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Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting

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Abstract

Background—Relative risk reduction with statin therapy has been consistent across nearly all subgroups studied to date. However, in analyses of two randomized controlled primary prevention trials (ASCOT and JUPITER), statin therapy led to a greater relative risk reduction among a subgroup at high genetic risk. Here, we sought to confirm this observation in a third primary prevention randomized controlled trial. Additionally, we assessed if those at high genetic risk had a greater burden of subclinical coronary atherosclerosis.

Methods—We studied participants from a randomized controlled trial of primary prevention with statin therapy (WOSCOPS, n=4,910) and two observational cohort studies (CARDIA and BioImage, n=1,154 and 4,392). For each participant, we calculated a polygenic risk score (PRS) derived from up to 57 common DNA sequence variants previously associated with coronary heart disease (CHD). We compared the relative efficacy of statin therapy in those at high genetic risk (top quintile of PRS) versus all others (WOSCOP)S as well as the association between the PRS and coronary artery calcification (CARDIA) and carotid artery plaque burden (BioImage).

Results—Among WOSCOPS trial participants at high genetic risk, statin therapy was associated with a relative risk reduction of 44% (95% CI, 22%–60%; $P < 0.001$) whereas in all others, relative risk reduction was 24% (95% CI 8%–37%; $P = 0.004$) despite similar LDL cholesterol lowering. In a study-level meta-analysis across the WOSCOPS, ASCOT, and JUPITER primary prevention, relative risk reduction in those at high genetic risk was 46% versus 26% in all others (P for heterogeneity = 0.05). Across all three studies, the absolute risk reduction with statin therapy was 3.6% (95% CI, 2.0%–5.1%) among those in the high genetic risk group and was 1.3% (95% CI, 0.6%–1.9%) in all others. Each standard deviation increase in the polygenic risk score was associated with 1.32-fold (95% CI, 1.04–1.68) greater likelihood of having coronary artery calcification and 9.7% higher (95% CI, 2.2–17.8%) burden of carotid plaque.

Conclusions—Those at high genetic risk have a greater burden of subclinical atherosclerosis and derive greater relative and absolute benefit from statin therapy to prevent a first CHD event.

Clinical Trial registration—WOSCOPS was carried out and completed prior to the requirement for clinical trial registration. BioImage: NCT00738725 (https://www.clinicaltrials.gov/ct2/show/NCT00738725). CARDIA: NCT00005130 (https://clinicaltrials.gov/ct2/show/NCT00005130).

Keywords

primary prevention; statin; human genetics; genetic polymorphism; and coronary artery calcification

INTRODUCTION

Coronary heart disease (CHD) is a complex, chronic disease responsible for about 7 million deaths worldwide in 2010.[1] Statin therapy reduces the risk of a first coronary event.[2, 3] Effect size as measured by relative risk reduction is approximately 20% per 1.0 mmol/L reduction of low density lipoprotein (LDL) cholesterol and has been consistent across nearly all subgroups defined by clinical and biochemical measures.[2, 4] However, if statin therapy was more efficacious in one subgroup versus another, this might impact decisions regarding who gets prescribed statin therapy in the primary prevention setting.

We recently reported that those at high genetic risk, defined as the top quintile of a 27-SNP polygenic risk score for CHD, derived greater *relative risk reduction* from statin therapy compared with all others.[5] In two primary prevention trials (ASCOT-LLA: Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm[6] and JUPITER: Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin[7]), this higher relative benefit from statin therapy was observed despite similar levels of LDL cholesterol lowering between those at high genetic risk and all others.

The present study had two main goals: first, to test in a third statin trial if statin treatment confers a greater relative risk reduction for a first coronary event in those at high genetic risk, as assessed by an expanded 57-SNP polygenic risk score, compared to all others; second, to test if there is a greater burden of subclinical coronary atherosclerosis present in those at high genetic risk compared to all others.

