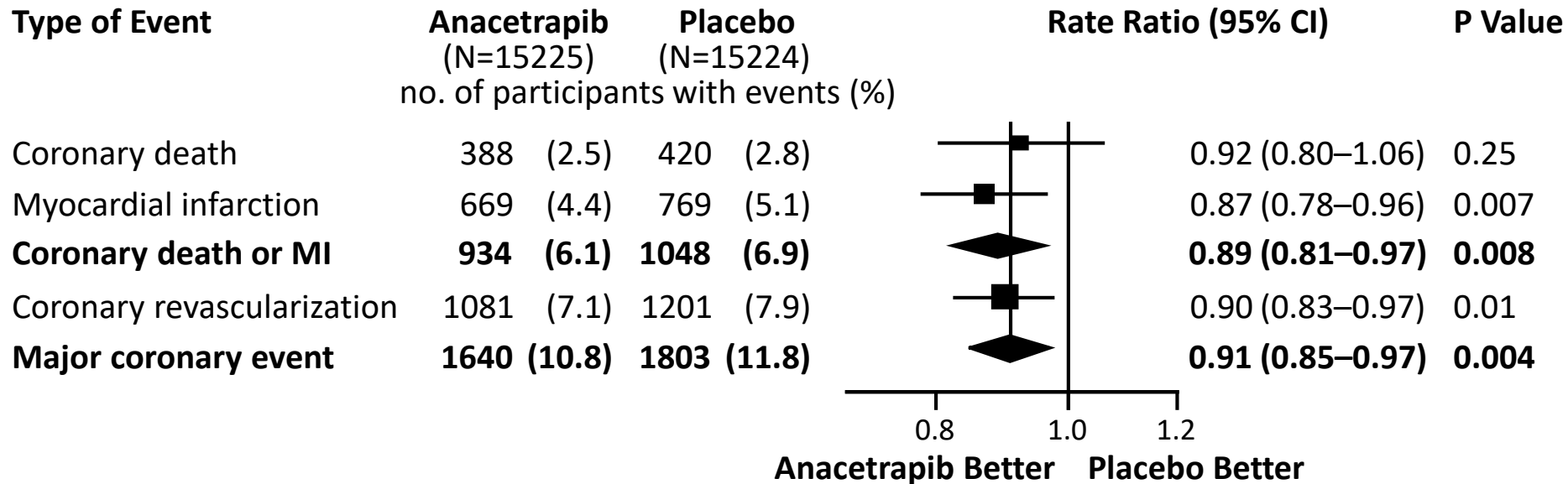
* measured in a random subset of 2000 participants

Primary outcome: Major coronary events

(Coronary death, myocardial infarction, or coronary revascularization)



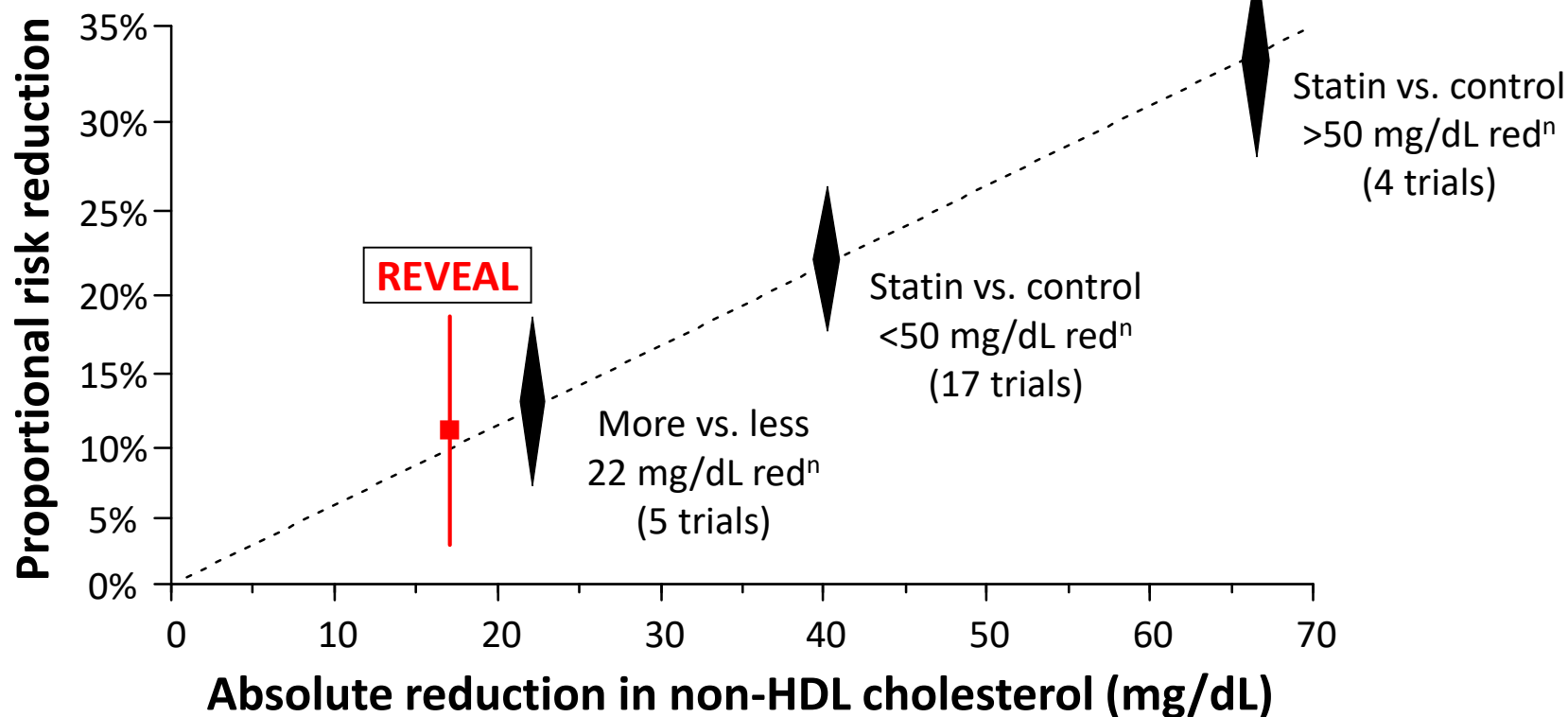
Components of the primary outcome



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)



Primary & secondary outcomes

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
Presumed ischaemic stroke	485 (3.2)	489 (3.2)	0.99 (0.87–1.12)	
Major atherosclerotic event	1383 (9.1)	1483 (9.7)	0.93 (0.86–1.00)	0.05
Major vascular event	2068 (13.6)	2214 (14.5)	0.93 (0.88–0.99)	0.02

Major coronary event: Coronary death, MI or coronary revascularization

Major atherosclerotic event: Coronary death, MI or presumed ischaemic stroke

Major vascular event: Coronary death, MI, coronary revascularization or presumed ischaemic stroke

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 adverse events

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



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Collaborative Group*

Available at www.nejm.org
together with supplementary methods, analyses,
and detailed tabulations of adverse events