Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Trial

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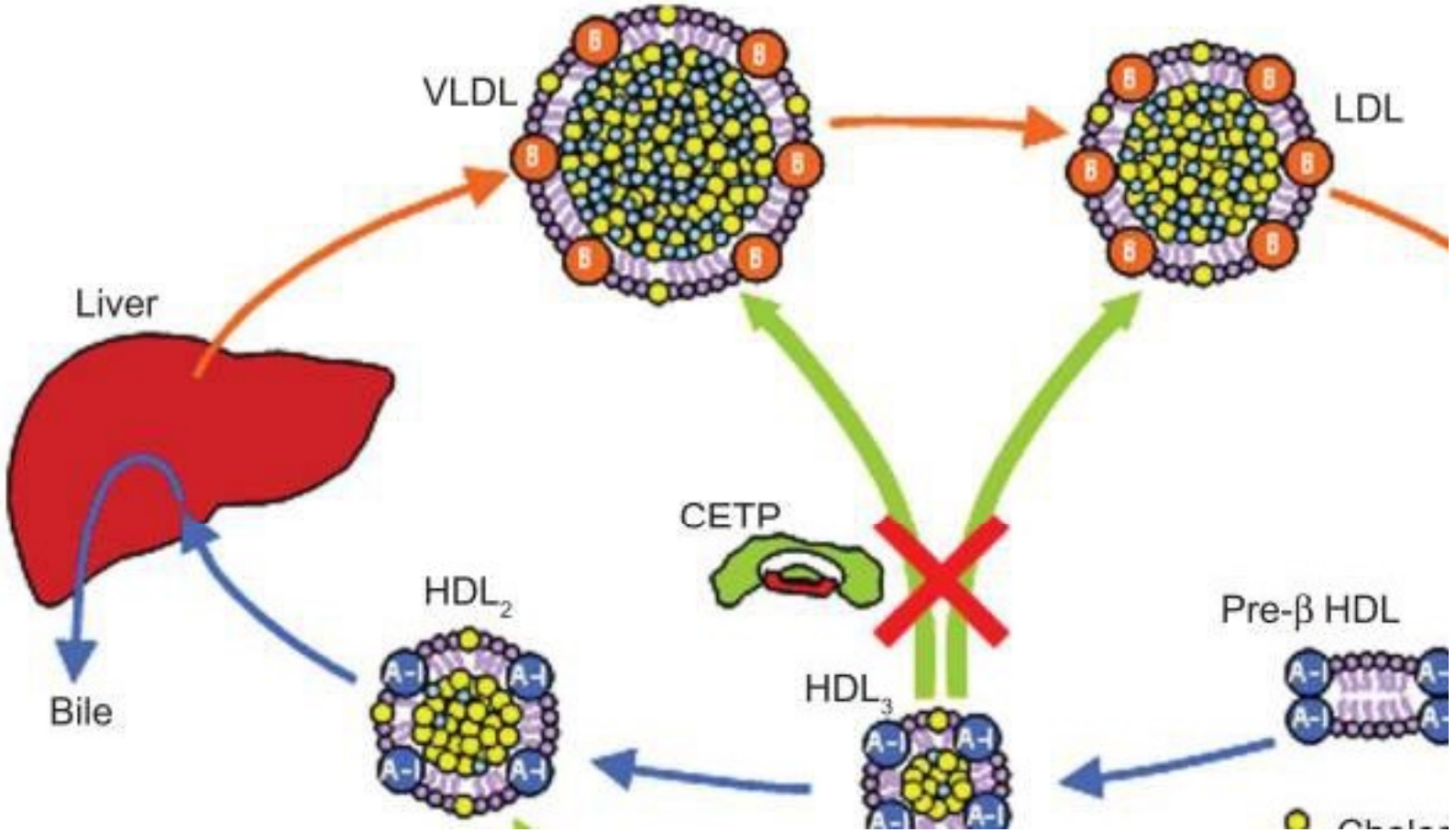
No conflict of interests

