SUPPLEMENTARY DATA

Supplementary Table S1. List of 204 independent CAD SNPs, representing 160 CAD loci, with year of discovery and their inclusion/exclusion in different genetic risk score (GRS). [Excel file]

Supplementary Table S2. List of 204 CAD SNPs and their associations with history of CAD (adjusted for sex and age). [Excel file]

Supplementary Table S3. Association of the GRS with incident of different cardiovascular outcomes. (Cox Hazards Model adjusted for age, sex, assignment to ACCORD treatment arms, clinical network, platform genotype and principal components of population structure).

Cardiovascular Outcomes in ACCORD trial	*No. of subjects/ No. of events*	P	HR (per SD increase in GRS)	95% lower C.I.	95% upper C.I.
Major CAD events (MCE – Fatal CAD events, non-fatal myocardial infarction and unstable angina).	5360/675	$4x10^{-10}$	1.27	1.18	1.37
Cardiovascular mortality, non-fatal myocardial infarction or stroke (Accord Primary Outcome)	5360/550	$9x10^{-6}$	1.21	1.11	1.31
Non-fatal Myocardial Infarction	5360/368	$1x10^{-4}$	1.22	1.10	1.35
Cardiovascular Mortality	5360/144	$6x10^{-3}$	1.26	1.07	1.48
Expanded: Accord Primary Outcome plus any revascularization procedure and hospitalization for congestive heart failure.	5360/1357	$72x10^{-9}$	1.17	1.11	1.23

SUPPLEMENTARY DATA

Supplementary Table S4. Exploratory analysis for the association between GRS and incident MCE in subjects self-reported as non-whites (Associations were tested by means of Cox Hazards Model adjusted for age, sex, assignment to ACCORD treatment arms, clinical network, platform genotype and principal components of population structure.

Self reported Race-Ethnic group	*No. of subjects/ No. of events*	P	HR (per SD increase in GRS)	95% lower C.I.	95% upper C.I.
Whites	5360/675	$4x10^{-10}$	1.27	1.18	1.36
African-Americans	1398/122	$6x10^{-1}$	0.95	0.79	1.14
Hispanics	529/61	$2x10^{-1}$	1.20	0.92	1.57
Asians	469/25	$1x10^{-3}$	1.98	1.31	2.99

Supplementary Table S5. GRS effect on expanded coronary events (MCE + coronary revascularization, Nummber of events =276) over follow-up in the ORIGIN trial.

	MODEL 1 (N=1931)		**MODEL 2 (N=1931)**		**MODEL 3 (N=1931)**	
	H.R. (95% C.I.)	P	H.R. (95% C.I.)	P	H.R. (95% C.I.)	P
Per Risk Allele		4x10-6		2x10-5		2x10-5
Per S.D.	1.32 (1.18-1.49)	4x10-6	1.30 (1.15-1.47)	2x10-5	1.30 (1.15-1.46)	2x10-5
By Tertile of GRS						
Low Risk	Ref		Ref		Ref	
Medium Risk	1.47 (1.07-2.02)	2x10-2	1.41 (1.02-1.94)	4x10-2	1.41 (1.03-1.95)	3x10-2
High Risk	1.88 (1.38-2.55)	6x10-5	1.79 (1.32-2.43)	2x10-4	1.77 (1.31-2.41)	2x10-4

