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

Declaration of interests

- Funding to support the REVEAL trial:
  - MSD (known as Merck in the USA and Canada)
  - British Heart Foundation
  - Medical Research Council
- Additional support for UK research sites in REVEAL:
  - National Institute for Health Research
- Other sources of research funding, not directly related to REVEAL:
  - Novartis, Pfizer, Medicines Company, Cancer Research UK
- Honoraria and consultancy fees:
  - The Clinical Trial Service Unit at the University of Oxford has a staff policy of not accepting honoraria or consultancy fees, either to staff or the institution, directly or indirectly from industry (see www.ctsu.ox.ac.uk)

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

N America: Christopher Cannon, Stephen Wiviott

Scandinavia: Terje Pedersen

China: Lixin Jiang

Italy: Aldo Maggioni

Germany: Georg Ertl, Christiane Angermann, Christoph Wanner

Other members:

Colin Baigent, Philip Barter, Yiping Chen, Zhengming Chen, Shinya Goto, Alastair Gray, Boby Mihaylova, Peter Sleight, Tamio Teramoto, Jonathan Tobert

Non-voting MSD representatives: Robert Blaustein, Paul DeLucca, Gerard van Leijenhorst, Yale Mitchel

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: ≥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

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%

		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

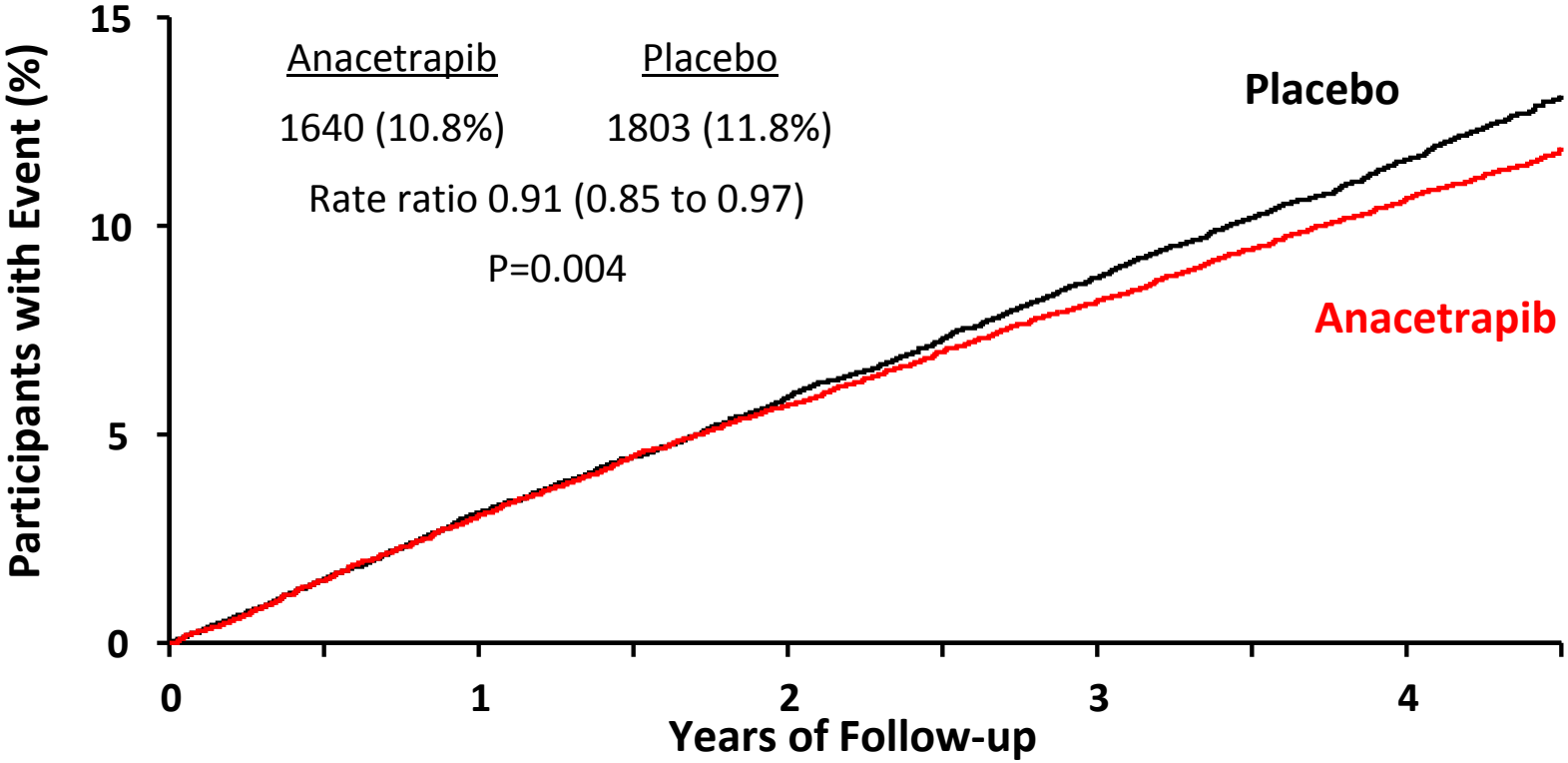
Effects of anacetrapib on lipids at trial midpoint

