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SCIENTIFIC SESSIONS 2017

Effects of Anacetrapib on the Incidence of New-Onset Diabetes Mellitus and on Vascular Events in People With Diabetes

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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: ≥4 years and ≥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-C (no evidence of significant impact of HDL-raising)

HPS 3/TIMI 55-REVEAL Collaborative Group. NEJM 2017 and Am Heart J 2017

Why assess the effects of anacetrapib in diabetes?

- Global burden of diabetes
  - 4-500 million people worldwide
- Burden of CVD in diabetes
  - Risk of vascular death: ↑ x 2
- “Diabetic dyslipidaemia”
  - Low HDL, raised triglycerides

Baseline characteristics

Characteristic		Diabetes (11320)	No diabetes (19129)
Age (years)	Mean	67	66
Gender	Male	9096 (80%)	16438 (86%)
	Female	2224 (20%)	2691 (14%)
Region	Europe	4678 (41%)	11060 (58%)
	North America	2682 (24%)	3400 (18%)
	China	3960 (35%)	4669 (24%)
Prior disease	Coronary heart disease	10375 (92%)	16304 (85%)
	Cerebrovascular disease	2401 (21%)	4380 (23%)

Baseline lipids

Lipid measurement (non-fasting samples)	Diabetes (11320)	No diabetes (19129)
LDL cholesterol	59 mg/dL (1.5 mmol/l)	62 mg/dL (1.6 mmol/l)
HDL cholesterol	38 mg/dL (1.0 mmol/l)	41 mg/dL (1.1 mmol/l)
Non-HDL cholesterol	91 mg/dL (2.3 mmol/l)	92 mg/dL (2.4 mmol/l)
Triglycerides	137 mg/dL (1.5 mmol/l)	117 mg/dL (1.3 mmol/l)

Follow-up and adherence to treatment

		Diabetes	No diabetes
Follow-up	Median duration	4.2 years	4.1 years
	Complete	99.7%	99.8%

		Anacetrapib	Placebo	Anacetrapib	Placebo
Adherence at midpoint	Randomized treatment*	89.9%	89.5%	89.9%	89.9%
	Study atorvastatin	90.4%	89.6%	90.2%	89.8%
	Any statin	94.3%	94.1%	94.9%	95.1%

* No difference in any reason for stopping allocated treatment

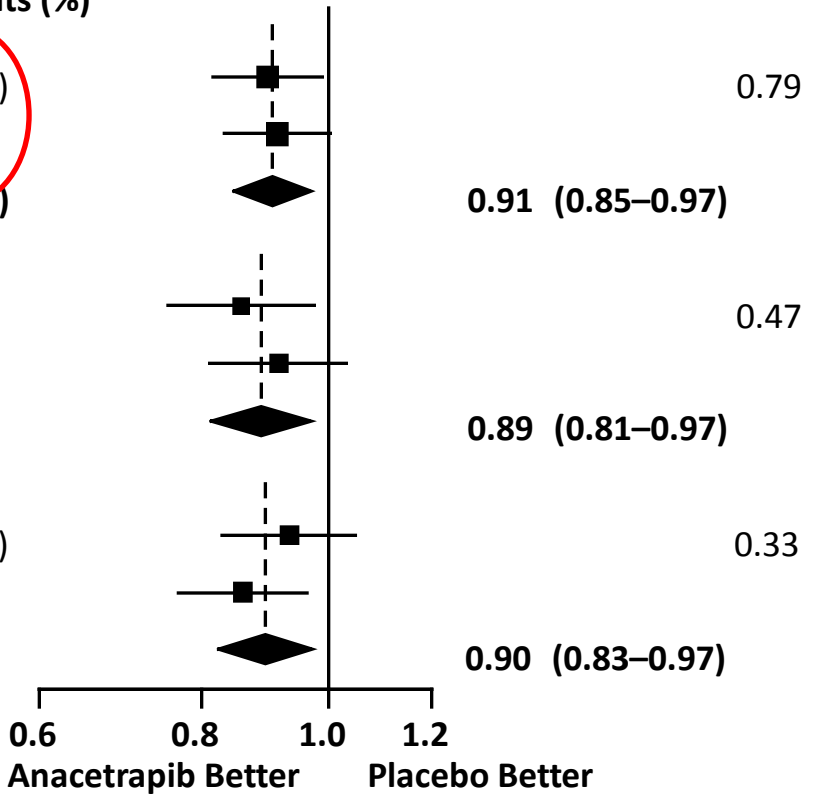
Effects of anacetrapib on lipids at trial midpoint