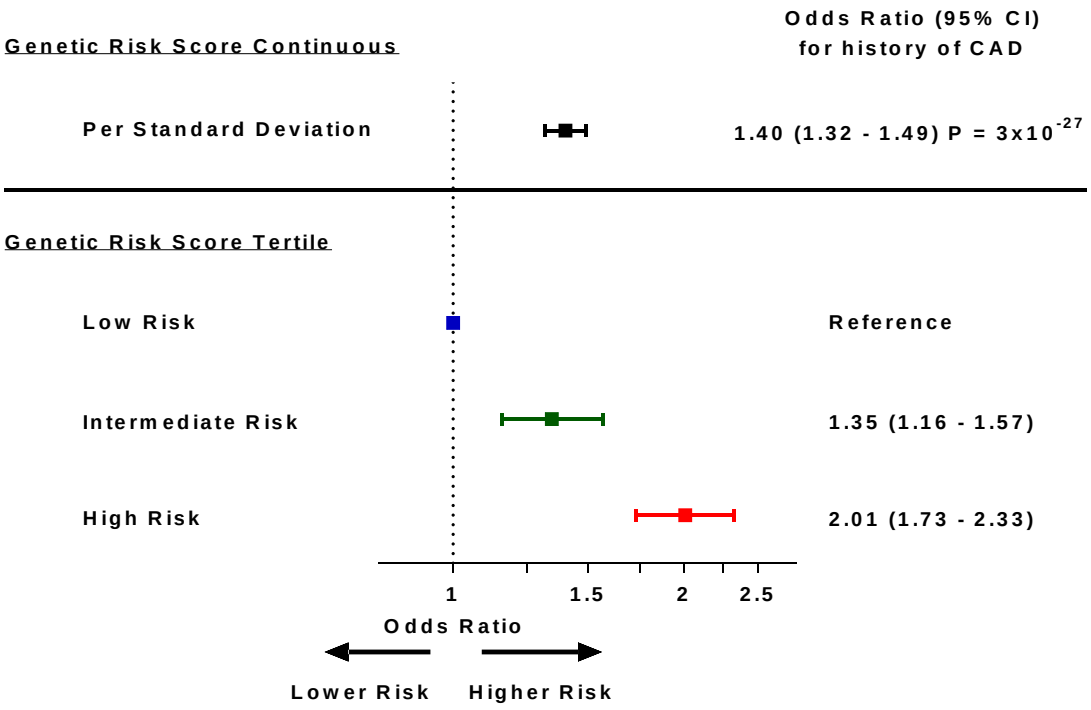
Model 1= adjusted for study variable (treatment arms, and principal components of population structure) plus age and sex; Model 2= Model 1 covariates plus history of CAD; Model 3= Model 2 covariates plus AHA/ACC-ASCVD risk score.

SUPPLEMENTARY DATA

Supplementary Table S6. Differences of GRS association with MCE across the population stratified on-trial glycemic control. On-trial glycemic control was defined in each subjects as the average of all measures of HbA1c available from baseline up to censoring time or up to MCE event). The on-trial median level of HbA1c was 7.25% (while it was 8% at baseline).

