

# The effects of prolonged anacetrapib therapy on first and subsequent occlusive vascular events

Emily Sammons, Louise Bowman & Martin Landray  
on behalf of the HPS 3 / TIMI 55 - REVEAL Collaborative Group  
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# 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)

## **Main results presented ESC 2017:**

- Significant 9% proportional reduction in major coronary events (effect appears to be greater in later years of treatment)
- Benefit consistent with anticipated effect from observed reduction in non-HDL cholesterol (no evidence of significant impact of HDL-raising)



# Rationale for assessing impact on the combination of first and subsequent cardiovascular events

- Patients may suffer multiple cardiovascular events
- Every event is a burden to patients and to the healthcare system
- Time-to-first event analyses ignore effects on subsequent events and may underestimate the benefits of treatment
- Previous trials of statins have shown reductions in both first and subsequent cardiovascular events
- In secondary prevention trials (such as REVEAL) every patient has already had at least one event prior to enrolment

# Pre-specified analyses

- Time to first event:
  - major coronary event (coronary death, MI or coronary revascularization)
  - major atherosclerotic event (coronary death, MI, or ischaemic stroke)
  - major vascular event (coronary death, MI, coronary revascularization or ischaemic stroke)
- Analysis of all events:
  - combination of first and subsequent events
  - events considered to be separate if they occurred on different days
  - assessed using the negative binomial method

## Baseline characteristics

Characteristic		Participants (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%)
<b>Prior disease</b>	Coronary heart disease	26679 (88%)
	Cerebrovascular disease	6781 (22%)
	Diabetes mellitus	11320 (37%)

## Effect of anacetrapib on lipids at study midpoint

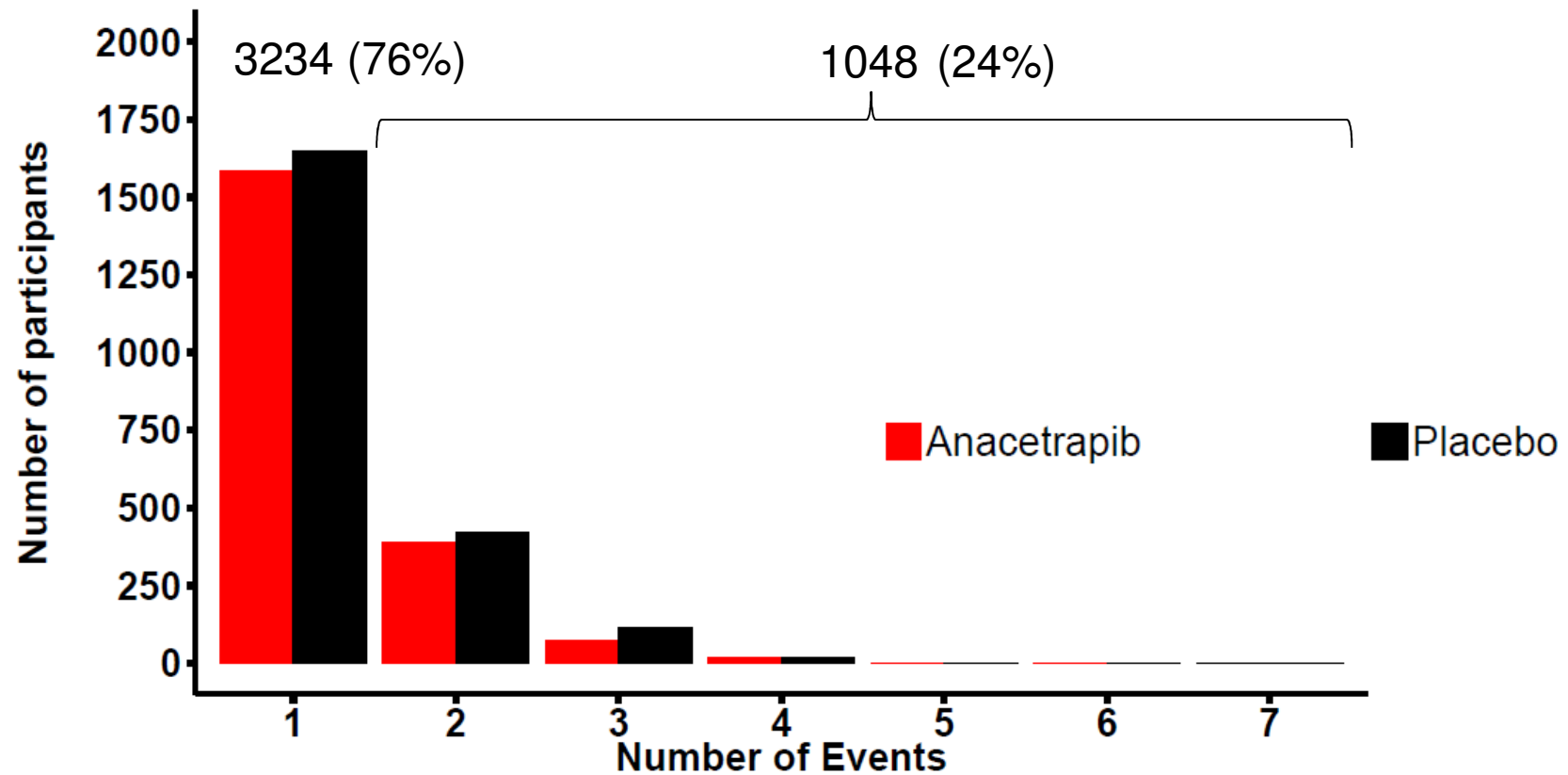
	<b>Baseline</b>	<b>Absolute difference</b>	<b>Proportional difference</b>
HDL cholesterol	40 mg/dL (1.0 mmol/L)	+43 mg/dl (+1.1 mmol/l)	+104%
LDL cholesterol*	61 mg/dL (1.6 mmol/L)	- 11 mg/dl (-0.3 mmol/l)	-17%
Non-HDL cholesterol	(92 mg/dL) (2.4 mmol/L)	-17 mg/dl (-0.4 mmol/l)	-18%

