Impact of *ADCY9* on Response to Anacetrapib Among 20,000 Participants in the HPS3/TIMI55-REVEAL Trial

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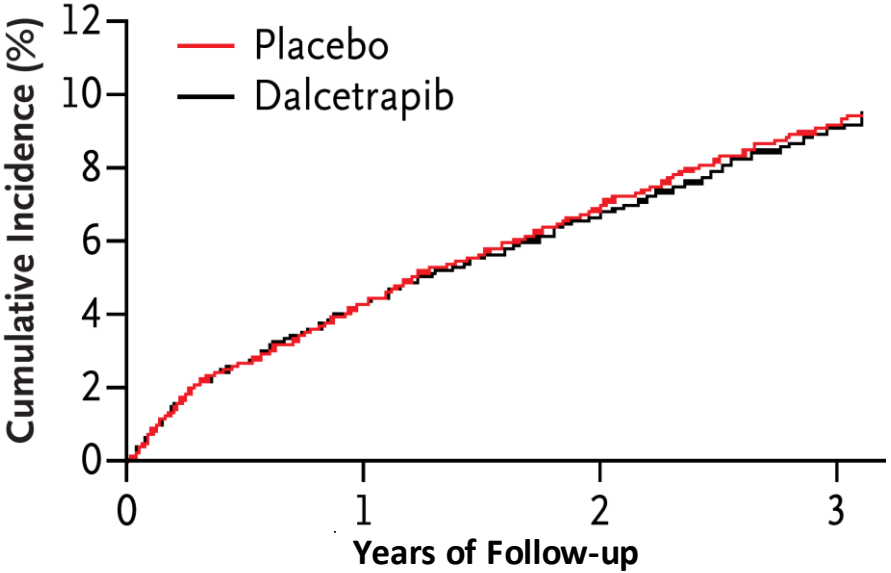
on behalf of the REVEAL Collaborative Group

Disclosures

- The REVEAL trial and genetic sub-study was supported by Merck & Co., Inc.
- JCH receives no personal payments from industry
- JCH is funded by the British Heart Foundation

Background: Dal-OUTCOMES pharmacogenetic study



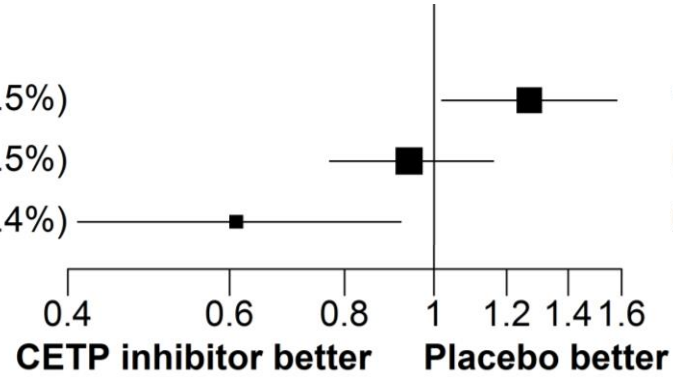
Randomized 15,871 participants with acute coronary syndrome

Stopped early for futility, and showed no impact of dalcetrapib on cardiovascular outcomes

Schwartz et al, NEJM, 2012

Background: Dal-OUTCOMES pharmacogenetic study

Trial (CETP inhibitor) rs1967309 genotype	CETP inhibitor allocated	Placebo allocated	Hazard ratio (95% CI)
Dal-OUTCOMES (dalcetrapib)			
GG	176/ 978 (18.0%)	146/1006 (14.5%)	1.27 (1.02-1.58)
AG	176/1379 (12.8%)	192/1417 (13.5%)	0.94 (0.77-1.16)
AA	38/ 485 (7.8%)	59/ 476 (12.4%)	0.61 (0.41-0.92)



Dal-OUTCOMES: treatment x genotype interaction: p=0.001 (additive), p=0.006 (genotypic)

Tardif et al, Circ CV Gen, 2015

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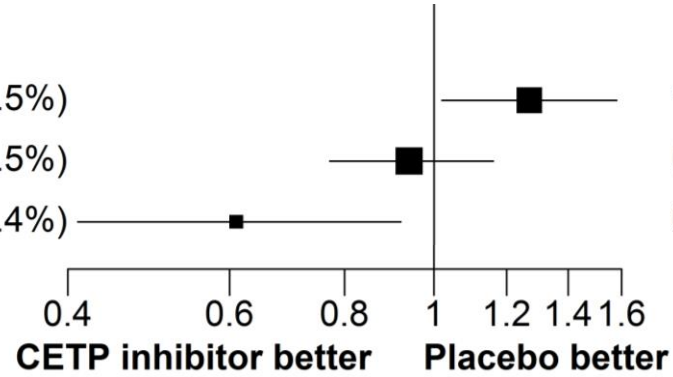