METHODS

Cohort Descriptions

The WOSCOPS (West of Scotland Coronary Prevention Study) trial has been described previously.[8, 9] In brief, WOSCOPS was a randomized controlled trial of 6,595 men (45–64 years) with hypercholesterolemia but without a history of myocardial infarction, allocated to pravastatin 40mg daily versus placebo to prevent coronary events. Genetic data were available in 4,892 men. Long-term WOSCOPS results beyond the study's end were included to assess the durable effects of primary preventive statin therapy by genetic risk. Results were also available from a prior analysis[5] that included a subset of 6,978 individuals with genetic data from ASCOT-LLA, a randomized trial of atorvastatin 10mg daily versus placebo in those with hypertension but without cardiovascular disease, and 8,769 individuals with genetic data from JUPITER, a randomized trial of rosuvastatin 20mg daily versus placebo in those with no history of cardiovascular events but elevated C-reactive protein.

In two observation cohorts (CARDIA and BioImage), we explored a potential reason for the greater clinical benefit of statin therapy in those at high genetic risk. We hypothesized that individuals at high genetic risk carried a greater burden of subclinical atherosclerosis. We assessed the association of a high genetic risk status with subclinical atherosclerosis in two vascular beds in those without clinical CHD. The CARDIA (Coronary Artery Risk Development in Young Adults) study (NCT00005130) is an observational study of cardiovascular risk factors in 5,115 young adults (18–30 years at baseline, 1989–1990) as

previously described.[10, 11] Of these participants, 1,154 European ancestry individuals without CHD at baseline, available genetic data and coronary arterial calcification (CAC) assessment at the 15-year follow-up were included in analyses. The BioImage study (NCT00738725) is a multi-ethnic, observational study aimed at characterizing subclinical atherosclerosis in 6,699 US adults (55–80 years at baseline, 2008–2009) at risk for, but without, clinical atherosclerotic cardiovascular disease.[12, 13] As current genome-wide association effect estimates for coronary heart disease are most robust in those of European ancestry[14], we focused on the 4,929 individuals of European ancestry. Of those individuals, 4,392 with both genetic data available and carotid plaque assessment were included in analyses. In WOSCOPS, CARDIA, and BioImage, participants were not screened for familial hypercholesterolemia, a monogenic disorder associated with increased risk of premature CHD events. Each trial was approved by institutional review boards, all subjects gave their informed consent, and the procedures that were followed were in accordance with institutional guidelines.

Polygenic Risk Score

Genome-wide association analyses have identified 67 single nucleotide polymorphisms (SNPs) across the genome independently associated with CHD (Supplementary Table 1).[14–16] We recently showed that an expanded set of SNPs compared to a polygenic risk score comprised of 27 SNPs provided modestly improves risk discrimination.[17] Fifty-seven of these variants were genotyped among WOSCOPS participants using the Illumina Metabochip[18] and included in analyses. Thirteen variants were directly genotyped among CARDIA participants using the Affymetrix Human SNP Array 6.0 and another 25 proxy variants available through statistical imputation. CARDIA genotypes were downloaded from the NIH dbGAP data repository (accession phs000613.v1.p2). Fifty-nine variants were directly genotyped among BioImage participants using the Illumina HumanExome Beadchip[19] and an additional four proxy variants ($r^2 > 0.8$) available through statistical imputation.

A polygenic risk score was constructed by weighting the total number of risk alleles by their effects (log of the odds ratios) of CHD risk from the published literature. Incremental scores from missing genotypes in individuals were imputed based on the allele frequency in each cohort. To account for the differences in the numbers of variants per cohort, a normalized polygenic risk score (mean = 0, standard deviation = 1) was created per cohort (Supplementary Figure 1).

Outcomes

The primary outcome for the WOSCOPS analysis was nonfatal myocardial infarction or death from CHD.[8] In WOSCOPS we also studied change in LDL cholesterol from baseline; on-treatment LDL cholesterol was obtained one year after study drug initiation.

An exploratory analysis focused on subclinical atherosclerosis - total CAC quantity by the Agatston method in CARDIA and total carotid plaque burden in BioImage.[20] In the CARDIA study, CAC was assessed by electrocardiographic-gated electron beam CT (Imatron C-150, GE Imatron, San Francisco, CA) or multidetector CT (GE LightSpeed, GE

Healthcare, Little Chalfont, UK; or Siemens VZ, Siemens Healthcare, Erlangen, Germany) at the 15 year-follow-up (33–45 years, 2000–2001).[11] In BioImage, carotid plaque was ascertained using the Philips iU22 carotid ultrasound system (Philips Healthcare, Bothell, Washington) interpreted by at the University of Copenhagen (Copenhagen, Denmark) as described previously.[12, 21] If carotid plaque was present based on local carotid intima media thickness, it was quantified using the Philips QLAB-VPQ software and carotid plaque burden was the sum of all areas of carotid plaque from the proximal common carotid artery to the distal internal carotid artery.

