#AHA23

Performance of a Polygenic Risk Score for CAD Across the Spectrum of ASCVD:

An Analysis of 60k Patients from 6 TIMI Randomized Trials

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TIMI

American Heart Association.

DISCLOSURES

I am a member of the TIMI Study Group which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Abiomed, Inc., Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Saghmos Therapeutics, Inc., Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc., Zora Biosciences.

BACKGROUND

Genetics can be used to refine risk prediction

Relative utility in primary vs. secondary prevention is unclear

Purpose: To compare the ability of a CAD PRS to predict coronary events according to presence and spectrum of ASCVD

METHODS

59,905 pts from 6 TIMI RCTs* stratified into **low (Q1), intermediate (Q2-4), or high (Q5) genetic risk** using an external genome-wide CAD polygenic risk score[1]

Pts were then **categorized by ASCVD status** at baseline:

- ASCVD with event: prior MI or ischemic stroke (N=40,877)
- ASCVD without event: prior revasc, CAD, PAD (N=6,579)
- No overt ASCVD: none of the above (N=12,449)

*ENGAGE AF, SOLID, SAVOR, PEGASUS, DECLARE, and FOURIER

[1]Aragam KG et al., *Nature Genetics* 2022

METHODS

Adjudicated **coronary endpoint**: CHD death, MI, or coronary revasc

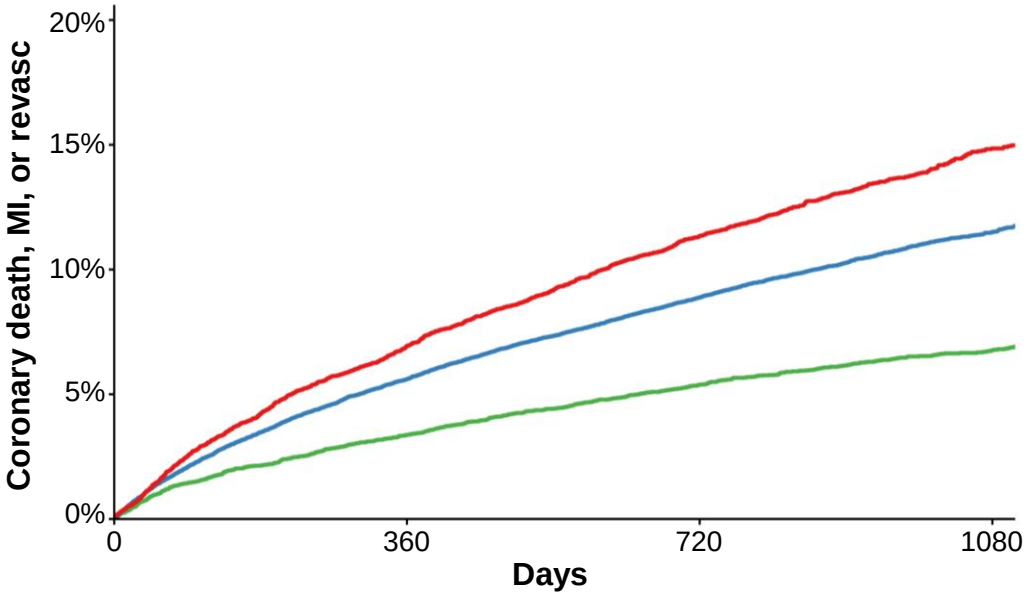
Cox models were adjusted for age, sex, ancestry, trial, and ASCVD risk factors (diabetes, eGFR, smoking, use of LLT, SBP)

BASELINE CHARACTERISTICS BY GENETIC RISK

	Low Risk N=11,981 (Q1)	Intermediate Risk N=35,943 (Q2-4)	High Risk N=11,981 (Q5)
Age, yrs (mean)	68	66	64
Male sex (%)	71	72	69
Smoking (%)	14	18	19
Diabetes (%)	51	49	48
Hypertension (%)	85	83	83
ASCVD status (%)			
No ASCVD	38	19	8
ASCVD w/o event	10	11	12
ASCVD w/ event	52	70	80

