Performance of a Genome-Wide Polygenic Risk Score to Predict Coronary Events in Patients with Diabetes without prior Myocardial Infarction

Nicholas A. Marston, MD[1,2], Carolina Roselli, MS[3], Francesco Nordio, PhD[1], Yared Gurmu, PhD[1], Steven A. Lubitz, MD, MPH[4], Ben M. Scirica, MD, MPH[1,2], Deepak L. Bhatt, MD, MPH[2], Itamar Raz, MD[5], Mosenzon Ofri, MD[6], Daniel Lindholm, MD[7], Eugene Braunwald MD[1,2], Marc S. Sabatine, MD, MPH[1,2]*, Patrick T. Ellinor, MD, PhD[3,4]*, Christian T. Ruff, MD, MPH[1,2]*.

*Contributed equally to this work

[1]TIMI Study Group, Boston, MA, USA; [2]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [3]Cardiovascular Disease Initiative, Broad Institute of MIT and Harvard Cambridge, MA, USA; [4] Cardiovascular Research Center, Massachusetts General Hospital, Boston, MA, USA; [5]Diabetes Medical Center, Tel Aviv, Jerusalem, Israel; [6]Hadassah University Hospital, Jerusalem, Israel; [7]Uppsala Clinical Research Center, Uppsala, Sweden

AHA Scientific Meeting
Polygenic Risk Scores
Sunday November 17, 2019

Background

- Patients with diabetes have an increased risk of myocardial infarction.
- Novel genetic tools have been developed to detect incident CAD using a genome-wide polygenic risk score.
- The predictive value of genetics in predicting coronary events specifically in patients with diabetes has not been established.