Effects of Anacetrapib in Patients with Atherosclero
Disease


VLDL
LDL
Liver
CETP
HDL2
Pre-β HDL
HDL3
Bile

CETP Inhibitor Clinical Trials

Trial	Benefit
ILLUMINATE[a]	**No** benefit (harm) of torcet
dal-OUTCOMES[b]	**No** benefit of dalcetrapi
ACCELERATE[c]	**No** benefit of evacetrap
REVEAL[d]	**Benefit** reported with anace

Summary of CETP Inhibitors

CETP Inhibitor	Other Lipid-Lowering Treatment	LDL-C	HDL-C	Sta
Torcetrapib[a]	Atorvastatin	-24%	+61%	ILLUMINATE termi 2006, for lack of ef effe
Dalcetrapib[b]	Statin	NS	+31%	Dal-OUTCOME September 2012 f
Evacetrapib[c]	Statin	-37%	+130%	ACCELERA terminate
Anacetrapib[d]	Statin	-36%	+139%	REVEAL completed benefit r

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

INCLUSION CRITERIA:

- At least 50 years of age with history of myocardial infarction (MI), cerebrovascular disease, peripheral artery disease, or diabetes with symptomatic coronary heart disease
- Receiving intensive atorvastatin therapy

Exclusion criteria:

- Acute coronary syndrome or stroke within the last 3 months
- Planned coronary revascularization
- Severe liver, kidney, or inflammatory muscle disease
- Current treatment with fibrate or niacin