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

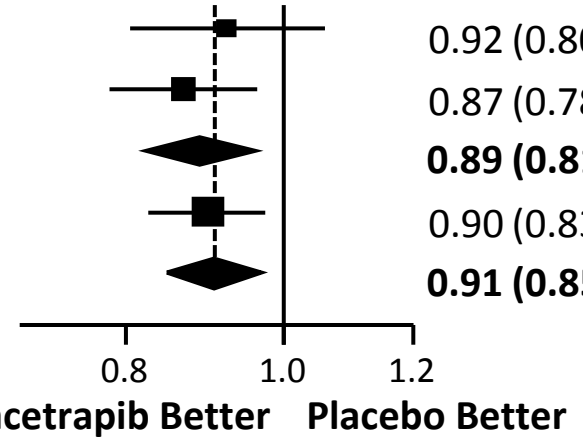
Primary outcome: Major coronary events

(Coronary death, myocardial infarction, or coronary revascularization)



Components of the primary outcome

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**

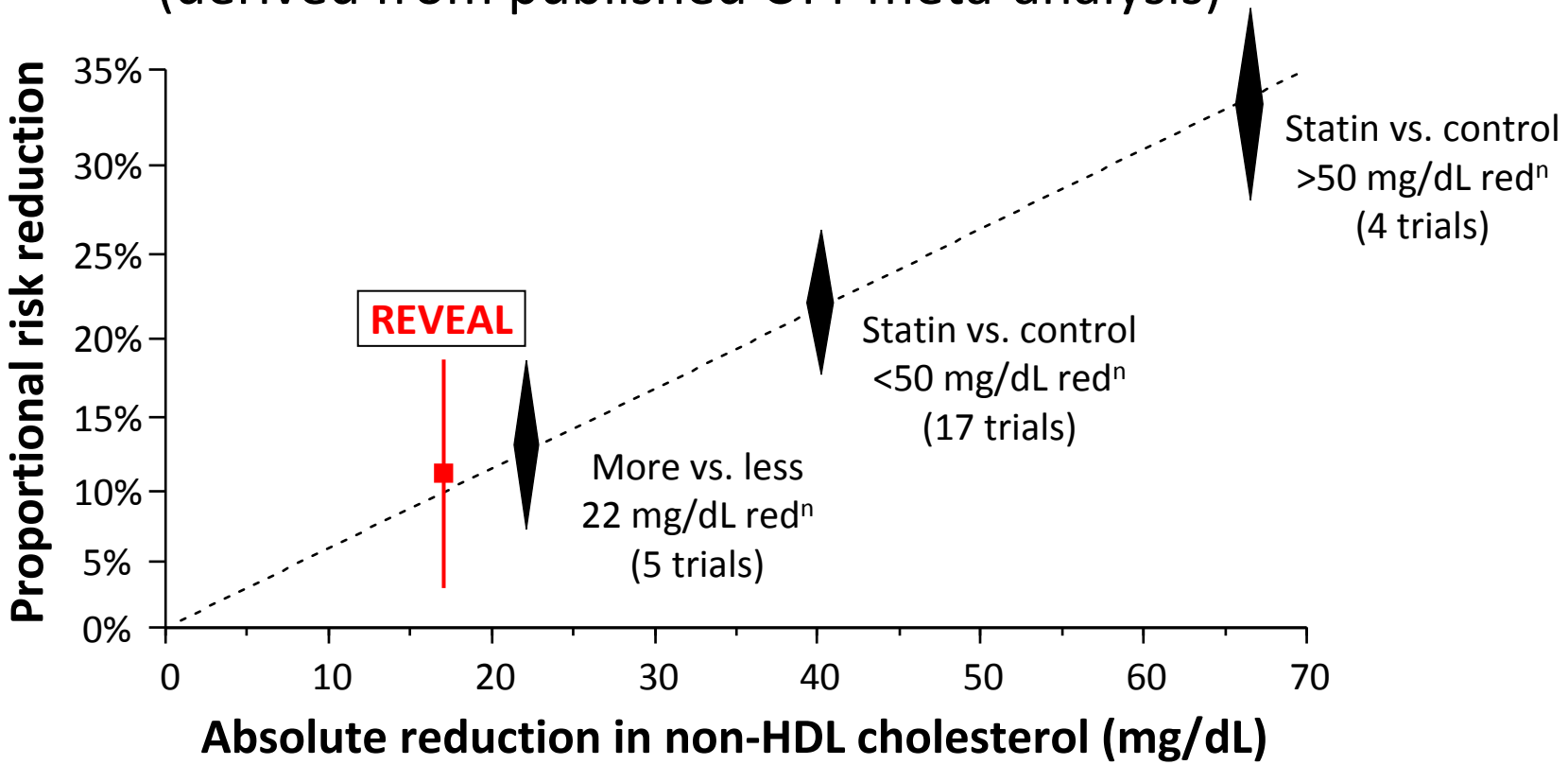


Major coronary event: Coronary death, MI or coronary revascularization

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)