All p<0.001

CORONARY EVENTS BY CAD PRS IN THE OVERALL POPULATION

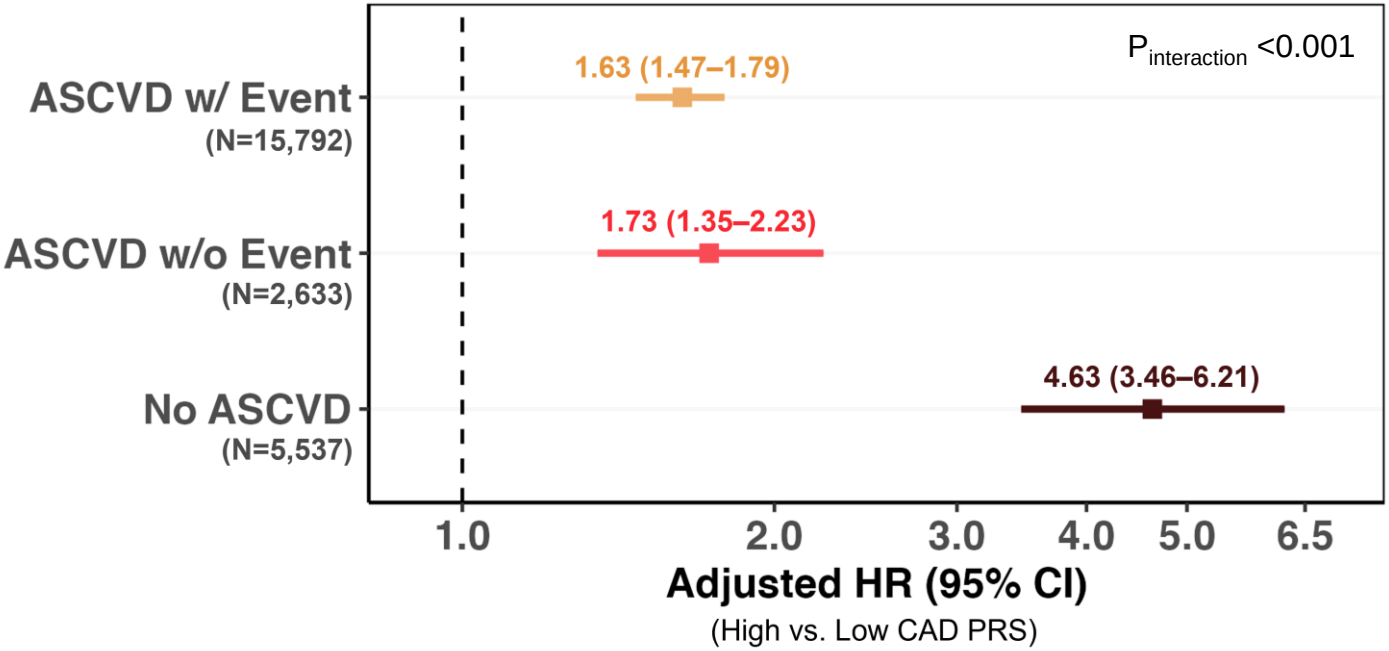


High risk — **HR_{adj} 2.08** (1.91–2.27), p<0.001

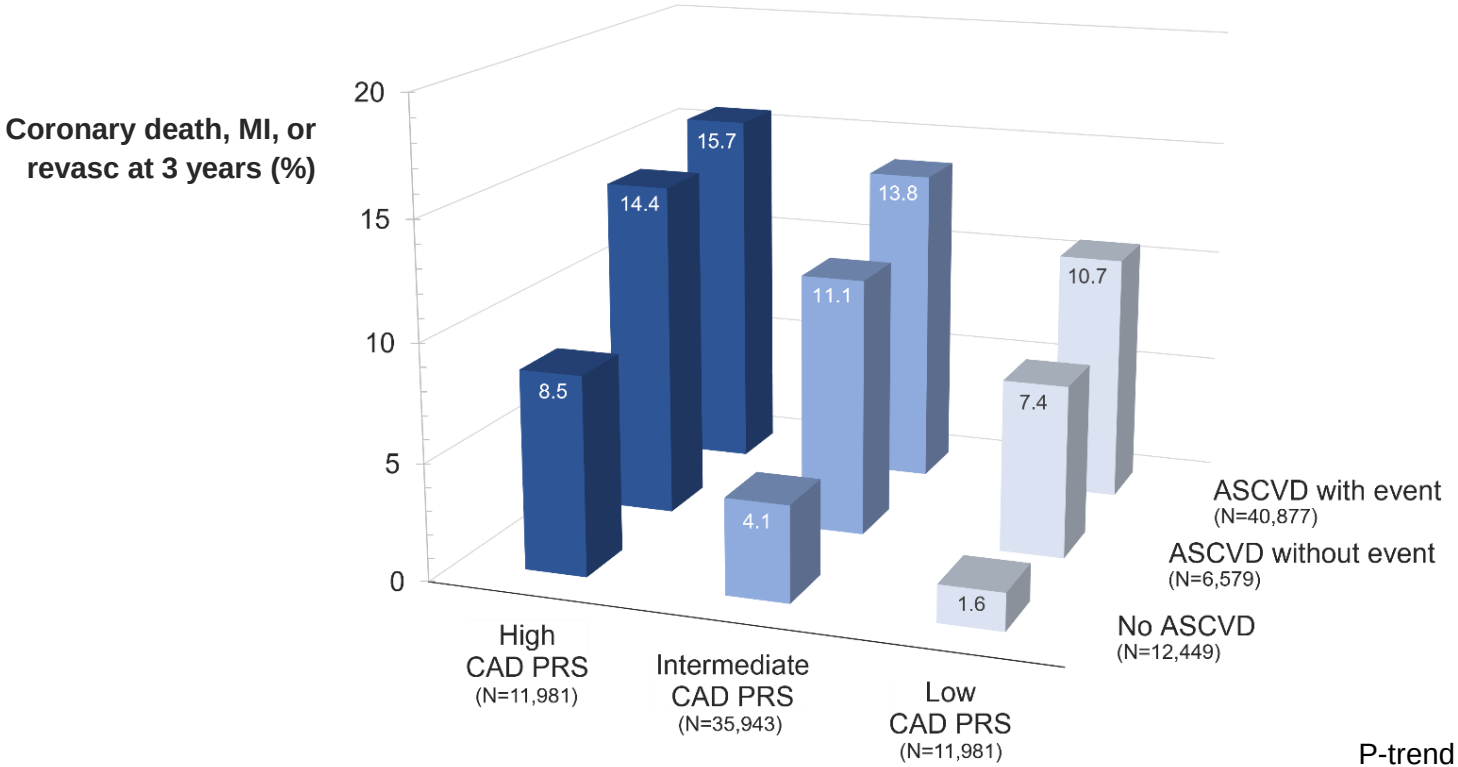
Intermediate — **HR_{adj} 1.59** (1.47–1.71), p<0.001

Low risk — Reference group

CORONARY EVENTS FOR HIGH VS. LOW CAD PRS, STRATIFIED BY ASCVD CATEGORY



ABSOLUTE RATES OF CORONARY EVENTS BY CAD PRS AND ASCVD CATEGORY



P-trend <0.001 for all rows

CONCLUSIONS

CAD PRS refined the prediction of coronary events across the spectrum of ASCVD, and the risk gradient was strongest in patients without established ASCVD

Application of CAD PRS may be most useful in patients without ASCVD to help focus preventive measures