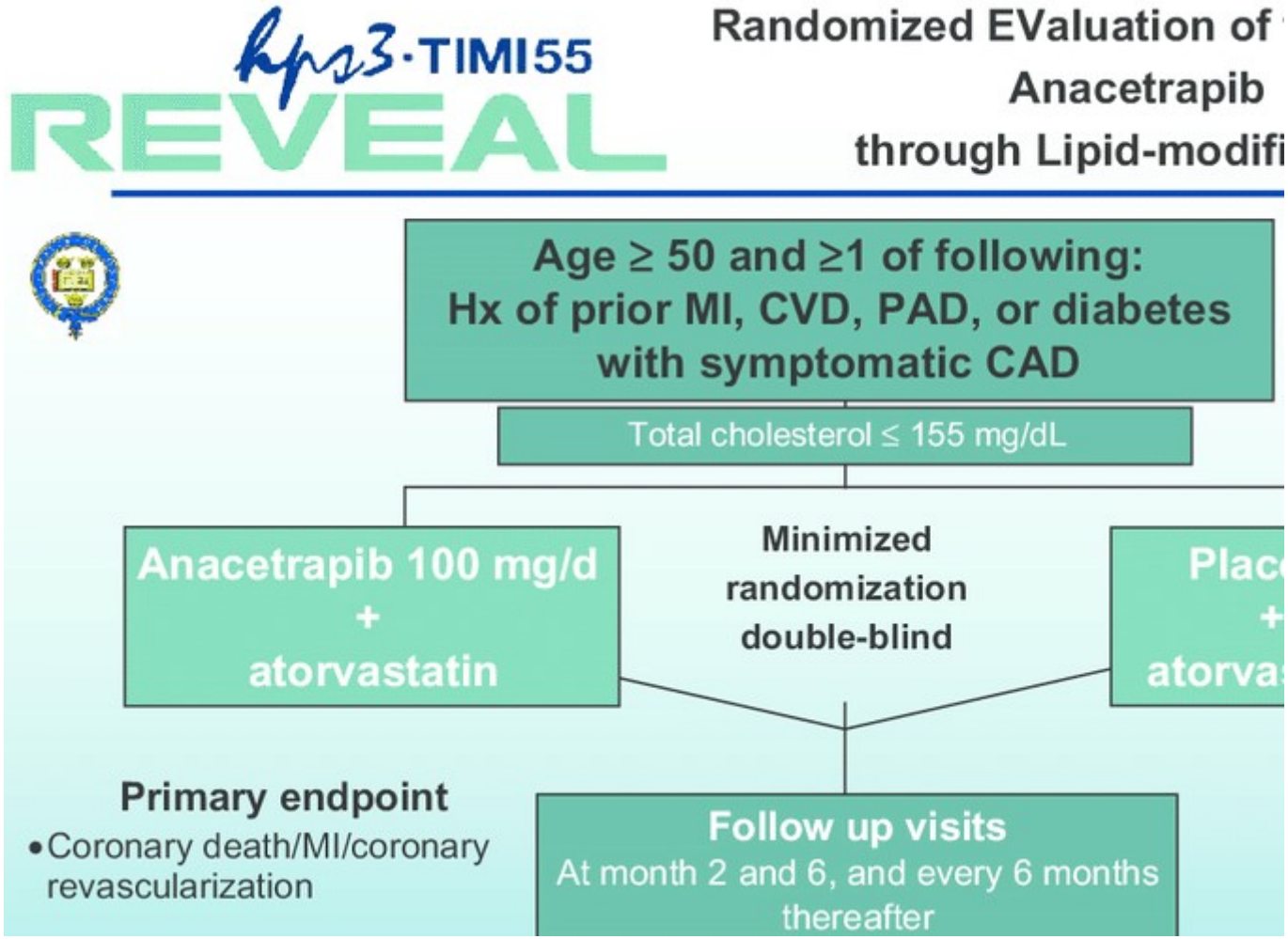
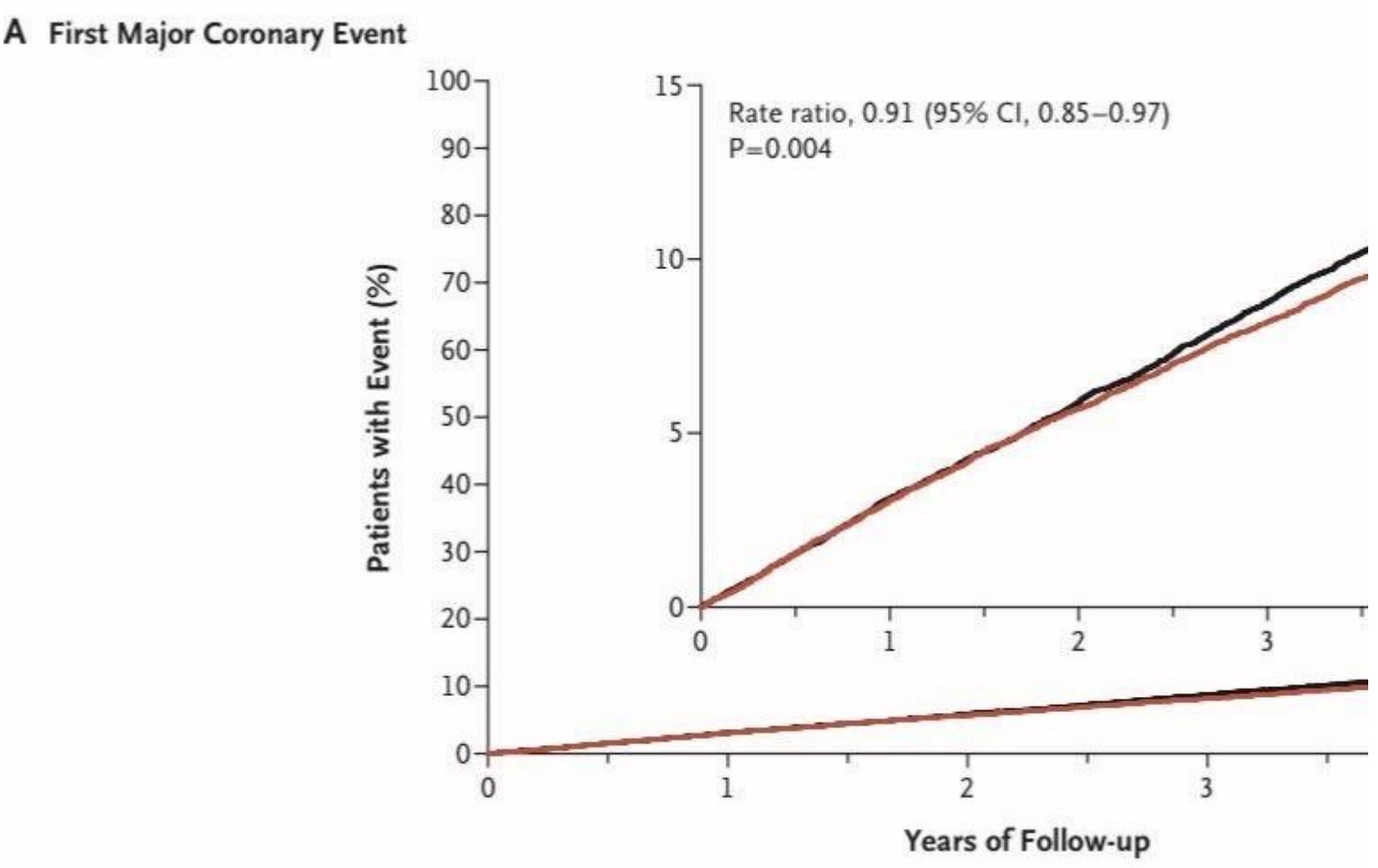

