Cardiovascular Outcomes in Patients with Established Atherosclerosis and LDLR Loss of Function: Results from the FOURIER Trial

Nicholas A. Marston, MD, MPH*, James Pirruccello, MD*, Giorgio Melloni, PhD, Frederick K. Kamanu, PhD, Seung Hoan Choi, PhD, Anthony Philippakis, MD, PhD, Peter S. Sever, PhD, FRCP, Anthony C. Keech, MD, Armando Lira Pineda, MD, Huei Wang, PhD, Robert P. Giugliano, MD, SM, Steven A. Lubitz, MD, MPH, Patrick Ellinor, MD, PhD*, Marc S. Sabatine, MD, MPH*, Christian T. Ruff, MD, MPH*

(*contributed equally)

TIMI Study Group

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Disclosures

Presenter: clinical trial involvement with Amgen, Pfizer, Novartis, and AstraZeneca without personal fees, payments, or salary increase.

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Background

- Approximately 1:500 (0.2%) individuals carry a loss of function (LoF) mutation in the LDL receptor (LDLR) gene.
- These individuals have lifelong elevations in LDL-C, putting them at greater risk of cardiovascular disease.
- The importance of such mutations in patients with established atherosclerosis, and their interaction with polygenic risk is not clear.
- **We aimed to:**
  1. Determine the risk of coronary events in patients with LDLR LoF compared with those with intact LDLR function.
  2. Evaluate whether polygenic risk for CAD adds to monogenic risk in this secondary prevention clinical trial cohort

Methods

- **We performed a prospective genetic cohort analysis from the FOURIER trial, including all 14,297 patients who consented for genetic testing, passed QC, and were of European ancestry.**

- **All patients had established ASCVD and were on moderate or high intensity statin therapy.**

- **The primary endpoint was major coronary events, a composite of:**
  - CHD death
  - Myocardial infarction
  - Coronary revascularization

Methods: Defining Monogenic and Polygenic Risk

- **Whole exome sequencing was performed and LoF mutations in LDLR were identified using LOFTEE, a tool for detecting protein-truncating variants.**