Genome-Wide Polygenic Risk Score

nature genetics

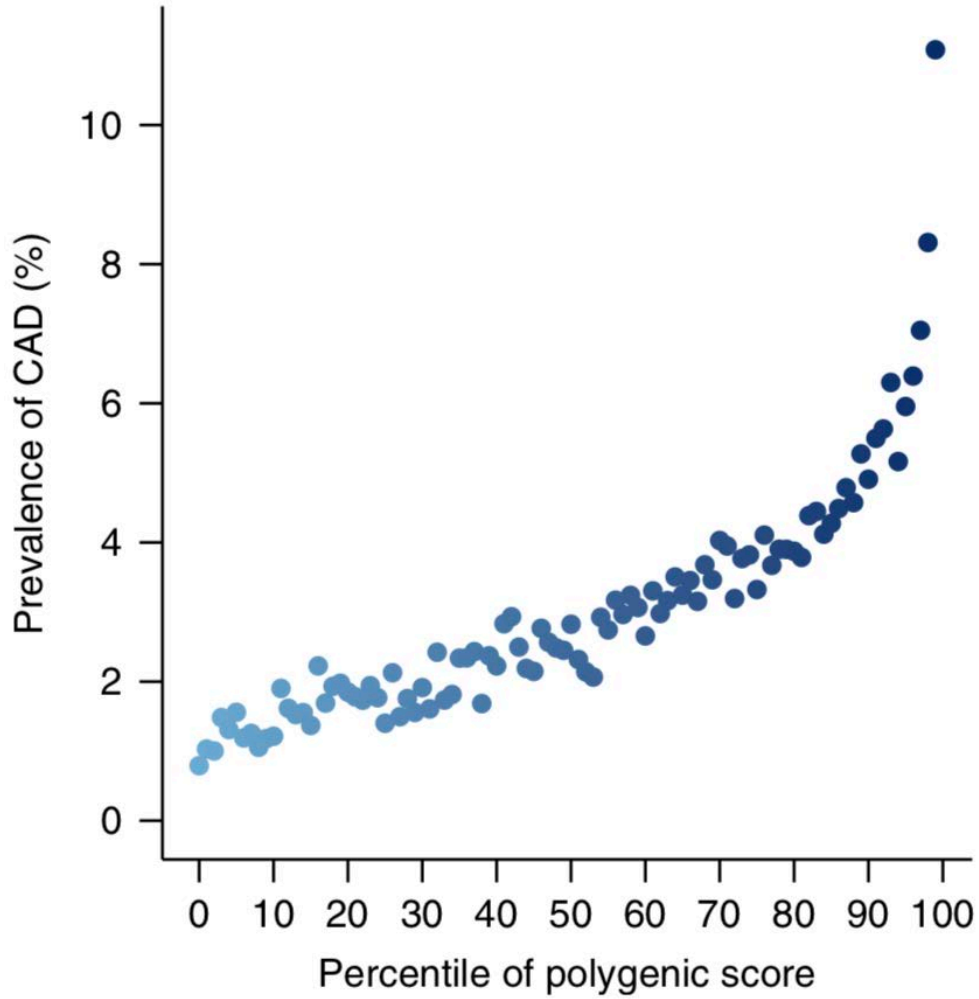
LETTERS

https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

- Score created to identify risk of incident CAD in the general population
- Gradient of risk across the population, with steep increase in top 10-20%.
- Top 8% at 3-fold greater risk



Khera A, et al. *Nature Genetics*. 2018.

Aims

1) To evaluate the prognostic value of a genome-wide polygenic risk score in the prediction of coronary events in patients with diabetes without prior MI

2) To determine whether genetic risk prediction is independent of traditional atherosclerotic clinical risk factors

Methods

- The SAVOR-TIMI 53 trial was a multinational, randomized, double-blind, placebo-controlled trial testing the safety of saxagliptin in patients **with diabetes**.
- We performed a nested cohort study of 4,090 unrelated European-ancestry patients who consented for genetic analysis and had **no history of myocardial infarction.**
- The 6 million SNP GPS was calculated using the genotype dosage for each allele, multiplied by its weight, and then summed across all variants.
- Centrally adjudicated outcome: **CHD death, MI, coronary revascularization, angina**
- Patients in the genetic cohort were followed for a median of 2 years.

