

# REVEAL:

## 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

## Steering Committee

*Principal Investigators:* Martin Landray, Louise Bowman

*Chair & Deputy Chair:* Rory Collins, Eugene Braunwald

*Trial Statistician:* Jemma Hopewell

### *Regional representatives:*

*United Kingdom:* Jane Armitage, Richard Haynes

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*Scandinavia:* Terje Pedersen

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### *Other members:*

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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.**

# 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:**  $\geq 4$  years and  $\geq 1900$  primary outcomes

**Primary outcome:** Major Coronary Event

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

# Baseline demographics

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

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# Prior disease & blood lipids at randomization

(after 8-12 weeks' treatment with atorvastatin)

Characteristic		Total (30449)	
<b>Prior disease</b>	Coronary heart disease	26679	(88%)
	Cerebrovascular disease	6781	(22%)
	Peripheral arterial disease	2435	(8%)
	Diabetes mellitus	11320	(37%)
<b>Lipids</b>	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

<b>Follow-up</b>	Median duration	4.1 years	
	Complete	99.8%	
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		<b>Anacetrapib</b>	<b>Placebo</b>
<b>Adherence at midpoint</b>	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

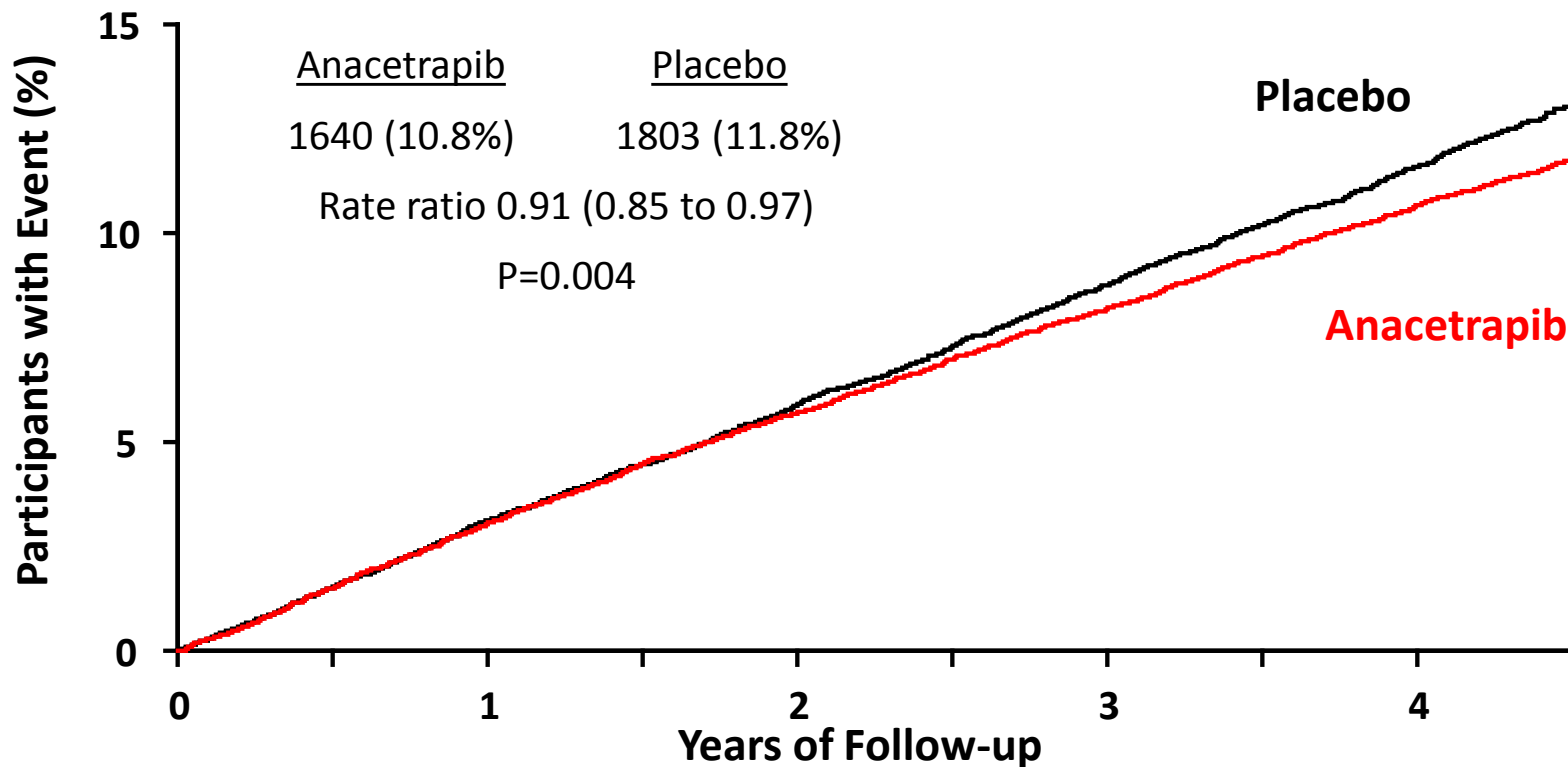
Measurement	Absolute difference		Proportional difference
	mg/dL	SI units	
HDL cholesterol	+43	+1.1 mmol/L	104%
Apolipoprotein AI	+42	+0.4 g/L	36%
LDL cholesterol			
- Direct (Genzyme)	-26	-0.7 mmol/L	-41%
- Beta-quantification*	-11	-0.3 mmol/L	-17%
Apolipoprotein B	-12	-0.1 g/L	-18%
Non-HDL cholesterol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