\*Measured by beta-quantification in a random sample of 2000 participants

## Follow-up and adherence to treatment

<b>Follow-up</b>	Median duration	4.1 years	
	Complete	99.8%	
		<b>Anacetrapib</b>	<b>Placebo</b>
<b>Randomized treatment</b>	2 months	96.5%	96.2%
	Midpoint	89.9%	89.7%
	4 years	84.9%	84.7%
<b>Statin</b>	2 months	97.2%	96.9%
	Midpoint	94.6%	94.7%
	4 years	92.3%	92.6%

# Number of participants with major vascular events





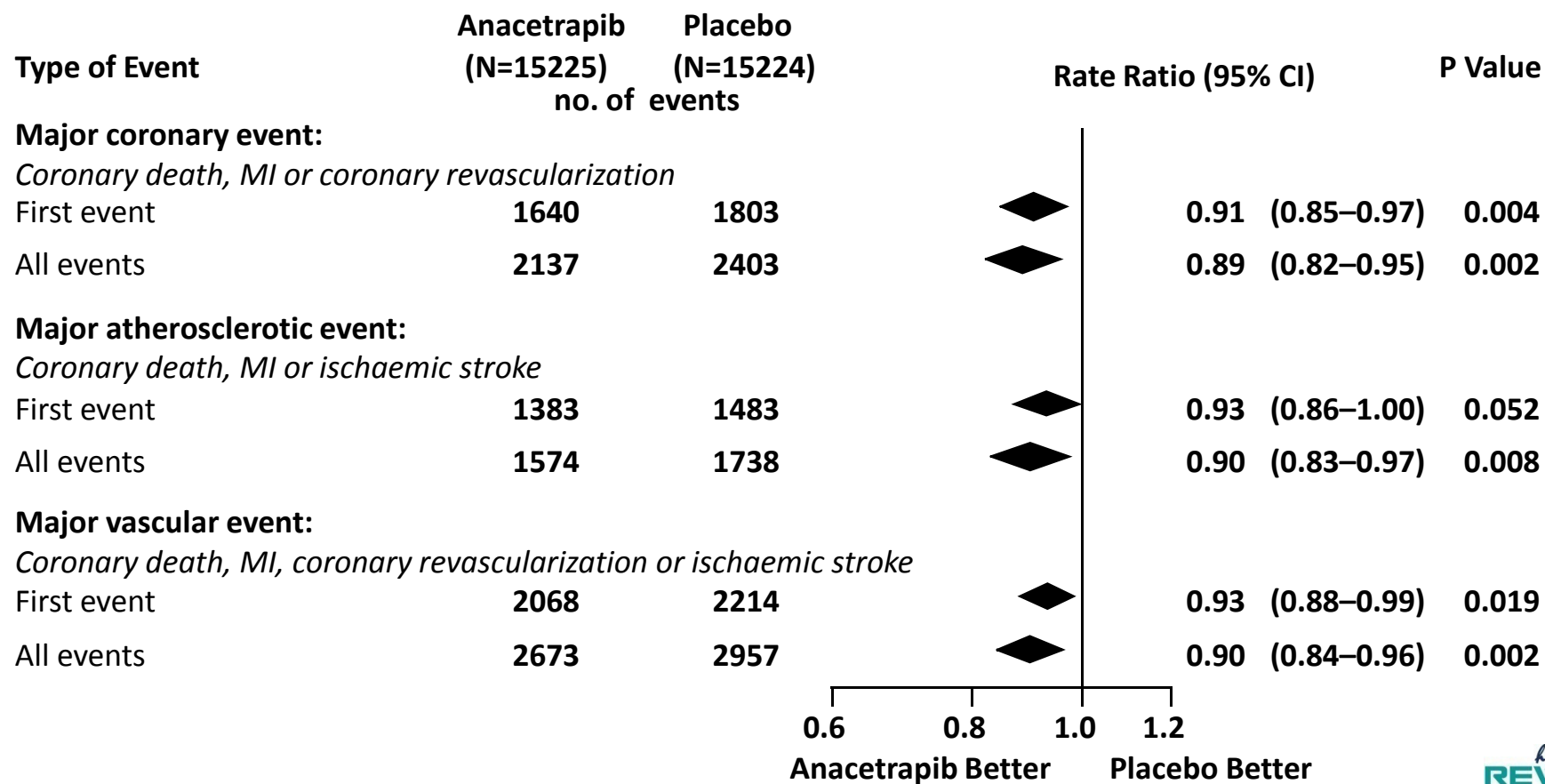
## Distribution of subsequent major vascular events