hps3·TIMI55
REVEAL
Randomized EValuation of
Anacetrapib
through Lipid-modifi
Age ≥ 50 and ≥1 of following:
Hx of prior MI, CVD, PAD, or diabetes
with symptomatic CAD
Total cholesterol ≤ 155 mg/dL
Anacetrapib 100 mg/d
+
atorvastatin
Minimized
randomization
double-blind
Plac
+
atorva
Primary endpoint
• Coronary death/MI/coronary revascularization
Follow up visits
At month 2 and 6, and every 6 months thereafter

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Anacetrapib (N = 15,225)	Placebo (N = 15,224)
Age		
Mean — yr	67±8	67±8
Age group — no. (%)		
<65	6,634 (43.6)	6,643 (43.6)
65 to <70	3,380 (22.2)	3,377 (22.2)
≥70	5,211 (34.2)	5,204 (34.2)
Sex — no. (%)		
Male	12,769 (83.9)	12,765 (83.8)
Female	2,456 (16.1)	2,459 (16.2)
Previous disease — no. (%)†		
Coronary heart disease	13,325 (87.5)	13,354 (87.7)
Cerebrovascular disease	3,385 (22.2)	3,396 (22.3)
Peripheral-artery disease	1,229 (8.1)	1,206 (7.9)
Diabetes	5,654 (37.1)	5,666 (37.2)
Heart failure	902 (5.9)	869 (5.7)
Region — no. (%)		
Europe	7,863 (51.6)	7,875 (51.7)
North America	3,048 (20.0)	3,034 (19.9)
China	4,314 (28.3)	4,315 (28.3)
Systolic blood pressure		
Mean — mm Hg	131.3±18.5	131.1±18.5
Level — no. (%)		
<125 mm Hg	5,678 (37.3)	5,760 (37.8)
125 to <140 mm Hg	4,819 (31.7)	4,740 (31.1)
≥140 mm Hg	4,728 (31.1)	4,724 (31.0)
Diastolic blood pressure		
Mean — mm Hg	78.1±10.9	78.0±11.0
Level — no. (%)		
<75 mm Hg	5,656 (37.1)	5,790 (38.0)
75 to <85 mm Hg	5,408 (35.5)	5,277 (34.7)
≥85 mm Hg	4,161 (27.3)	4,157 (27.3)
Body-mass index‡		
Mean	28.6±5.0	28.6±5.1
Level — no. (%)		

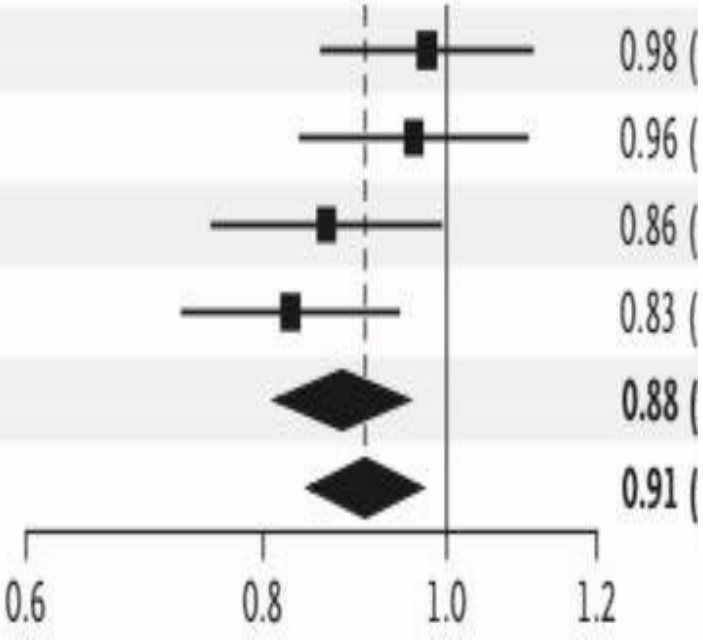
Table 1. (Continued.)