\* measured in a random subset of 2000 participants

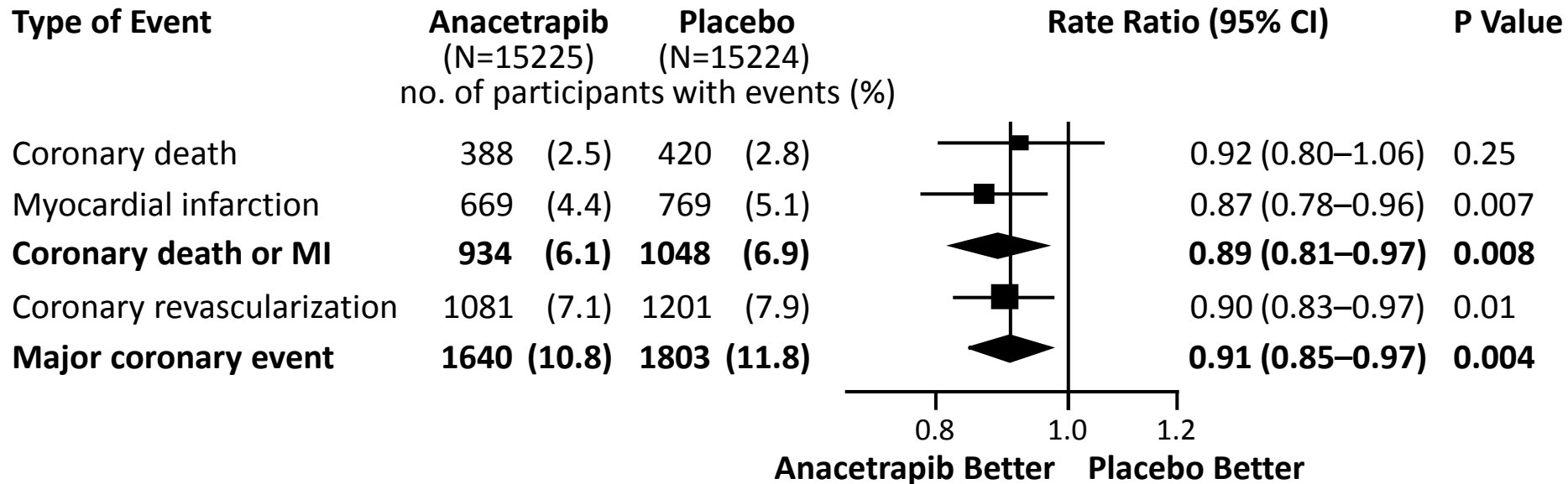


# Primary outcome: Major coronary events

(Coronary death, myocardial infarction, or coronary revascularization)