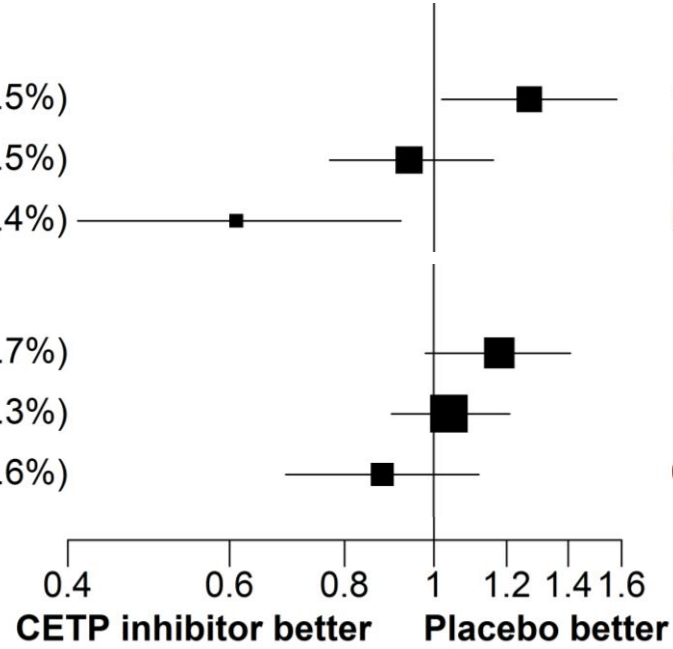
Dal-OUTCOMES: treatment x genotype interaction: p=0.001 (additive), p=0.006 (genotypic)

The ongoing Dal-genE trial is examining the effects of dalcetrapib in 6150 patients with acute coronary syndrome and the AA genotype

Tardif et al, Circ CV Gen, 2015

Background: ACCELERATE pharmacogenetic study

Trial (CETP inhibitor) rs1967309 genotype	CETP inhibitor allocated	Placebo allocated	Hazard ratio (95% CI)
Dal-OUTCOMES (dalcetrapib)			
GG	176/ 978 (18.0%)	146/1006 (14.5%)	1.27 (1.02-1.58)
AG	176/1379 (12.8%)	192/1417 (13.5%)	0.94 (0.77-1.16)
AA	38/ 485 (7.8%)	59/ 476 (12.4%)	0.61 (0.41-0.92)
ACCELERATE (evacetrapib)			
GG	245/ 499 (49.1%)	212/ 474 (44.7%)	1.18 (0.98-1.41)
AG	349/ 728 (47.9%)	353/ 731 (48.3%)	1.04 (0.90-1.21)
AA	125/ 255 (49.0%)	143/ 272 (52.6%)	0.88 (0.69-1.12)



ACCELERATE: treatment x genotype interaction: p=0.06 (additive), p=0.17(genotypic)

Nissen et al, JAMA Cards 2018

Biological support for an *ADCY9* x CETP interaction

- *ADCY9* encodes adenylyl cyclase type 9. Adenylate cyclase is an enzyme that catalyses the formation of cyclic AMP from ATP
- *ADCY9* genotype dependent treatment effects on plaque regression, C-reactive protein and cholesterol efflux
- Experimental data suggest that, in the absence of CETP activity, *ADCY9* inactivation protects against atherosclerosis

Tardif et al, Circ CV Gen, 2015; Tardif et al, ATVB, 2017; Rautureau et al, Circ, 2018

ADCY9 pharmacogenetic study characteristics

	Dal-OUTCOMES	ACCELERATE
a) Main study characteristics		
CETP inhibitor	Dalcetrapib	Evacetrapib
Inclusion criteria	Acute coronary syndrome (ACS)	ACS or stable cardiovascular disease
Study duration	~2 years	~2 years
Effect on HDL-C	~30%	~130%
Effect on LDL-C	~0%	~40%
Effect on apoB	~0%	~20%
b) *ADCY9* pharmacogenetic study		
Major vascular events	787	1427