Characteristic	Anacetrapib (N=15,225)	Placebo (N=15,224)
Non-HDL cholesterol		
Mean — mg/dl	92±19	92±19
Level — no. (%)		
<85 mg/dl	5,642 (37.1)	5,701 (37.4)
85 to <101 mg/dl	4,896 (32.2)	4,853 (31.9)
≥101 mg/dl	4,687 (30.8)	4,670 (30.7)
HDL cholesterol		
Mean — mg/dl	40±10	40±10
Level — no. (%)		
<35 mg/dl	4,583 (30.1)	4,590 (30.1)
35 to <43 mg/dl	5,438 (35.7)	5,269 (34.6)
≥43 mg/dl	5,204 (34.2)	5,365 (35.2)
Glomerular filtration rate§		
Mean — ml/min/1.73 m^2	83±17	83±17
Level — no. (%)		
<60 ml/min/1.73 m^2	1,655 (10.9)	1,698 (11.2)
≥60 ml/min/1.73 m^2	13,570 (89.1)	13,526 (88.8)


A First Major Coronary Event
Rate ratio, 0.91 (95% CI, 0.85–0.97)
P=0.004
Patients with Event (%)
Years of Follow-up
100
90
80
70
60
50
40
30
20
10
0
15
10
5
0
0
1
2
3

B First Major Coronary Event, According to Year of Follow-up

Year of First Event	Anacetrapib (N=15,225)	Placebo (N=15,224)	Rate Ratio (95% CI)
	no. of patients with event (%)		
1	465 (3.1)	476 (3.1)	0.98 (
2	398 (2.7)	414 (2.8)	0.96 (
3	370 (2.6)	427 (3.0)	0.86 (
≥4	407 (3.0)	486 (3.7)	0.83 (
>1	**1175 (8.0)**	**1327 (9.1)**	**0.88 (**
All	**1640 (10.8)**	**1803 (11.8)**	**0.91 (**



Test for trend across years, χ^2=4.87 (P=0.03)

Primary & secondary outcomes

Type of Event	Anacetrapib (N=15225)		Placebo (N=15224)		Rate Ratio (95
	no. of participants with events (%)				
Coronary death	388	(2.5)	420	(2.8)	0.92
Myocardial infarction	669	(4.4)	769	(5.1)	0.87
Coronary death or MI	**934**	**(6.1)**	**1048**	**(6.9)**	**0.89**
Coronary revascularization	1081	(7.1)	1201	(7.9)	0.90
Major coronary event	**1640**	**(10.8)**	**1803**	**(11.8)**	**0.91**
Presumed ischaemic stroke	485	(3.2)	489	(3.2)	0.99
Major atherosclerotic event	**1383**	**(9.1)**	**1483**	**(9.7)**	**0.93**
Major vascular event	**2068**	**(13.6)**	**2214**	**(14.5)**	**0.93**

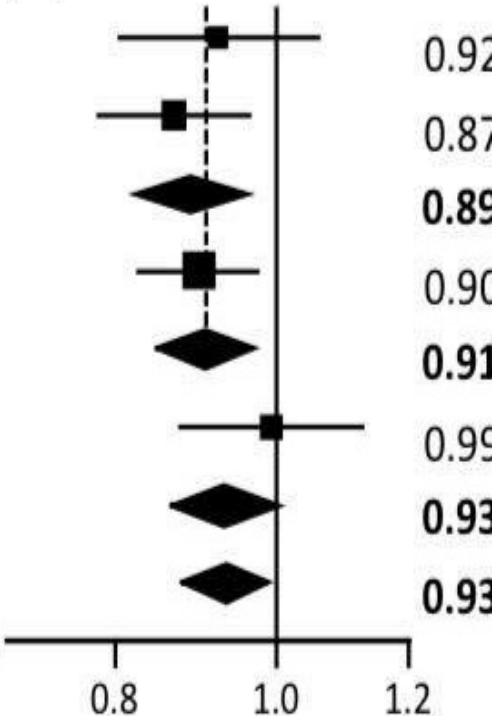


Table 2. Effects of Anacetrapib on Blood Lipids and Lipoproteins at Trial Midpoint.*