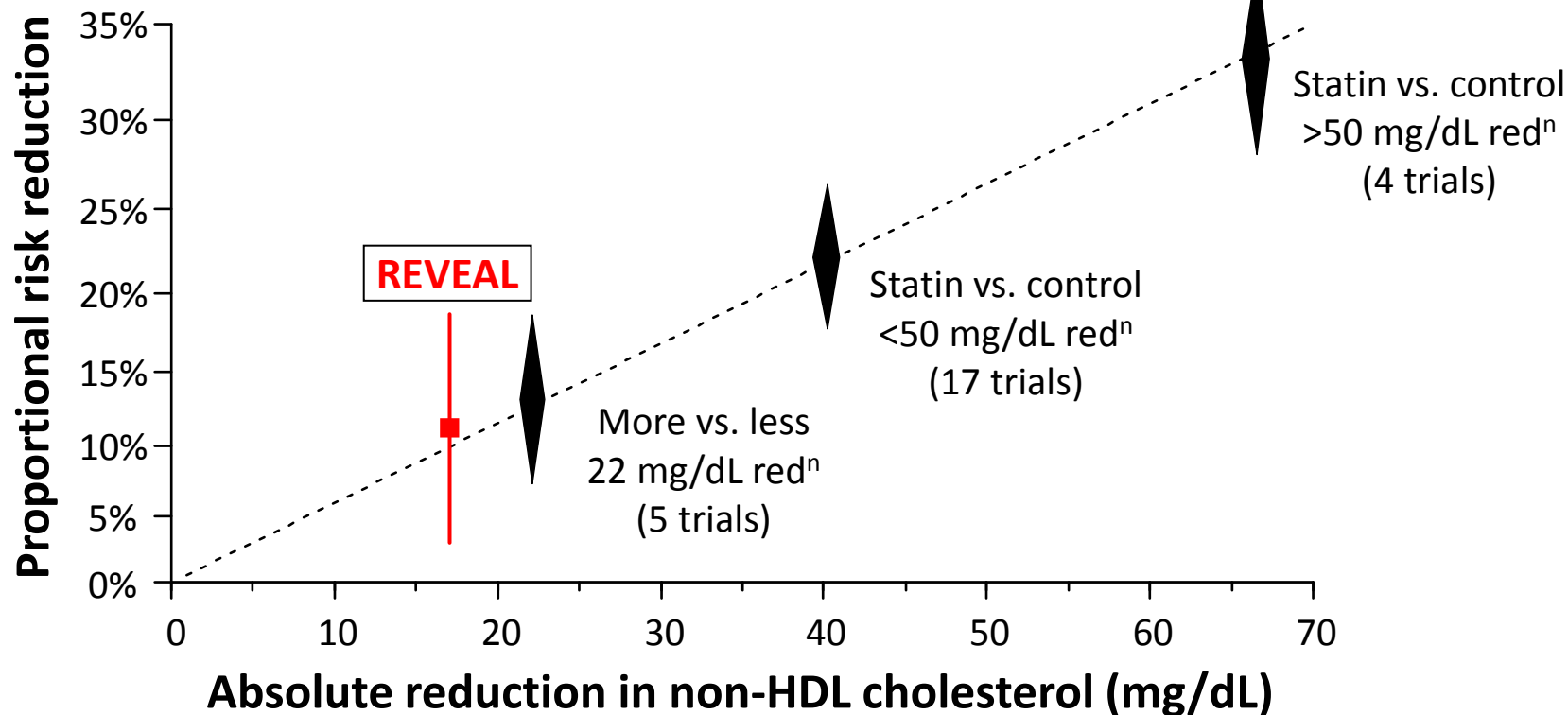
# Components of the primary outcome



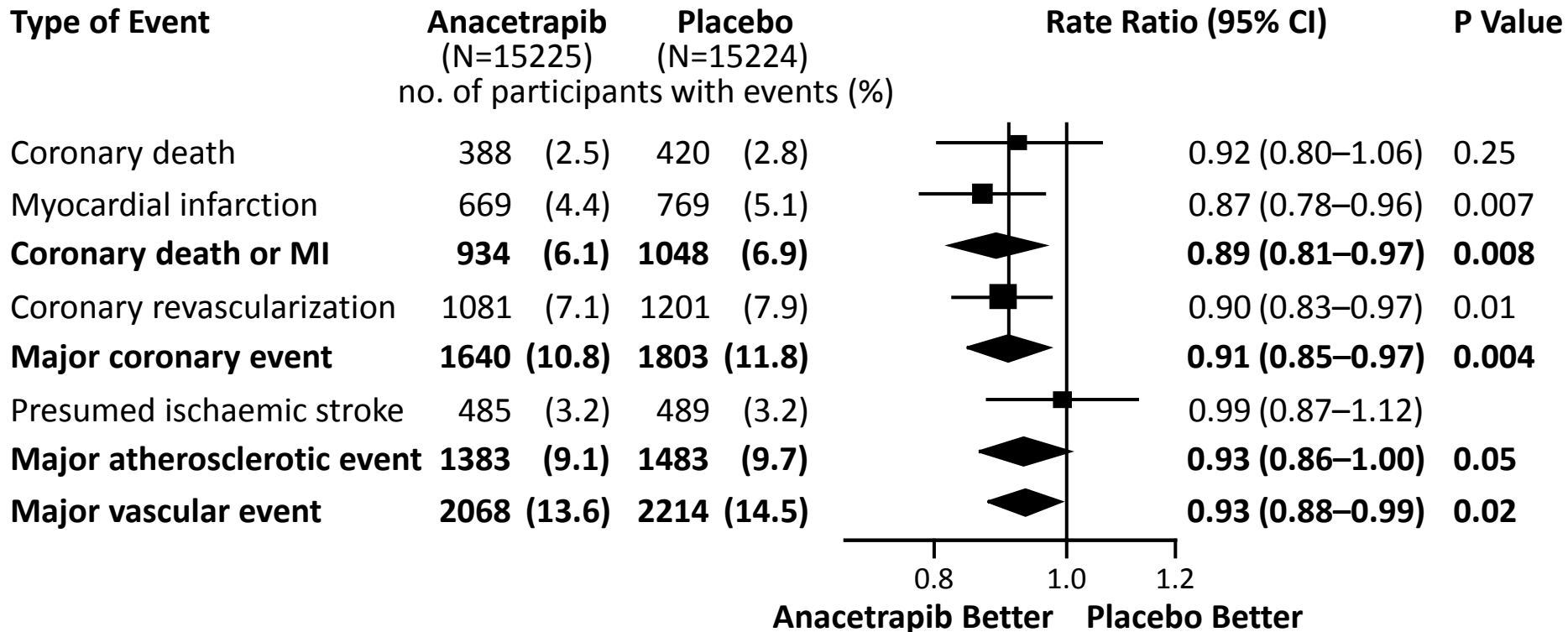
Major coronary event: Coronary death, MI or coronary revascularization

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



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
<b>New-onset diabetes mellitus</b>	510 (5.3%)	571 (6.0%)	-0.6%	0.05
<b>Blood pressure</b>				
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
<b>Kidney disease</b>				
New-onset eGFR <60 mL/min/1.73m <sup>2</sup>	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](http://www.nejm.org)  
together with supplementary methods, analyses,  
and detailed tabulations of adverse events