#AHA24

THE EFFECT OF PCSK9 INHIBITION WITH ALIROCUMAB IN PATIENTS WITH PROBABLE FAMILIAL HYPERCHOLESTEROLEMIA OR TYPE III HYPERLIPOPROTEINEMIA: RESULTS FROM THE ODYSSEY OUTCOMES TRIAL

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DISCLOSURES

Gregory Geba, Kusha Mohammadi, Amy Damask, Charles Paulding, Luca A. Lotta, George Hindy, Robert Pordy, Garen Manvelian, and **Sergio Fazio** are employees and shareholders of Regeneron Pharmaceuticals, Inc.

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BACKGROUND

- Patients with ACS and elevated LDL-C levels despite statin therapy may have genetic dyslipidemias, such as HeFH or T3HLP, which convey heightened cardiovascular risk due to lifelong exposure[1–3]
- The Phase 3 ODYSSEY OUTCOMES trial compared the effect of alirocumab, a PCSK9 inhibitor, with placebo on cardiovascular outcomes after ACS in 18,924 patients receiving high-intensity or maximum tolerated statin therapy
  - The study met the primary endpoint of a 15% reduction in MACE (alirocumab vs placebo; HR [95% CI]: 0.85 [0.73, 0.98])[4]
- In this post hoc analysis of data from the ODYSSEY OUTCOMES trial, we evaluated the lipid-lowering and cardiovascular efficacy of alirocumab in patients likely affected by HeFH or T3HLP

ACS, acute coronary syndrome; CI, confidence interval; HeFH, heterozygous familial hypercholesterolemia; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; PCSK9, proprotein convertase subtilisin/kexin type 9; T3HLP, type III hyperlipoproteinemia.

1. Kastelein JJ et al. *Eur Heart J*. 2015;36:2996–3003; 2. Santos RD et al. *J Am Coll Cardiol*. 2020;75:565–574; 3. Khalil YA et al. *Atherosclerosis*. 2021:328:11−22; 4. Schwartz GG et al. *N Engl J Med*. 2018;379:2097–2107.

STUDY DESIGN AND METHODS

- Patients were randomized 1:1 to blinded treatment with subcutaneous alirocumab 75 mg or matching placebo every 2 weeks; the dose of alirocumab was adjusted under blinded conditions to target an LDL-C level of 25–50 mg/dL (0.6–1.3 mmol/L)

Criteria Defining Genetic Dyslipidemias	
HeFH	**T3HLP**

• Back-calculated untreated LDL-C ≥250 mg/dL and presence of early-onset CAD:
  • Males <55 years old
  • Females <60 years old
OR
• ACS at any age with back-calculated LDL-C ≥330 mg/dL
	• Non-HDL-C:ApoB ratio >2.6
	
	(validated using the UK Biobank database: prevalence of ratio >2.6 = 0.09%; prevalence of the ApoE2/2 homozygote genotype among those with ratio >2.6 = 89%)

Pharmacogenomic analysis

- Conducted in a subset of 11,880 patients from ODYSSEY OUTCOMES who were studied for variants in genes causing HeFH and for ApoE genotypes (T3HLP)

ACS, acute coronary syndrome; Apo, apolipoprotein; CAD, coronary artery disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; T3HLP, type III hyperlipoproteinemia.

PREVALENCE OF CLINICAL HeFH

- **Full trial cohort**: Clinical HeFH was identified in 6.7% (1266/18,924) of study participants
- **Pharmacogenomics subgroup**:
  - Clinical HeFH was identified in 5.9% (701/11,880) of study participants
  - Genetic HeFH was confirmed in 2.5% (295/11,880) of study participants
    - *Probable clinical HeFH*[a] was identified in 26.8% (79/295) of study participants with genetically confirmed HeFH
    - *Definite clinical HeFH*[b] was identified in 19.0% (56/295) of study participants with genetically confirmed HeFH

[a]Score of 6–8 (Dutch Lipid Clinic Network Criteria for FH)
[b]Score of 8 or higher (Dutch Lipid Clinic Network Criteria for FH)
HeFH, heterozygous familial hypercholesterolemia.

EFFECT OF ALIROCUMAB ON LDL-C AND MACE IN THE HeFH POPULATION

- Baseline LDL-C was higher in patients with clinical or genetic HeFH than in those without HeFH
- In patients with clinical or genetic HeFH versus those without HeFH:
  - Percent LDL-C–lowering was lower
  - HRs for MACE with alirocumab (vs placebo) were similar

Endpoint	Patients without HeFH (N=17,826)		Patients with HeFH (N=1098)	
	Placebo (n=8915)	Alirocumab (n=8911)	Placebo (n=547)	Alirocumab (n=551)
LDL-C, mg/dL				
Baseline, median (IQR)	84.9 (72.2, 100.0)	84.9 (72.2, 100.0)	154.0 (134.0, 178.2)	155.2 (134.9, 180.8)
Absolute change from baseline to Month 4, median (IQR)	0.8 (–11.2, 13.9)	–54.1 (–68.8, –39.0)	–18.9 (–52.1, 4.0)	–101.0 (–129.0, –79.0)
Percentage change from baseline to Month 4, median (IQR)	1.0 (–12.5, 17.4)	–65.7 (–76.0, –50.8)	–12.4 (–32.9, 2.9)	–66.5 (–78.7, –51.7)
Difference, median (95% CI)[a]	–	–65.1 (–65.8, –64.5)	–	–50.1 (–53.3, –46.9)
MACE				
n (%)	974 (10.9)	836 (9.4)	78 (14.3)	67 (12.2)
HR (95% CI)	–	0.85 (0.77, 0.93)	–	0.85 (0.61, 1.19)

[a]The median treatment differences and 95% CIs were calculated from the Hodges-Lehmann estimation and Moses distribution free CI, respectively.
CI, confidence interval; HeFH, heterozygous familial hypercholesterolemia; HR, hazard ratio; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events.