Measurement	Diabetes			No diabetes		
	Absolute difference		Proportional difference	Absolute difference		Proportional difference
	mg/dL	SI units		mg/dL	SI units	
HDL cholesterol	+41	+1.1 mmol/L	104%	+45	+1.2 mmol/L	103%
Apolipoprotein AI	+42	+0.4 g/L	36%	+43	+0.4 g/L	36%
LDL cholesterol						
- Direct (Genzyme)	-26	-0.7 mmol/L	-42%	-27	-0.7 mmol/L	-41%
- Beta-quantification*	-12	-0.3 mmol/L	-20%	-10	-0.2 mmol/L	-15%
Apolipoprotein B	-12	-0.1 g/L	-19%	-12	-0.1 g/L	-17%
Non-HDL cholesterol	-19	-0.5 mmol/L	-20%	-16	-0.4 mmol/L	-17%

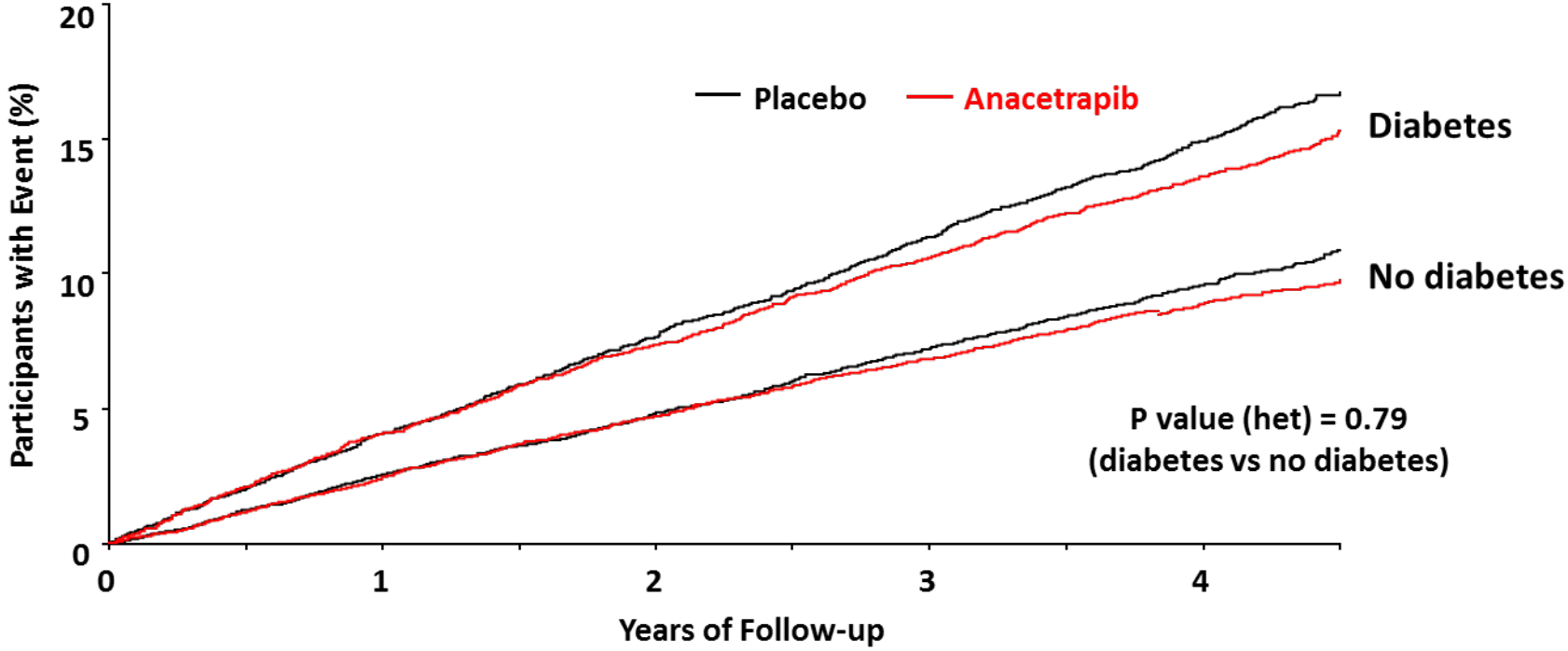
* measured in a random subset of 2000 participants

