LEUKOCYTE TELOMERE LENGTH POLYGENIC RISK SCORE AND CARDIOVASCULAR EVENTS ACROSS THE SPECTRUM OF ASCVD

An Analysis of 74,534 Patients from 6 TIMI Randomized Trials

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Scientific Sessions

American Heart Association.

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DISCLOSURES

No personal disclosures.

The TIMI Study Group has received institutional research grant support through Brigham and Women's Hospital from 4TEEN4 Pharmaceuticals GmbH, Abbott, Abiomed, Inc., Amgen, ARCA Biopharma, Inc., AstraZeneca, Beijing Inno Medicine Co., Ltd., Boehringer Ingelheim, Cleerly, Inc., Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, Marea Therapeutics, Inc., Merck, Novartis, Pfizer, Softcell Medical Limited.

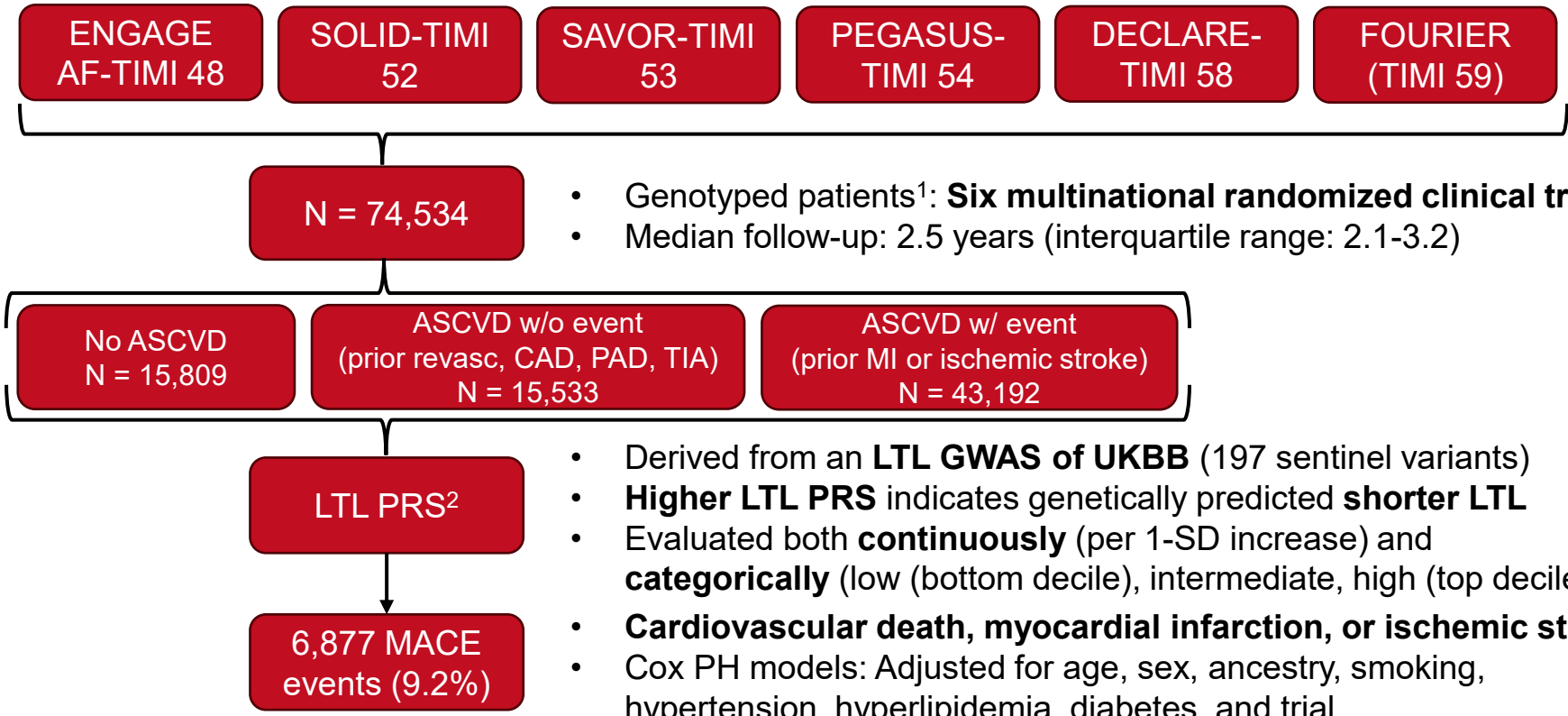
ENGAGE AF-TIMI 48 was funded by Daiichi Sankyo Pharma; SOLID-TIMI 52 was funded by GlaxoSmithKline; SAVOR-TIMI 53 was funded by AstraZeneca and Bristol-Myers Squibb; PEGASUS-TIMI 54 and DECLARE-TIMI 58 were funded by AstraZeneca; FOURIER (TIMI 59) was funded by Amgen.