ADCY9 pharmacogenetic study characteristics

	Dal-OUTCOMES	ACCELERATE	REVEAL
a) Main study characteristics			
CETP inhibitor	Dalcetrapib	Evacetrapib	Anacetrapib
Inclusion criteria	Acute coronary syndrome (ACS)	ACS or stable cardiovascular disease	Stable cardiovascular disease
Study duration	~2 years	~2 years	~4 years
Effect on HDL-C	~30%	~130%	~100%
Effect on LDL-C	~0%	~40%	~40%
Effect on apoB	~0%	~20%	~20%
b) *ADCY9* pharmacogenetic study			
Major vascular events	787	1427	2504

REVEAL pharmacogenetic sub-study

Genotyping: 19,245 individuals of European ancestry successfully genotyped and passed quality control. *ADCY9* rs1967309 genotypes available in 19,210 individuals (99.8%)

Outcome: Major vascular events (MVE) i.e. coronary death, myocardial infarction, coronary revascularization, or presumed ischaemic stroke

Statistical analyses: Cox proportional hazards models, adjusted for 5 principal components of ancestry, used to conduct intention-to-treat analyses and assess treatment-by-genotype interactions

REVEAL: *ADCY9* study characteristics

- The rs1967309 A allele frequency was 39.8%, and genotypes did not deviate from Hardy-Weinberg equilibrium (p=0.93)

- Among 19,210 genotyped participants, there were 2504 (13%) clinically adjudicated major vascular events

- No meaningful differences in characteristics between genotypes

  86% male, mean age 68 years

  87% stable coronary heart disease, 33% diabetic

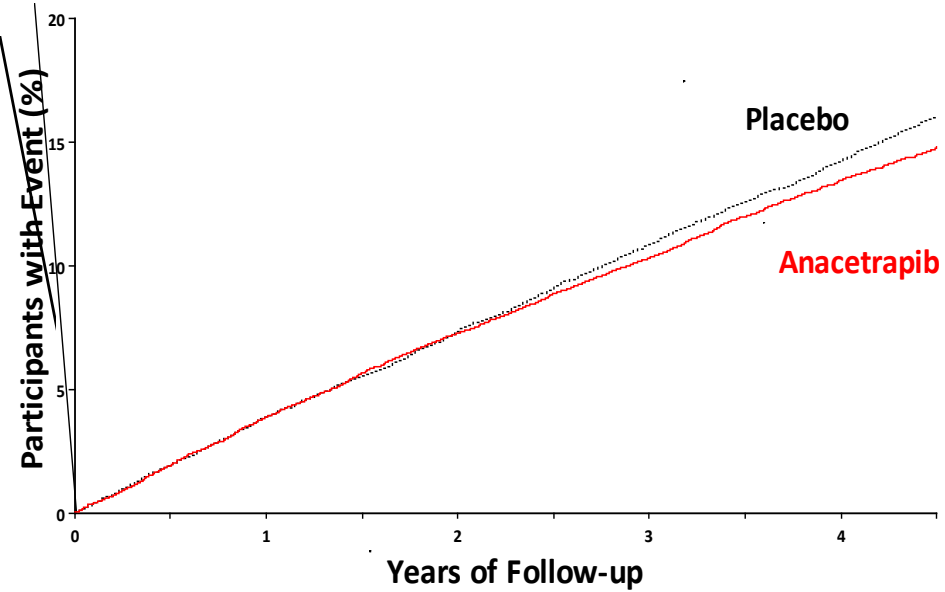
  LDL-C 62 mg/dl, with 51% on high dose study atorvastatin

REVEAL: Effect of anacetrapib on lipids, by *ADCY9*

At study mid-point, there were no meaningful differences between genotypes in the effects of anacetrapib on non HDL-cholesterol, or on HDL-cholesterol levels

Genotype	Difference (mg/dl) in	
	Non HDL-C	HDL-C
GG	-16.8	43.3
AG	-17.3	43.0
AA	-19.0	43.7
Overall	-17.4	43.2