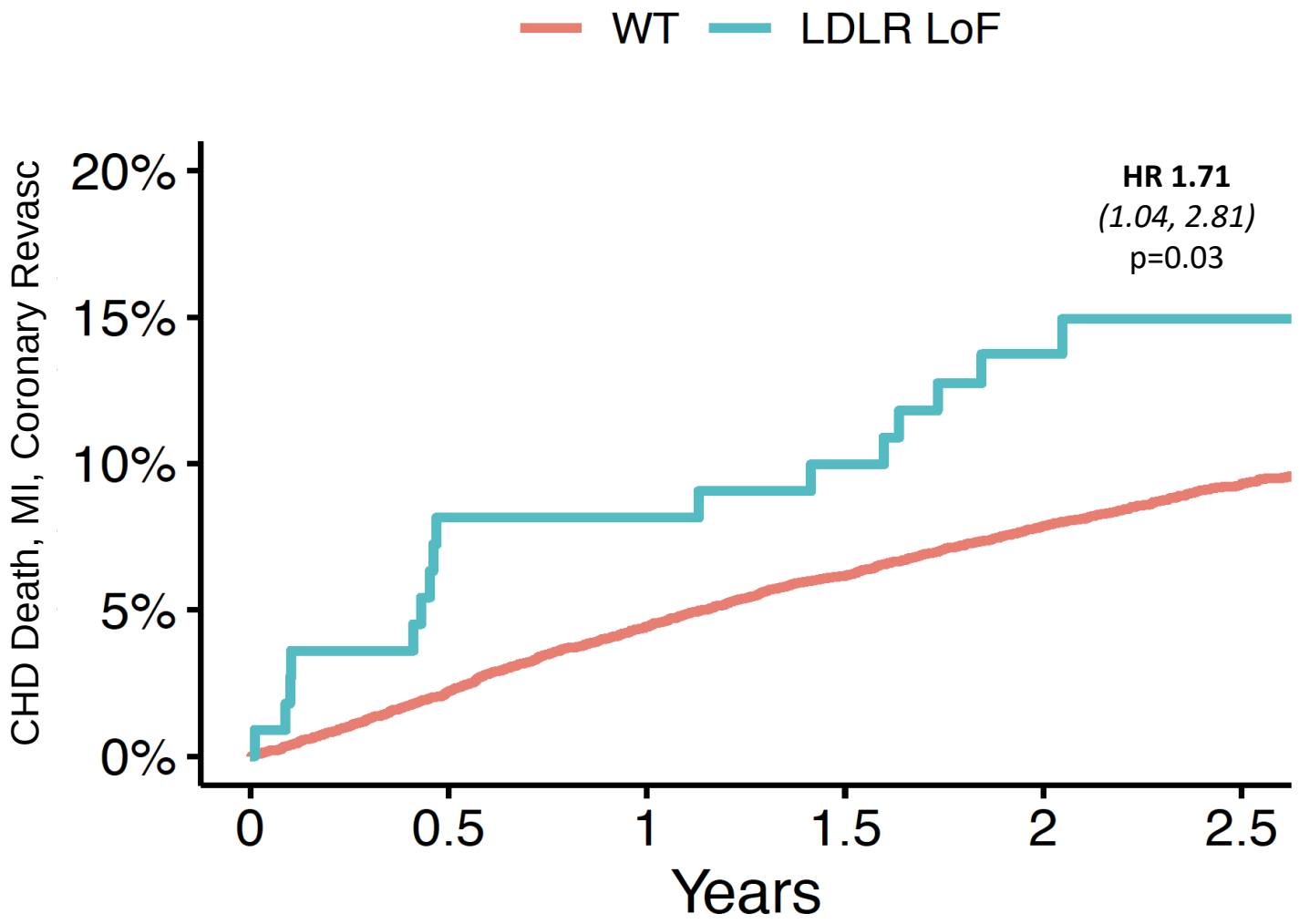
- **Polygenic risk for CAD was calculated for each patient using a previously validated 27-SNP genetic risk score*.**
  - high genetic risk >= the median
  - low genetic risk < the median

Mega J, et al. Lancet. 2015.
Marston N, et al. Circulation. 2019.