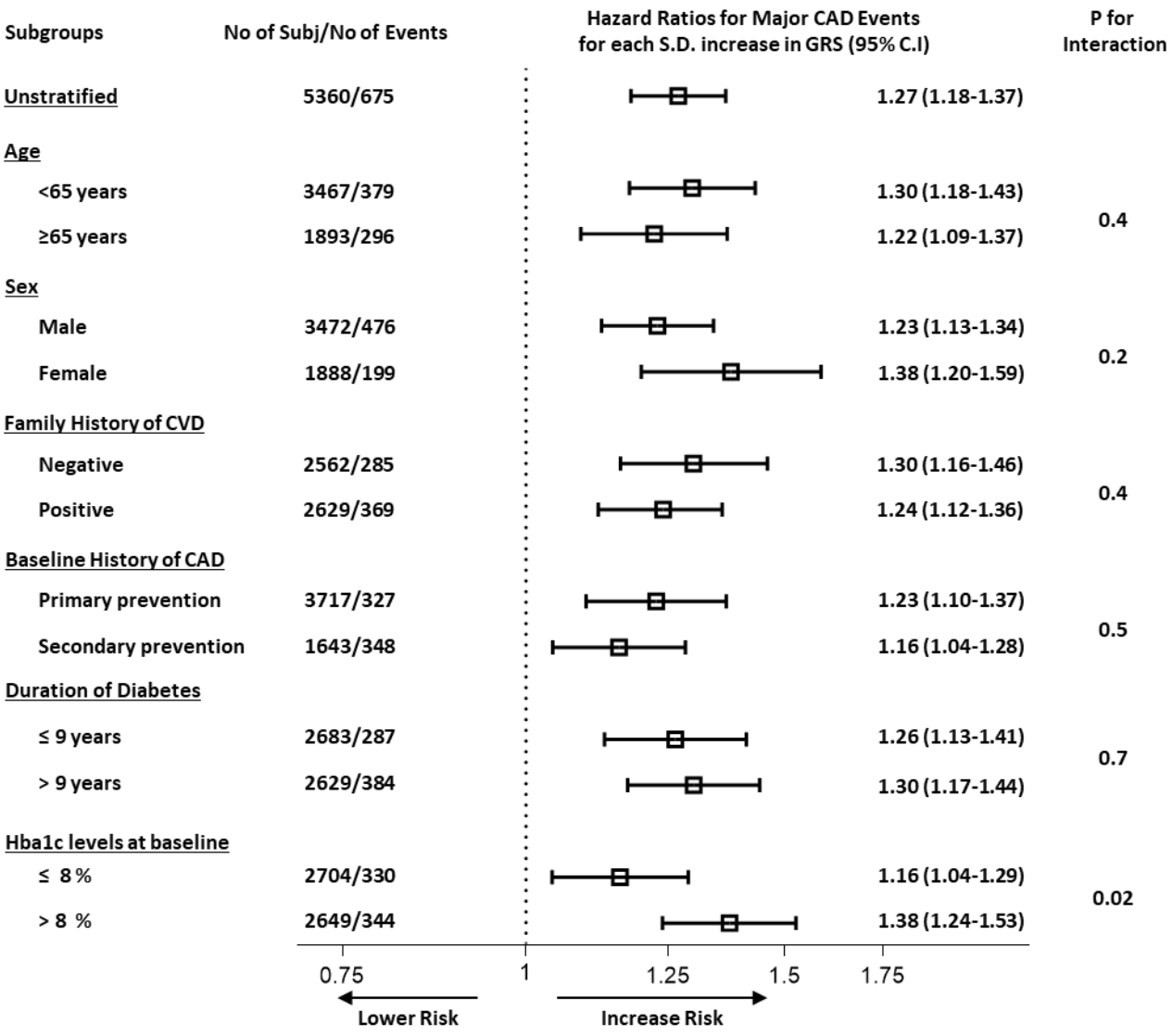
Groups	Num/Ev	HR (95% C.I.)	P for interaction
Entire population			
HbA1c <= 8%	4506/517	1.27 (1.17-1.38)	0.86
HbA1c > 8%	854/158	1.29 (1.10-1.51)	
HbA1c <= 7.25%	2678/269	1.27 (1.13-1.43)	0.84
HbA1c > 7.25%	2682/406	1.28 (1.16-1.41)	
Stratified analysis			
Standard arm			
HbA1c <= 7.25%	604/70	1.11 (0.88-1.39)	0.24
HbA1c > 7.25%	2089/294	1.25 (1.11-1.40)	
Intensive arm			
HbA1c <= 7.25%	2074/199	1.34 (1.16-1.54)	0.83
HbA1c > 7.25%	593/112	1.34 (1.12-1.61)	