BACKGROUND

- **Leukocyte telomere length** (LTL), a marker of biological aging, has been associated with multiple age-related diseases, including coronary artery disease (CAD).
- Mendelian randomization studies have supported a causal effect of **genetically predicted shorter LTL** with the development of **CAD**.
- Whether an **LTL polygenic risk score** (PRS) predicts incident events across the spectrum of **ASCVD** remains uncertain.

Objective: To evaluate the ability of an LTL PRS to predict major adverse cardiovascular events (MACE; CVD, MI or ischemic stroke) among patients without overt ASCVD and in patients with ASCVD with and without a prior event

METHODS



- Genotyped patients[1]: **Six multinational randomized clinical trials**
- Median follow-up: 2.5 years (interquartile range: 2.1-3.2)

- Derived from an **LTL GWAS of UKBB** (197 sentinel variants)
- **Higher LTL PRS** indicates genetically predicted **shorter LTL**
- Evaluated both **continuously** (per 1-SD increase) and **categorically** (low (bottom decile), intermediate, high (top decile))

- **Cardiovascular death, myocardial infarction, or ischemic stroke**
- Cox PH models: Adjusted for age, sex, ancestry, smoking, hypertension, hyperlipidemia, diabetes, and trial

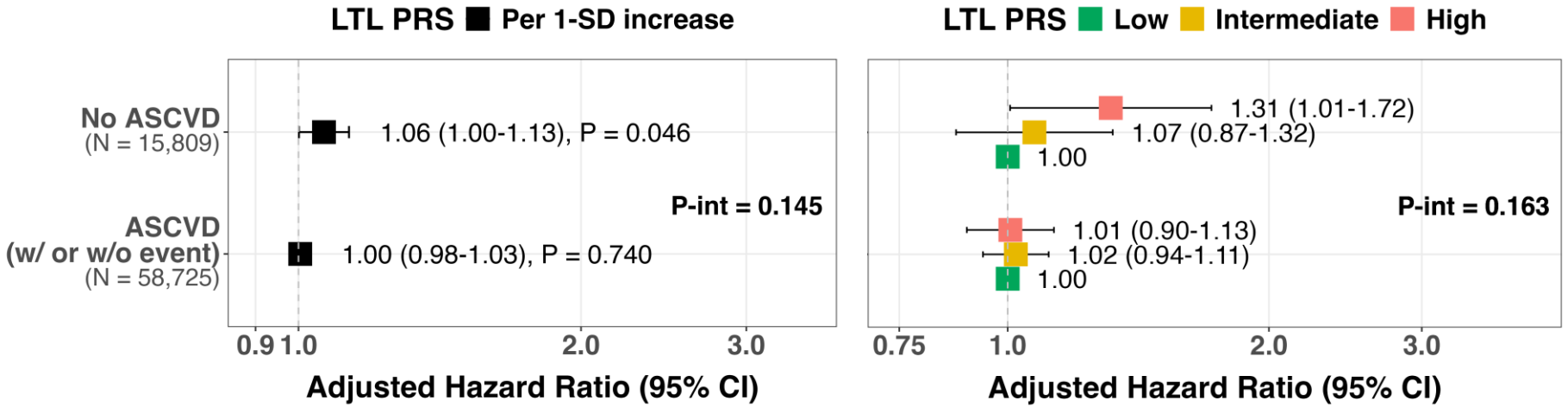
[1]Ancestry: AFR, AMR, EAS, EUR, SAS, and unassigned; [2]Codd V. *et al., Nat Genet* (2021)