GENETIC CONFIRMATION OF T3HLP

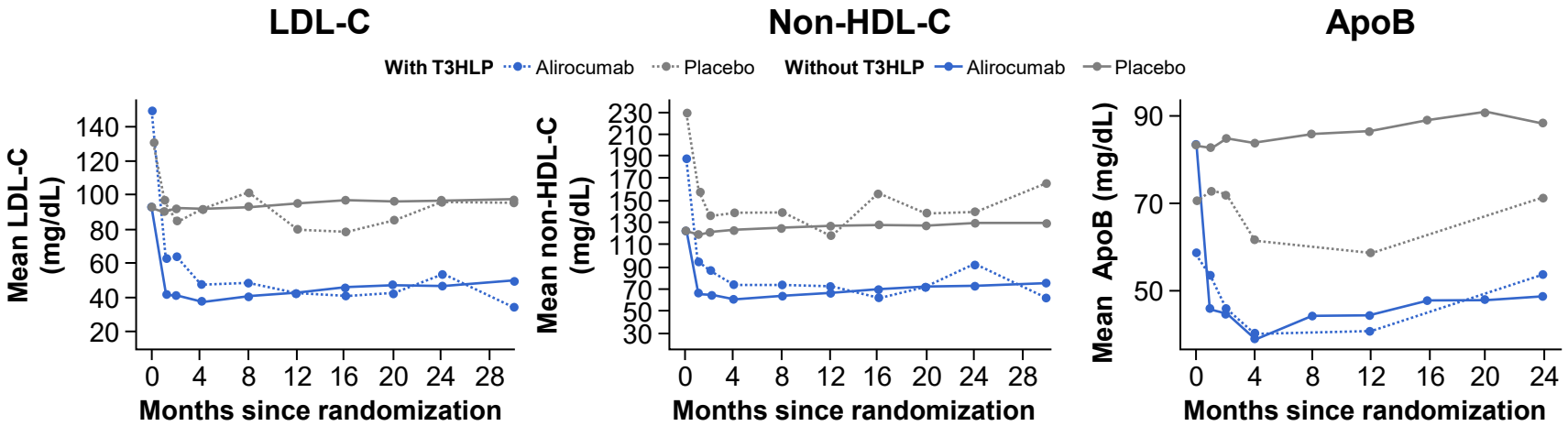
- In the UK Biobank, only 0.09% of participants carried the T3HLP biomarker ratio (non-HDL-C:ApoB >2.6), and 89% of these carried the ApoE2/2 homozygote genotype
- In the full ODYSSEY OUTCOMES cohort, only 0.16% (30/18,924) of participants carried the T3HLP biomarker ratio (non-HDL-C:ApoB >2.6)
  - Thirteen of these 30 participants were in the pharmacogenomics subgroup (n=11,880), which included a total of 30 patients with the ApoE2/2 genotype
    - Of the 13 participants who met clinical criteria for T3HLP, 7 (53.8%) carried the ApoE2/2 genotype
    - Of the 30 participants with ApoE2/2 genotype, 7 (23%) met clinical criteria for T3HLP
    - Of 11,850 non-carriers of ApoE2/2, only 6 (0.05%) met clinical criteria for T3HLP

ACS, acute coronary syndrome; Apo, apolipoprotein; non-HDL-C, non-high-density lipoprotein cholesterol; T3HLP, type III hyperlipoproteinemia.

EFFECT OF ALIROCUMAB ON LIPIDS IN THE T3HLP POPULATION

- Lipid responses to alirocumab in patients with T3HLP were comparable to those in the overall population, with >50% LDL-C lowering from baseline to Month 24/28

Changes in lipids over time in patients with or without clinically defined T3HLP



Apo, apolipoprotein; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high density lipoprotein cholesterol; T3HLP, type III hyperlipoproteinemia.

EFFECT OF ALIROCUMAB ON MACE BY T3HLP STATUS

- The incidence of MACE was numerically lower in patients with T3HLP treated with alirocumab versus those treated with placebo (9% vs 25%, respectively)

Endpoint	Subgroup	Placebo, n/N (%)	Alirocumab, n/N (%)
MACE[a]	Overall	1052/9462 (11.1)	903/9462 (9.5)
	T3HLP	2/8 (25.0)	2/22 (9.1)
	Not T3HLP	1050/9454 (11.1)	901/9440 (9.5)

[a]MACE is defined as composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization.
MACE, major adverse cardiovascular events; T3HLP, type III hyperlipoproteinemia.

LIMITATIONS

- Post hoc analysis
- Back-calculated LDL-C levels to derive HeFH diagnosis
- Phenotypic definition of T3HLP did not account for statin use

CONCLUSIONS

- In this post hoc analysis of ODYSSEY OUTCOMES, individuals with HeFH were common and those with T3HLP were rare
- Carriers of either genetic condition benefited from alirocumab treatment in terms of lipid response and clinical outcomes

HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; T3HLP, type III hyperlipoproteinemia.

THANK YOU

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