Supplementary Figure S1. **GRS association with history of CAD at baseline.**



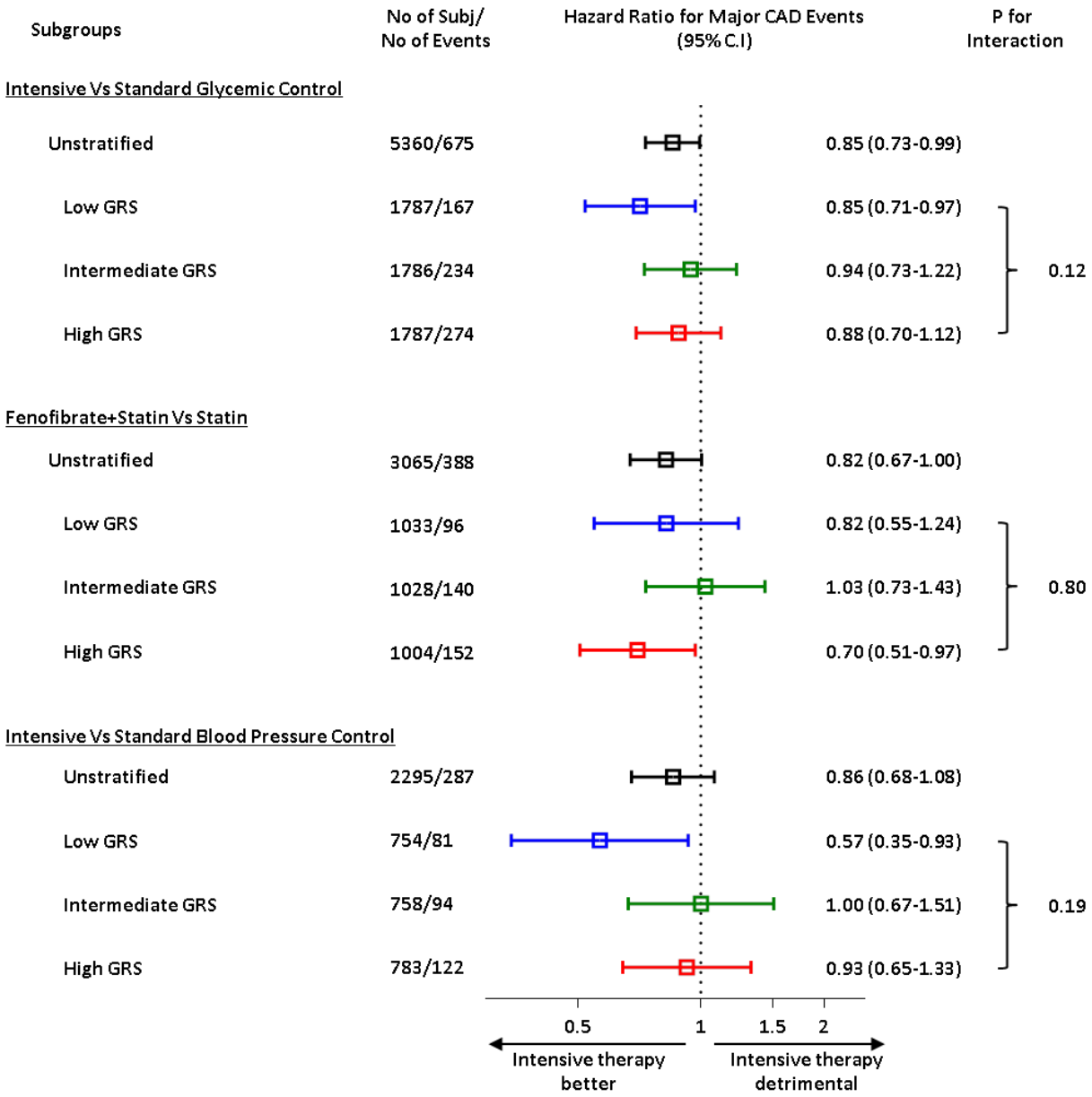
SUPPLEMENTARY DATA

Supplementary Figure S2. Association of GRS with MCE according to baseline participants' clinical characteristics.



SUPPLEMENTARY DATA

Supplementary Figure S3. Effect of different interventions in ACCORD clinical trials according to Genetic Risk Score Tertile



SUPPLEMENTARY DATA

Supplementary Figure S4. **Improvement in reclassification and discrimination of future MCE using the 2010-, 2013- and 2017- updated list of CAD loci into different Genetic Risk Score**. Receiver Operating Characteristic curves for the predictive performance of MCE using the GRS (green), clinical predictors (history of CAD, AHA-ACC ASCVD risk score, age, sex and ACCORD study covariates) (blue), or the combination of them (red) in ACCORD (number of subjects included in the analysis = 5322, Events= 667).