Primary outcome: Major coronary events

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 (het)
Major coronary event						
Diabetes	787	(13.9)	874	(15.4)		0.79
No diabetes	853	(8.9)	929	(9.7)		
Subtotal: MCE	**1640**	**(10.8)**	**1803**	**(11.8)**	**0.91 (0.85–0.97)**	
Coronary death or MI						
Diabetes	425	(7.5)	494	(8.7)		0.47
No diabetes	509	(5.3)	554	(5.8)		
Subtotal: Coronary death or MI	**934**	**(6.1)**	**1048**	**(6.9)**	**0.89 (0.81–0.97)**	
Coronary revascularization						
Diabetes	532	(9.4)	568	(10.0)		0.33
No diabetes	549	(5.7)	633	(6.6)		
Subtotal: Coronary revascularization	**1081**	**(7.1)**	**1201**	**(7.9)**	**0.90 (0.83–0.97)**	



Major coronary events
with and without diabetes



Benefit per 1000 participants in anacetrapib group					
	DM	0±4	3±5	8±6	13±7
	No DM	1±2	1±3	4±4	7±4

Why assess the effects of anacetrapib on diabetes?

Statins:

- Common SNPs in the HMGCR gene associated with ↑ risk of type 2 diabetes
- Modest ↑ in risk of type 2 diabetes observed with statins

PCSK9 inhibition:

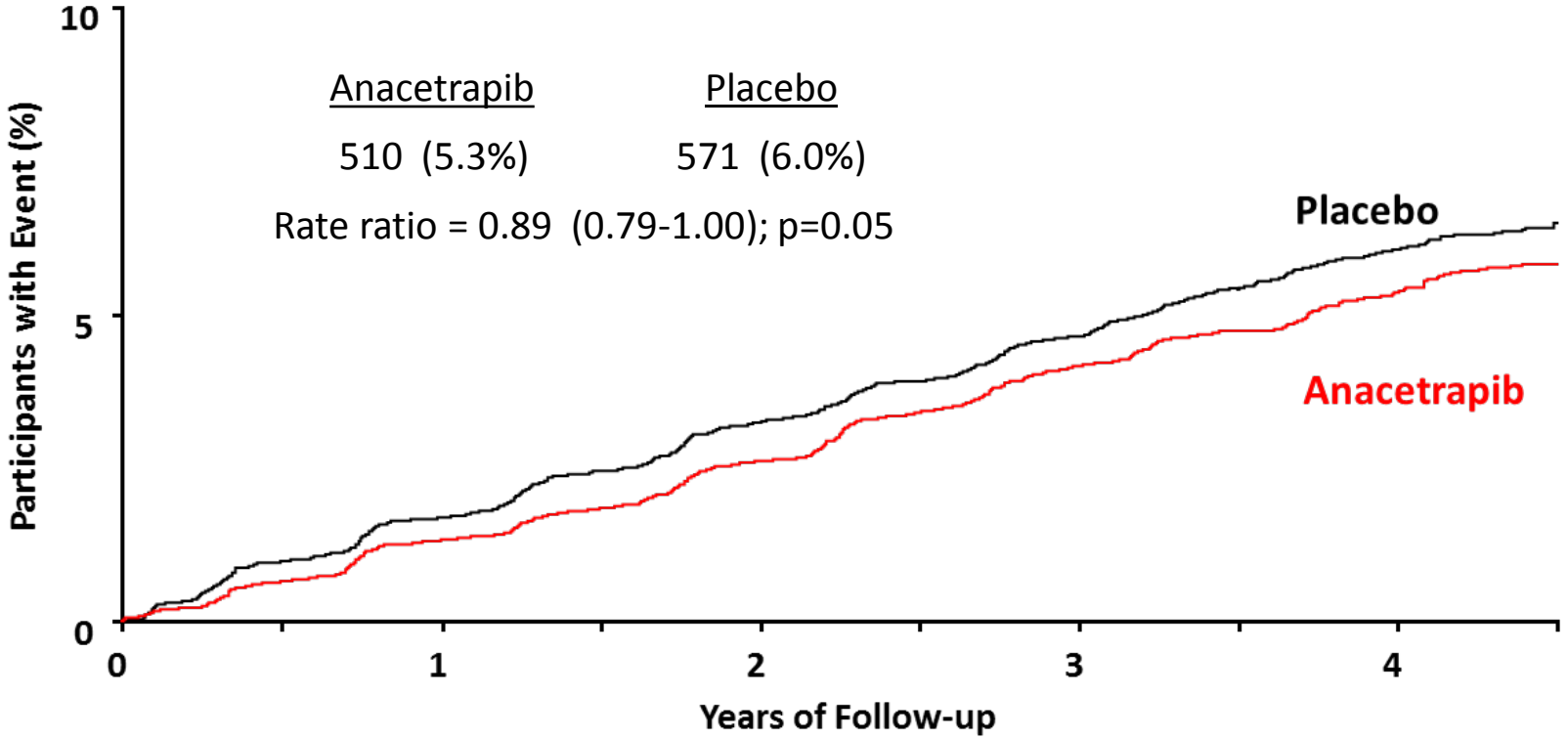
- Variants in genes encoding PCSK9 associated with ↑ risk of diabetes
- In FOURIER, evolocumab did not ↑ risk of new-onset diabetes (HR 1·05, 95% CI 0·94–1·17)

CETP inhibition:

- Torcetrapib associated with ↓ plasma glucose & insulin levels in ILLUMINATE
- Evacetrapib associated with ↓ risk of new-onset diabetes in ACCELERATE

Diagnosis of new-onset diabetes

(Diabetes-related adverse event or use of hypoglycaemic medication)



Effects of anacetrapib on glycated haemoglobin (at final visit)

Diabetes at baseline	HbA1c assay*	Anacetrapib Mean (SE)	Placebo Mean (SE)	Absolute difference Mean (SE)	P value
No prior diabetes	DCCT (%)	5.50 (0.01)	5.53 (0.01)	-0.03 (0.01)	<0.001
	IFFC (mmol/mol)	36.62 (0.07)	36.95 (0.07)	-0.33 (0.10)	
Prior diabetes	DCCT (%)	6.86 (0.02)	6.86 (0.02)	-0.00 (0.03)	0.92
	IFFC (mmol/mol)	51.45 (0.20)	51.48 (0.20)	-0.03 (0.28)	
Overall	DCCT (%)	5.99 (0.01)	6.01 (0.01)	-0.02 (0.01)	0.12
	IFFC (mmol/mol)	41.96 (0.11)	42.19 (0.11)	-0.23 (0.15)	

*DCCT: Diabetes Control and Complications Trial method

IFFC: International Federation of Clinical Chemistry and Laboratory Medicine method

Summary

- In REVEAL, individuals with diabetes were at higher absolute risk of major coronary events
- Anacetrapib lowered non-HDL cholesterol and reduced major coronary events with similar efficacy in patients with and without diabetes
- Patients with diabetes had a numerically greater absolute risk reduction with anacetrapib treatment
- A small reduction in risk of new-onset diabetes mellitus was observed
- Post-trial follow-up of all consenting participants (off-drug) to assess longer-term efficacy and safety of anacetrapib is ongoing