BASELINE CHARACTERISTICS BY LTL PRS

Data in % or median	Low PRS (Bottom 10%) N = 7,454	Intermediate PRS (Middle 80%) N = 59,626	High PRS (Top 10%) N = 7,454	*P* value
Age [IQR], years	65 [60, 72]	65 [59, 72]	65 [59, 72]	0.013
Sex Male	69	70	71	0.051
Smoking (Current)	17	17	18	0.540
Hypertension	85	83	83	<0.001
Hypercholesterolemia	63	63	64	0.228
Diabetes Mellitus	53	53	53	0.317
Ancestry (EUR)	82	82	82	0.592
ASCVD category				0.033
No ASCVD	22	21	20	
ASCVD w/o event	21	21	21	
ASCVD w/ event	57	58	59	

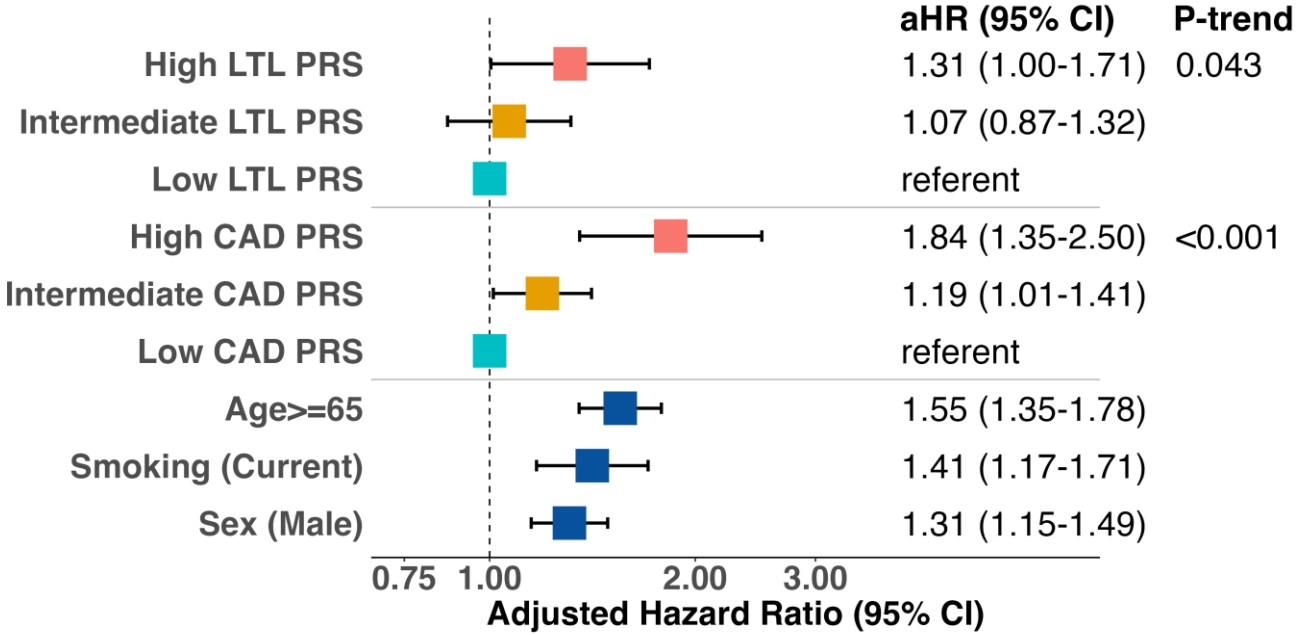
IQR=interquartile range

LTL PRS WAS ASSOCIATED WITH MACE AMONG PATIENTS WITHOUT ASCVD



Adjusted for age, sex, ancestry, smoking, hypertension, hyperlipidemia, diabetes, and trial.

LTL PRS REMAINED ASSOCIATED WITH MACE AFTER ADJUSTMENT FOR CAD PRS AMONG PATIENTS WITHOUT ASCVD



A restricted CAD PRS[1] was derived by excluding variants that overlapped with LTL-associated loci to account for shared genetic architecture.

[1]Patel A.P. *et al., Nat Med* (2023); ~1.3M variants; Median follow-up 2.5 years (IQR: 2.1-3.2)

CONCLUSIONS

- Among patients without overt ASCVD, with a median follow-up of 2.5 years, an LTL PRS was associated with MACE, independent of clinical risk factors and CAD PRS.

- LTL PRS may provide an ability to improve cardiovascular risk stratification in individuals without ASCVD.

THANK YOU