REVEAL: Effects of anacetrapib on MVE



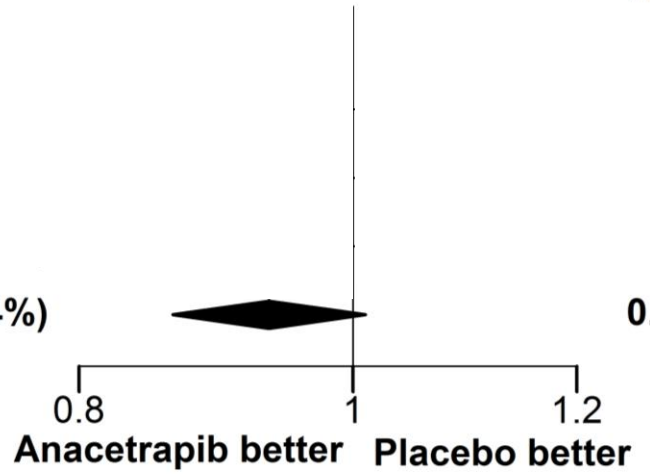
Randomized 30,449 participants with stable cardiovascular disease

7% risk reduction in MVE (p=0.019)

HPS3/TIMI55-REVEAL Collaborative Group, NEJM, 2017

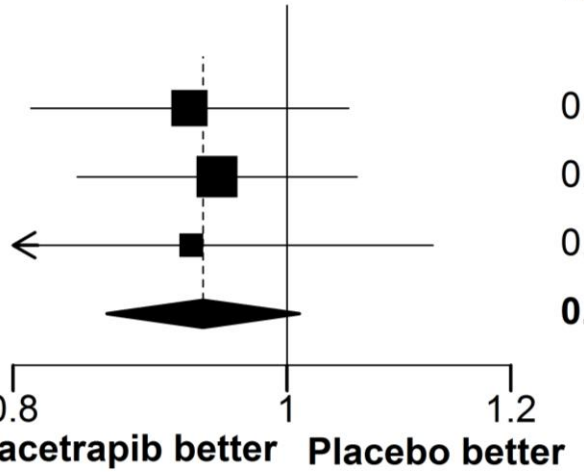
REVEAL: Effect of anacetrapib on MVE, by *ADCY9*

ADCY9 rs1967309 genotype	Anacetrapib-allocated	Placebo-allocated	Hazard ratio (95% CI)
All participants	1216/9633 (12.6%)	1288/9577 (13.4%)	0.93 (0.86-1.01)



REVEAL: Effect of anacetrapib on MVE, by *ADCY9*

***ADCY9* rs1967309 genotype**	**Anacetrapib-allocated**	**Placebo-allocated**	**Hazard ratio (95% CI)**
GG	451/3553 (12.7%)	468/3421 (13.7%)	0.92 (0.81-1.05)
AG	572/4560 (12.5%)	615/4636 (13.3%)	0.94 (0.84-1.06)
AA	193/1520 (12.7%)	205/1520 (13.5%)	0.93 (0.76-1.13)
All participants	**1216/9633 (12.6%)**	**1288/9577 (13.4%)**	**0.93 (0.86-1.01)**



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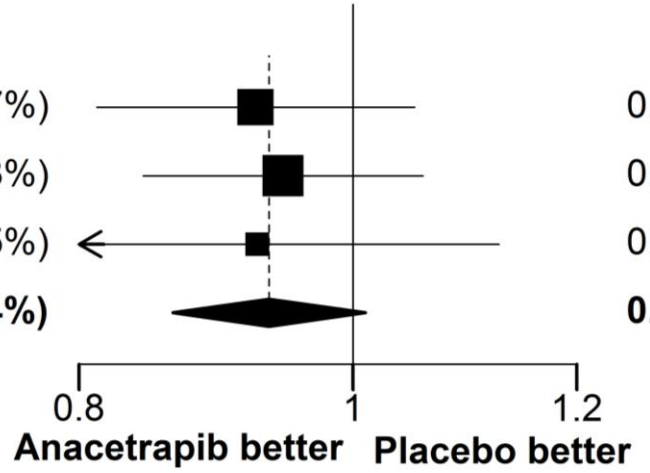

Similarly, there were no treatment x genotype interactions for separate components of major vascular events (i.e. coronary death, myocardial infarction, coronary revascularization, or presumed ischaemic stroke)

Conclusions

- REVEAL provides no evidence to support a material effect of *ADCY9* on response to anacetrapib, and rules out >25% risk reduction in rs1967039 AA carriers

- Further studies will assess whether any other genetic variants can identify individuals who obtain particular benefit from anacetrapib

- The Dal-genE trial will provide a specific test of the effects of dalcetrapib among people with the rs1967309 AA genotype