Lipid or Lipoprotein	Anacetrapib (N = 15,225)	Placebo (N = 15,224)	Absolut Differenc
Mean LDL cholesterol (mg/dl)			
Direct method	38	64	−26
Beta quantification‡	53	63	−11
Mean non-HDL cholesterol (mg/dl)	79	96	−17
Mean HDL cholesterol (mg/dl)	85	42	43
Mean apolipoprotein A1 (mg/dl)	160	118	42
Mean apolipoprotein B (mg/dl)	54	66	−12

Other clinical assessments

Assessment	Anacetrapib	Placebo	Di
New-onset diabetes mellitus	510 (5.3%)	571 (6.0%)	
Blood pressure			
Systolic (mmHg)	132.4	131.7	
Diastolic (mmHg)	77.6	77.4	
Hypertensive serious adverse events	151 (1.0%)	141 (0.9%)	
Kidney disease			
New-onset eGFR <60 mL/min/1.73m^2	1344 (11.5%)	1236 (10.6%)	+
Renal failure serious adverse events	169 (1.1%)	146 (1.0%)	+

Table S4: Effect of anacetrapib on serious adverse events (fatal and non-fatal comb

Type of Event*	Anacetrapib (N=15225)		Placebo (N=15224)		R
Blood and lymphatic system disorders	188	(1.2%)	182	(1.2%)	
Cardiac disorders	2568	(16.9%)	2766	(18.2%)	(
Congenital, familial & genetic disorders	9	(0.1%)	4	(0.0%)	2
Ear & labyrinth disorders	114	(0.7%)	91	(0.6%)	
Endocrine disorders	50	(0.3%)	49	(0.3%)	
Eye disorders	204	(1.3%)	232	(1.5%)	(
Gastrointestinal disorders	813	(5.3%)	788	(5.2%)	
General disorders	691	(4.5%)	736	(4.8%)	(
Hepatobiliary disorders	217	(1.4%)	238	(1.6%)	(
Immune system disorders	12	(0.1%)	29	(0.2%)	(
Infections and infestations	1559	(10.2%)	1537	(10.1%)	
Injury, poisoning & procedural complications	753	(4.9%)	777	(5.1%)	(
Investigations	1105	(7.3%)	1135	(7.5%)	(
Metabolism & nutrition disorders	642	(4.2%)	687	(4.5%)	(
Musculoskeletal & connective tissue	438	(2.9%)	432	(2.8%)	
Neoplasms benign, malignant & unspecified	1323	(8.7%)	1295	(8.5%)	
Nervous system disorders	1399	(9.2%)	1455	(9.6%)	(
Psychiatric disorders	104	(0.7%)	111	(0.7%)	(
Renal & urinary disorders	415	(2.7%)	398	(2.6%)	
Reproductive system & breast disorders	49	(0.3%)	56	(0.4%)	(
Respiratory, thoracic & mediastinal	606	(4.0%)	605	(4.0%)	
Skin & subcutaneous tissue disorders	84	(0.6%)	97	(0.6%)	(

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 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

Comparing Biomarker Profiles in Patients with Stable Atherosclerosis Treate
Anacetrapib versus Placebo: a Nested Proteomic Study from HPS3/TIMI 55-RE

David D. Berg, David A. Morrow, & Eugene Braunwald, on behalf of the HPS3/TIMI 55-REVEAL Collaborat
TIMI Study Group, Brigham and Women's Hospital, & Harvard Medical School, Boston, MA

BACKGROUND

- The cholesteryl ester transfer protein (CETP) inhibitor anacetrapib modestly improved CV outcomes in pts with stable atherosclerosis
- The potential interaction of HDL-C, LDL-C, and possible nonlipid-mediated effects remains unknown
- The aim of this nested exploratory study was to identify biological pathways influenced by treatment with anacetrapib