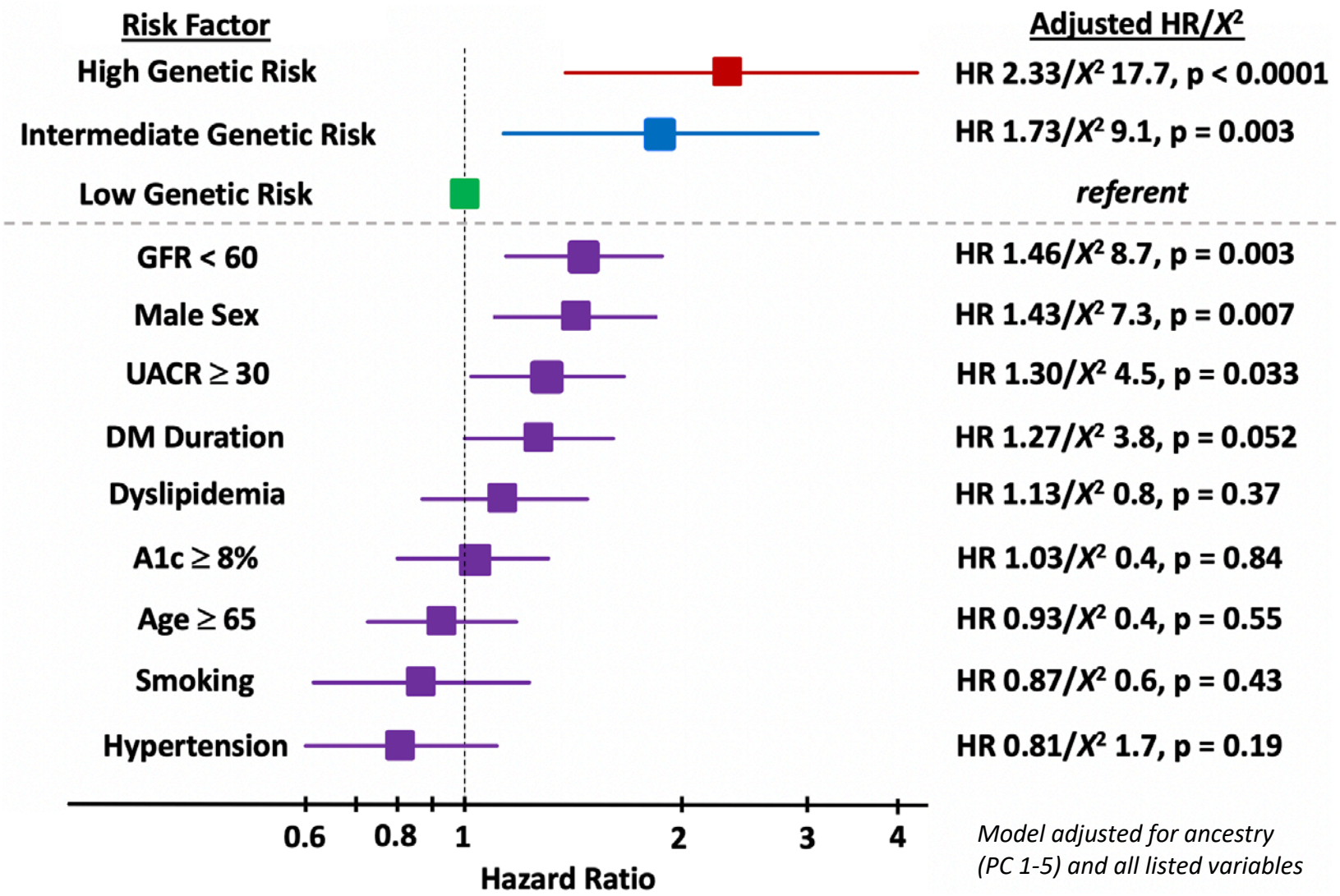
Statistical Analysis

- Patients were stratified into genetic risk categories based on their genetic risk quintiles:
  - **Low Genetic Risk = quintile 1**
  - **Intermediate Genetic Risk = quintiles 2-4**
  - **High Genetic Risk = quintile 5**
- Cox proportional hazards regression was used to calculate adjusted hazard ratios (HR) across genetic risk categories, using the low genetic risk category as a reference.
- Analyses were adjusted for age, sex, ancestry, and atherosclerotic clinical risk factors.