Results: Baseline Characteristics

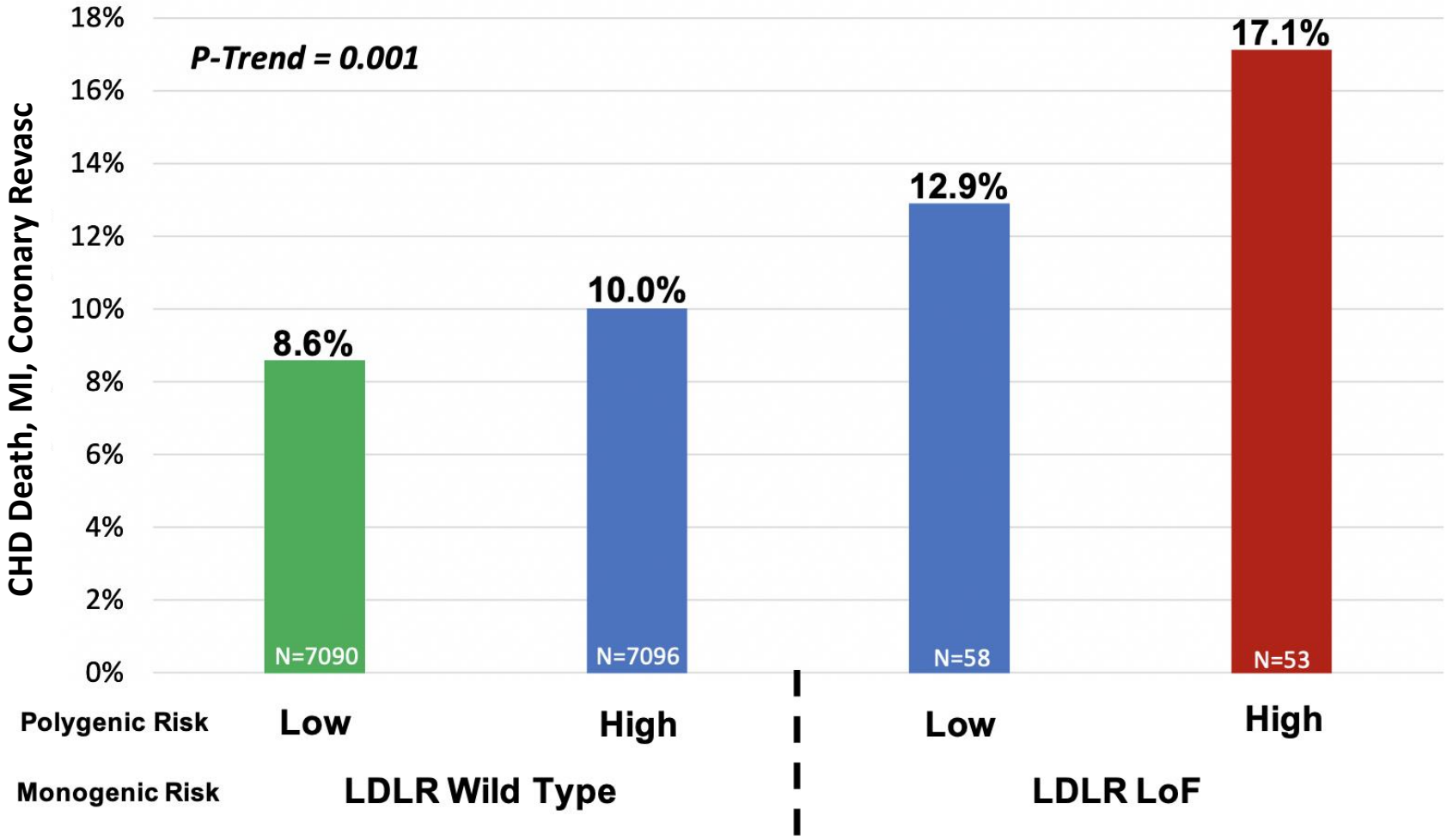
Variable	LDLR LoF N = 111 (0.8%)	Wild Type N = 14186	P-value
Demographics			
Age (years)	56 ± 10	63 ± 9	<0.001
Male	76%	76%	0.44
Baseline BMI (kg/m^2)	29 ± 6	30 ± 5	0.48
Comorbidities			
Prior Myocardial Infarction	86%	82%	0.35
History of Coronary Revascularization	82%	69%	0.003
History of Cerebrovascular Disease	22%	22%	0.96
Diabetes	24%	24%	1.00
Baseline Laboratory Value (mg/dL)			
LDL-C	160 ± 45	98 ± 27	<0.001
Total Cholesterol	233 ± 51	175 ± 32	<0.001
HDL	45 ± 13	47 ± 13	0.20
Triglycerides	140 ± 75	151 ± 70	0.14

Results: Major Coronary Events stratified by LDLR Loss of Function Mutation Status



HR adjusted for age + sex

Results: Major Coronary Events stratified by LDLR Loss of Function Mutation Status and Polygenic Risk for CAD



2.5-year follow up

Limitations

- **LDLR mutations are rare, and therefore the number of patients identified in this study is limited**

- **Since all patients in FOURIER have established atherosclerosis and are on intensive lipid-lowering therapy, the effects of LDLR LoF may be more attenuated than they would be in a primary prevention population**

Conclusions

- **The FOURIER trial was enriched for individuals with LDLR LoF mutations, with a 4-fold greater prevalence than the general population.**
- **Among patients with ASCVD, those with LDLR LoF mutations were 7 years younger than those with normal LDLR function.**
- **Patients with LDLR LoF mutations had persistently elevated LDL-C and increased CV risk despite intensive statin therapy.**
- **The combination of a monogenic LDLR mutation with high polygenic risk for CAD appeared additive in this secondary prevention cohort.**