METHODS

- HPS3/TIMI 55-REVEAL was a randomized, double-blind, placebo-controlled trial of anacetrapib in pts with stable atherosclerotic CV disease (ASCVD)
- We performed a nested prospective biomarker study in 500 pts, analyzing 274 candidate biomarkers (Proseek® Olink CV II, CV III, Inflammation panels)
- We compared changes in biomarker levels between

RESULTS

- Eleven biomarkers were significantly modified by anacetrapib vs. placebo (**Fig 1**)
- These proteins represent pathways implicated in inflammation, lipid metabolism, and hematopoiesis (**Table 1**)
- Treatment with anacetrapib vs. placebo decreased circulating LDL-R (**Fig 1**)
- Among anacetrapib-treated pts, changes in 5/11 biomarkers were not significantly correlated with changes in either serum HDL-C or serum LDL-C (**Table 2**)

Figure 1. Comparing Δ in Biomarkers for Anacetrapib vs. Placebo.

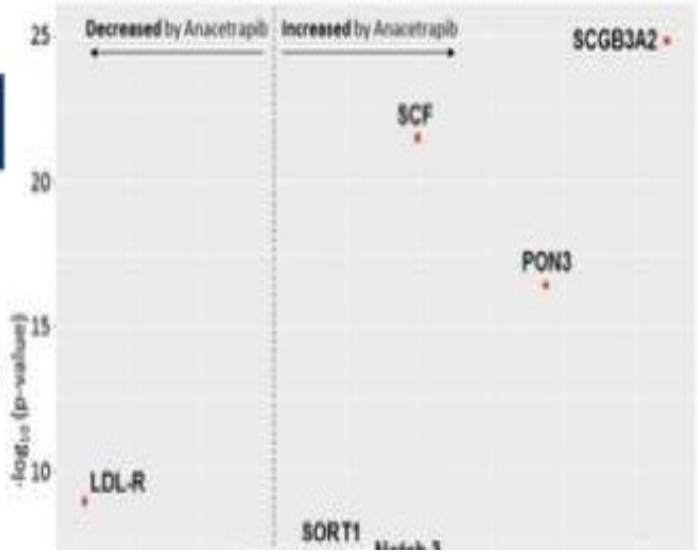


Table 1. Selected Biomarkers.

SCGB3A2	Secretogobin Family 3A Member 2
SCF	Stem Cell Factor
PON3	Paraoxanase 3
LDL-R	Low-Density Lipoprotein Receptor
Notch 3	Neurogenic locus notch homolog protein 3
SORT1	Sortilin 1
KIM-1	Kidney injury molecule 1

Table 2. Lipid Correla

Δ Biomarker	
Δ SCGB3A2	
Δ SCF	
Δ PON3	
Δ LDL-R	
Δ Notch 3	
Δ SORT1	
Δ KIM-1	
Δ SELE	
Δ THPO	
Δ HO-1	
Δ IL-27	

CONCLUSIO

- In pts with stal anacetrapib re expression ex
- Some change anacetrapib-m
- It is unknown investigation,

CETP inhibitor class finally dies a
Merck abandons anacetrapib

Cholesterol drug fails to “support regulatory filir

13th October 2017

ESC European Society of Cardiology

European Heart Journal (2022) **43**, 1416–1424
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CLINIC

Long-term safety and efficacy of anac in patients with atherosclerotic vascul disease

The HPS3/TIMI55-REVEAL Collaborative Group

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News | Heart Failure | March 04, 2022

NewAmsterdam Pharı Doses First Patient in PREVAIL Study

PREVAIL evaluates whether obicetrapib, a novel cholesteryl transfer protein (CETP) inhibit lowers the risk of adverse cardiovascular outcomes (MAC individuals with Atherosclerotic Cardiovascular Disease (ASCVI

THANK YOU


Κατατάξεις Πρωτάθλημα Ελλάδας
ΑΓΩΝΕΣ
ΕΙΔΗΣΕΙΣ
ΒΑΘΜΟΛΟΓΙΕΣ
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