Statistical Analysis

Within each cohort, we defined high genetic risk as individuals in the top quintile of the distribution of polygenic risk score. Among placebo-treated participants in WOSCOPS, we first used a Cox proportional hazards model to determine if polygenic risk score (per standard deviation, and high genetic risk versus all others) associated with risk of developing incident nonfatal myocardial infarction or death due to CHD. The models were adjusted for age, sex, diabetes mellitus status, smoking status, baseline LDL cholesterol, baseline HDL cholesterol, systolic blood pressure, antihypertensive medication status, and family history of myocardial infarction or stroke. Sex was not used as a covariate in WOSCOPS as all participants were male. Higher order terms for PRS were not significantly associated with outcome and the linear assumption was not violated. Next, we stratified participants in two groups (high genetic risk, all others) and tested the difference in relative risk reduction with statin therapy versus placebo in each subgroup. Analysis of Schoenfeld residuals demonstrated similar proportionality across the follow-up time.

To determine the confidence interval of the absolute risk reduction from statin therapy for each polygenic risk score group, we calculated the standard error of the absolute reduction for each group as $\mathrm{SE}_{\mathrm{ARR}} = \sqrt{\left(\frac{a}{n_1}\right)\left(1-\frac{a}{n_1}\right)/n_1 + \left(\frac{c}{n_2}\right)\left(1-\frac{c}{n_2}\right)/n_2}$ where a is statin-treated individuals who had events, n_1 is all statin-treated individuals, c is placebo-treated individuals who had events, and n_2 is all placebo-treated individuals. A chi square test for heterogeneity was used to test the differences in absolute risk reduction from statins between those at high genetic risk versus all others.

In order to summarize all currently available data across primary prevention trials, we performed a study-level meta-analysis combining the present study results with those published earlier from the JUPITER and ASCOT-LLA trials[5]. The analyzed outcome was the primary outcome for each primary prevention trial. Effect estimates for high genetic risk versus all others was combined using a fixed-effects meta-analysis. A chi-square test for heterogeneity was used to compare the proportional risk reductions between the meta-analyzed effect estimates as previously described.[22]

In two population-based cohort studies, we tested whether prevalent subclinical atherosclerosis differed between those at high genetic risk versus all others. Given the younger age of CARDIA participants and a consequential lower prevalence of individuals with any CAC, a dichotomous outcome variable (CAC>0 versus CAC=0) was used in in

CARDIA. We determined whether two predictors (polygenic risk score as a continuous variable or a dichotomized high genetic risk versus all others) was associated with CAC using multivariate logistic regression in CARDIA. We similarly tested whether polygenic risk score was associated with prevalent carotid plaque in BioImage. The outcome variable was the natural log transformation of total bilateral carotid plaque + 1. The models were adjusted for age, sex, diabetes mellitus status, smoking status, LDL cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication status, and family history of CHD.

All tests were two-tailed with alpha threshold of 0.05. Statistical analyses were conducted in R v3.2.1 (R Foundation, Vienna, Austria).

RESULTS

The mean length of follow-up for WOSCOPS participants in trial was 4.8 years (SD, 0.7 years) for both placebo and statin groups, and out of trial was 8.7 years (SD, 2.6 years) in the placebo group and 8.9 years (SD, 2.4 years) in the statin-treated group; baseline characteristics by genetic risk (Table 1) and by randomized treatment groups (Supplementary Table 2) are presented. Individuals at high genetic risk (top quintile of polygenic risk scores) were more likely to report a family history of CHD (7% vs 5%; $P = 0.004$) and were less likely to be current smokers (40% vs 45%, $P = 0.006$) compared to all others whereas there was no difference in other baseline characteristics including treatment allocation. In placebo-treated WOSCOPS participants, predicted 10-year risks for atherosclerotic cardiovascular disease (calculated using ACC/AHA pooled cohort equations) were similar across quintiles of polygenic risk score (ACC/AHA pooled cohort equations) were similar (Supplementary Table 3).