First Event		Subsequent event			
		Myocardial infarction	Coronary revascularization	Ischaemic stroke	Coronary death
Myocardial infarction	<b>1320</b>	126	423	34	82
Coronary revascularization	<b>1559</b>	87	216	28	35
Ischaemic stroke	<b>906</b>	31	25	99	16
Coronary death	<b>497</b>	0	0	0	0
Any	<b>4282</b>	244	664	161	133

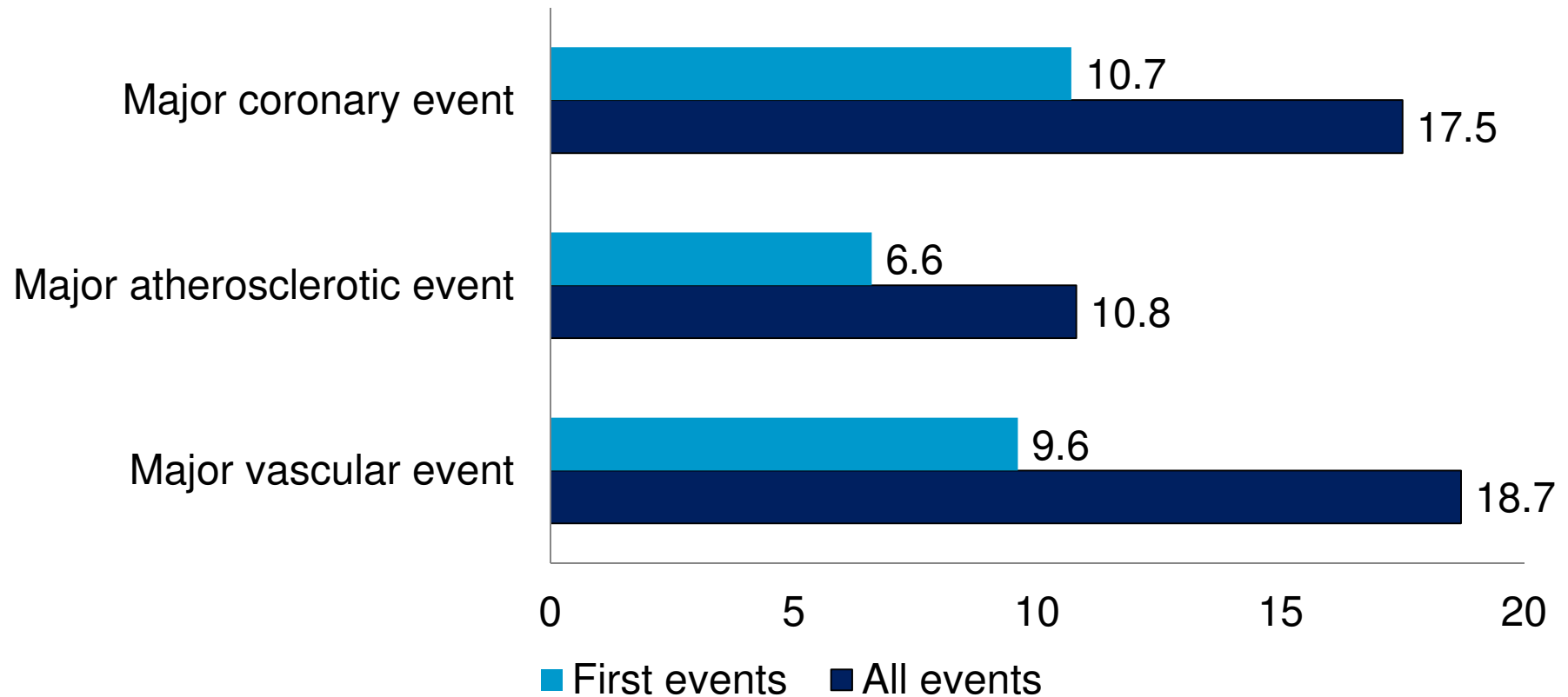
Mean time to first event: 2.0 years post randomization

Mean time to second event: 2.3 years post randomization

# Effect of anacetrapib on cardiovascular events



## Absolute benefits of anacetrapib: Events avoided per 1000 patients treated for 4 years



## Summary

- Among this well treated population (baseline LDL cholesterol 61 mg/dL), further lowering LDL cholesterol reduced the risk of cardiovascular events
- Around one quarter of patients who had a cardiovascular event went on to have at least one further event
- There were similar proportional reductions in first events and in all (first + subsequent) events
- Consequently, the absolute benefits of treatment are greater when all events are taken into account
- Post-trial follow-up of all consenting participants (off-drug) is ongoing to assess longer-term effects of treatment