Baseline Characteristics

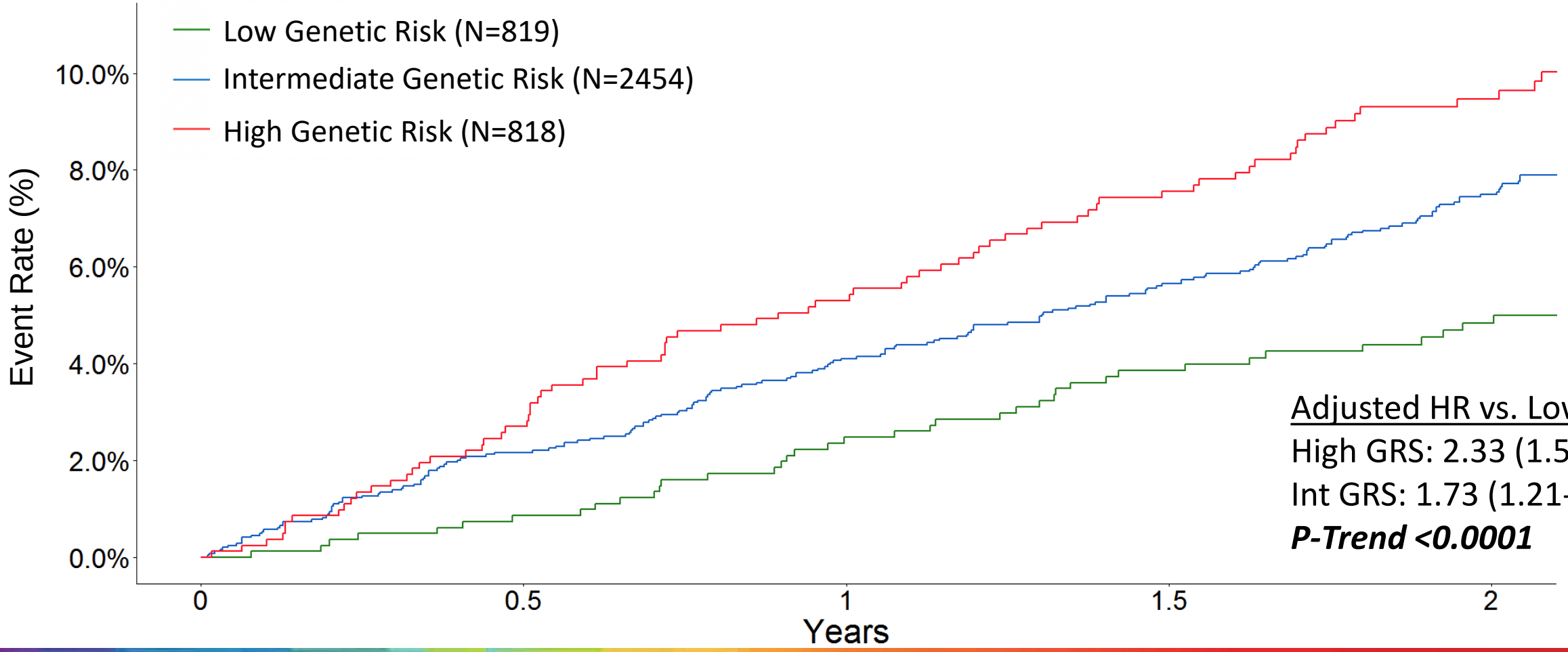
	Low (N=819)	Intermediate (N=2454)	High (N=818)	P-value
Demographics				
Age-yrs (median)	67	66	66	0.03
Female sex (%)	34	36	39	0.09
Medical History				
DM duration-yrs (median)	14	15	13	0.384
Current smoker (%)	10	10	10	0.076
Hypertension (%)	87	85	85	0.302
Dyslipidemia (%)	69	71	73	0.166
Glycated hemoglobin - (median)	7.4	7.4	7.4	0.134
eGFR < 60 mL/min (%)	34	29	26	0.002
UACR > 30 (%)	36	32	31	0.038

RESULTS



Model adjusted for ancestry (PC 1-5) and all listed variables

RESULTS


CHD Death, MI, Coronary Revascularization, Angina
Low Genetic Risk (N=819)
Intermediate Genetic Risk (N=2454)
High Genetic Risk (N=818)
Event Rate (%)
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
0
0.5
1
1.5
2
Years
Adjusted HR vs. Low GRS
High GRS: 2.33 (1.57-3.46)
Int GRS: 1.73 (1.21-2.46)
P-Trend <0.0001

RESULTS

Event Rates for Individual Outcomes by Genetic Risk Category

	Low (N=819)	Intermediate (N=2454)	High (N=818)	P-Trend
MI/CHD Death	2.4%	3.9%	4.8%	<0.001
Coronary Revascularization	2.4%	3.6%	4.9%	<0.001
Angina	0.6%	1.0%	1.7%	<0.001

Limitations

- This was a subgroup analysis of a clinical trial population and therefore the results may not be generalizable to all populations.
- This study focused on patients of European ancestry because this is where the majority of GWAS data is derived.
- Standard cut-points for high genetic risk have not been developed in the general population. Therefore, genetic risk is relative to this study cohort.
  - In this higher risk population, some patients are forced into lower risk categories than if compared to general population, which may have attenuated the gradient of risk seen.

Summary

1. In patients with diabetes without prior myocardial infarction, a polygenic risk score is a strong independent predictor of coronary events that has prognostic value beyond established clinical risk factors.
2. Patients in the top 20% of the risk score have a nearly 2.5-fold higher risk of coronary events, stronger than other traditional clinical risk factors.
3. Future efforts should be aimed at testing whether increased genetic risk is modifiable by cardiometabolic therapies.

Thank you!

American Heart Association.
Scientific Sessions