Among those allocated to placebo, those at high genetic risk were at increased risk for a first CHD event (HR 1.62; 95% CI, 1.29–2.05; $P < 0.001$) after adjustment for traditional cardiovascular risk factors (Table 2) (Supplementary Figure 2, Supplementary Table 4). Furthermore, among placebo-treated participants in WOSCOPS, a one SD increase in polygenic risk score was associated with a 25% increased risk in incident CHD (HR 1.25; 95% CI, 1.20–1.35, $P < 0.001$). Association of polygenic risk score with CHD did not vary between those with and without a self-reported family history of CHD (P for interaction = 0.47) (Supplementary Table 5). The mean baseline LDL cholesterol was 192 (SD, 17.5) mg/dl in the high genetic risk group and 192 (SD, 17.3) mg/dl among all others ($P = 0.4$).

Among those at high genetic risk, statin therapy reduced risk for a first CHD event by 44% (HR 0.56; 95% CI, 0.40–0.78; $P < 0.001$) whereas statin therapy reduced risk by 24% among all others (HR 0.76; 95% CI, 0.63–0.92; $P = 0.004$). Absolute risk reduction with statin therapy was 7.9% (95% CI, 3.4%–12.4%) among those at high genetic risk whereas it was 2.7% (95% CI, 0.7%–4.7%) among all others during the 13-year follow-up (P for heterogeneity = 0.04) (Figure 1). Thus, the number needed to treat (NNT) to prevent one coronary event was 13 among high genetic risk participants and 38 among all others (Table 3). The degree of LDL cholesterol reduction achieved with statin treatment was similar in

the high genetic risk group (−44 mg/dL, 22.9% reduction) compared to all others (−43 mg/dL, 22.2% reduction) ($P = 0.52$).

We performed a meta-analysis combining the results of this study with those published earlier from JUPITER and ASCOT-LLA (5). With all three studies combined, statin therapy reduced risk for a first CHD event by 46% (HR 0.54; 95% CI, 0.41–0.71; $P < 0.001$) whereas statin therapy reduced risk by 26% among all others (HR 0.74; 95% CI, 0.63–0.86; $P < 0.001$) (P for heterogeneity = 0.05) (Figure 2). Across all three studies, the absolute risk reduction with statin therapy was 3.6% (95% CI, 2.0%–5.1%) among those in the high genetic risk group and was 1.3% (95% CI, 0.6%–1.9%) in all others. This translates to a NNT to prevent one coronary event of 28 (95% CI, 20–50) in the high genetic risk score group and of 80 (95% CI, 52–175) in all others.

We tested if individuals at high genetic risk for CHD were more predisposed to developing subclinical atherosclerosis. Baseline characteristics of the CARDIA Study (ages 32–47 years at the time of CAC ascertainment) and the BioImage Study (ages 55–80 years) are presented in Supplementary Table 6. In CARDIA, for every standard deviation increase in polygenic risk score, the multi-variable adjusted odds ratio for CAC presence was 1.32 (95% CI, 1.04–1.68; $P = 0.02$) (Table 4).

In BioImage, for every standard deviation increase in polygenic risk score, there was a 9.7% increase (95% CI, 2.2% to 17.8%; $P = 0.01$) in carotid artery plaque burden. The median carotid plaque burden among those at high genetic risk was 215 mm^2 (IQR, 52 mm^2 to 618 mm^2) compared to 208 mm^2 (IQR: 39 mm^2 to 581 mm^2) among all other participants ($P = 0.02$) (Supplementary Table 7, Supplementary Table 8). Unlike this expanded 57-SNP score, we did not observe an association of a prior restricted 27-SNP score[5] with carotid artery plaque burden (Supplementary Table 9).

DISCUSSION

Among men with hyperlipidemia enrolled in a randomized controlled trial of primary prevention of CHD, statin therapy conferred greater relative benefit among those at high genetic risk when compared with all others. Relative risk reduction with statin therapy was 46% in those at high genetic risk and 26% among all others; this greater relative benefit was seen despite similar levels of LDL lowering by statin therapy in the high genetic risk subgroup compared to all others. Additionally, an expanded 57-SNP score was associated with subclinical atherosclerosis in two vascular beds.

