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

David D. Berg, David A. Morrow, & Eugene Braunwald, on behalf of the HPS3/TIMI 55-REVEAL Collaborators
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 randomization and mid-study (~2 years) in pts treated with anacetrapib vs. placebo using a Bonferroni threshold for statistical significance
- We evaluated associations between Δ in selected biomarkers and Δ in HDL-C and LDL-C from baseline to mid-study in each treatment group

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.

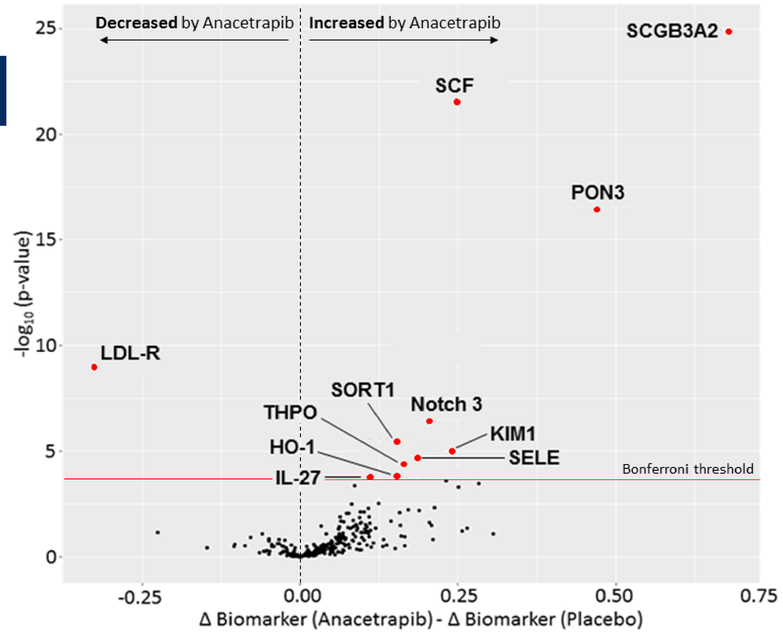

Table 1. Selected Biomarkers.

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
SELE	E-Selectin
THPO	Thrombopoietin
HO-1	Heme oxygenase 1
IL-27	Interleukin-27

Table 2. Lipid Correlations in Anacetrapib-Treated Patients (n=250).

Δ Biomarker	Correlation with Δ HDL-C*	Correlation with Δ LDL-C*
Δ SCGB3A2	0.39 (p<0.001)	-0.19 (p<0.01)
Δ SCF	0.05 (p=0.465)	-0.13 (p=0.078)
Δ PON3	0.22 (p<0.01)	-0.08 (p=0.248)
Δ LDL-R	-0.20 (p<0.01)	0.23 (p<0.001)
Δ Notch 3	0.07 (p=0.314)	-0.08 (p=0.228)
Δ SORT1	0.16 (p<0.05)	0.08 (p=0.237)
Δ KIM-1	0.18 (p<0.01)	0.04 (p=0.572)
Δ SELE	0.06 (p=0.368)	-0.06 (p=0.426)
Δ THPO	0.08 (p=0.273)	0.05 (p=0.486)
Δ HO-1	0.18 (p<0.01)	-0.07 (p=0.321)
Δ IL-27	-0.02 (p=0.818)	0.00 (p=0.995)

*Spearman correlation coefficients

CONCLUSIONS

- In pts with stable atherosclerosis, treatment with anacetrapib results in changes in protein expression extending beyond lipid metabolism
- Some changes appear to be independent of anacetrapib-mediated effects on HDL-C and LDL-C
- It is unknown, and subject to further investigation, whether these changes relate to the observed efficacy or safety of anacetrapib

DECLARATION OF INTEREST: **D.D. Berg:** none. **D.A. Morrow:** Research grants and/or consulting fees from Abbott Labs, Amgen, Aralez, Astra Zeneca, Bayer, BRAHMS, Eisai, GSK, InCardia, Medicines Co, Merck, Novartis, Peloton, Pfizer, Roche, Takeda, Verseon. **E. Braunwald:** Research grants through his institution from AstraZeneca, Daiichi Sankyo, GlaxoSmithKline, Merck, and Novartis; personal fees for consultancy from Cardurion, MyoKardia, Sanofi, and Verve; fees for lectures from Medscape; uncompensated consultancies and lectures from Merck, Novartis, and The Medicines Company. The **HPS3/TIMI 55-REVEAL** study was funded by Merck.

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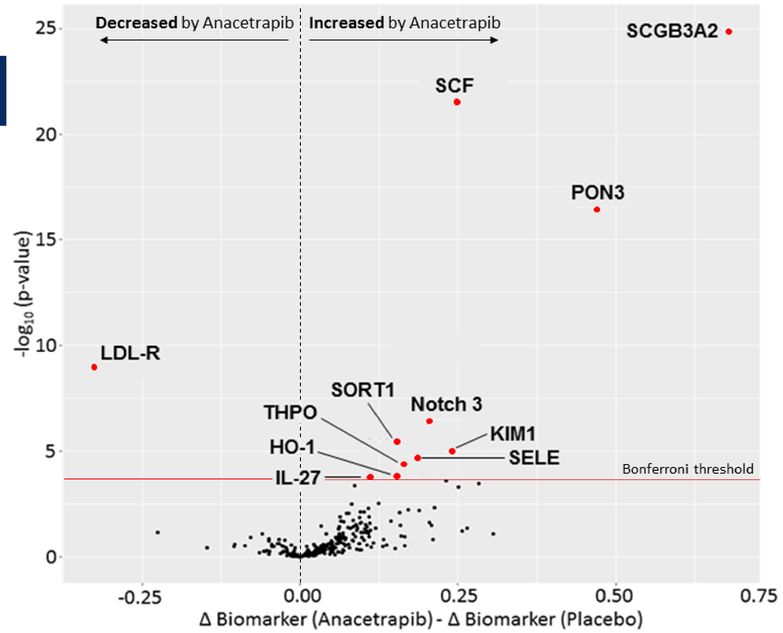

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