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
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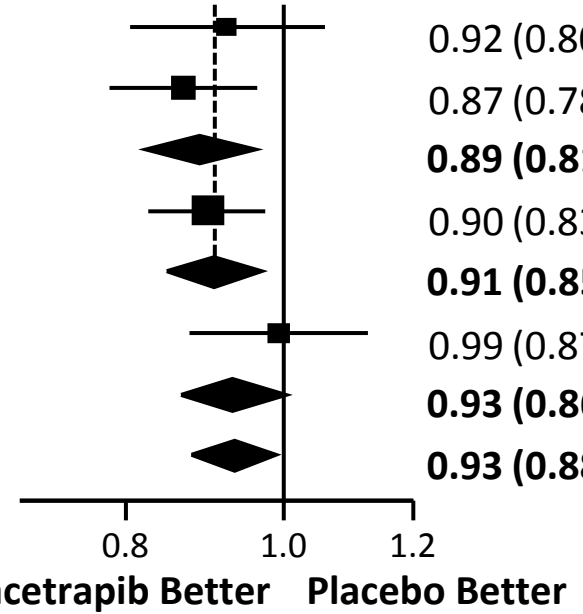
Coronary revascularization	1081	(7.1)	1201	(7.9)	0.90 (0.83–0.97)	0.01
Major coronary event	**1640**	**(10.8)**	**1803**	**(11.8)**	**0.91 (0.85–0.97)**	**0.004**
Presumed ischaemic stroke	485	(3.2)	489	(3.2)	0.99 (0.87–1.12)	
Major atherosclerotic event	**1383**	**(9.1)**	**1483**	**(9.7)**	**0.93 (0.86–1.00)**	**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