These results permit several conclusions. First, on average, prior trials have shown that degree of LDL cholesterol lowering linearly associates with degree of coronary event risk reduction;[22, 23] however, our data suggests that statins might confer greater relative risk reduction in one subgroup - those at high genetic risk. Across three primary prevention trials, those at high genetic risk have a nearly three-fold lower number needed to treat to prevent one CHD event. In those at high genetic risk, the lower number needed to treat to prevent one CHD event is driven by both an elevated baseline rate of events (1.6-fold greater) as well as a greater relative risk reduction of events from statin therapy.

Large-scale genetic association analyses have expanded the number of SNPs associated with CHD.[14, 16] Compared to initial reports,[24, 25] polygenic risk scores using expanded sets of SNPs show improved discrimination for incident CHD events.[17, 26] We now show that, in the setting of hyperlipidemia, the 57-SNP score remains associated with incident CHD in those with or without a self-reported family history of CHD. Furthermore, although the 57-SNP score does not associate LDL cholesterol level or extent of LDL cholesterol lowering from statins, those with the highest scores still are more likely to experience clinical benefit among those with at least moderate hyperlipidemia.

Second, young and middle-aged asymptomatic individuals at high genetic risk for CHD have a greater burden of subclinical atherosclerosis. An increased number of CHD variants is linked to subclinical atherosclerosis in two vascular beds even after accounting for traditional cardiovascular risk factors. We recently demonstrated a step-wise increase in CAC among middle-aged asymptomatic adults in BioImage.[27] We now extend these findings to a low-risk young cohort of essentially statin-ineligible individuals.

CAC and carotid plaque are both strong predictors of CHD events independent of traditional risk factors.[12, 28, 29] Subclinical atherosclerosis is a highly heritable trait.[30, 31] We and others showed that the genetic architectures of CHD and subclinical coronary atherosclerosis are highly concordant.[32–35] Non-coding genomic variants at 9p21 and 6p24 are strongly associated with both CAC and CHD but do not appear to be associated with traditional risk factors.[14, 32, 35] Furthermore, CHD polygenic risk score is strongly associated with CAC in both a cohort with the presence of traditional risk factors (BioImage)[27] and a younger cohort with a paucity of traditional risk factors (CARDIA). This indicates that lifelong exposure to CHD risk alleles predisposes to both the development of subclinical and clinical atherosclerosis. The association with subclinical atherosclerosis burden may highlight a potential reason why those at high genetic risk derive enhanced clinical benefit from primary preventive statin therapy. Further study is required to compare genetic versus atherosclerosis imaging markers to refine decision-making for initiation of primary preventive therapy with statins.

Third, increased CHD risk conferred by genetics seems to be modifiable. We recently showed that adherence to a healthy lifestyle[27] can modify high genetic risk and now, demonstrate that statin therapy may modify risk as well. Overall, these data may contribute to the conversation regarding statin eligibility in the primary prevention setting. Currently, statin eligibility is determined based on an estimation of absolute 10-year risk from demographic and clinical parameters. Age remains the key determinant of cardiovascular risk estimation.[36] High genetic risk may identify statin candidates to prevent a first myocardial infarction event who otherwise would not have been considered by clinical criteria, a hypothesis that can be tested in more contemporary cohorts with sizeable proportions of statin-ineligible patients. Furthermore, disclosure of genetic risk may motivate greater adherence with statin therapy.[37]

Our analyses have potential limitations. First, the entry criteria in the three randomized controlled trials were different with varying follow-up times. However, there was no significant heterogeneity in effect estimates in the genetic risk groups across clinical trials.

Second, our analyses were performed on individuals of European ancestry. The genetic determinants of CHD and their effects on statin benefit in other ancestries may be different.[38, 39]. Third, in the WOSCOPS trial, we included events beyond trial cessation. However, likely crossover occurring after the termination of the trial would bias results to the null. Finally, the polygenic risk score captures common genetic variation, but about 1 in 200 individuals are affected by a monogenic disease, namely familial hypercholesterolemia, that markedly increases risk for CHD.[40, 41] The clinical utility of a polygenic risk score in those with familial hypercholesterolemia is uncertain.

A key goal of precision medicine is to identify subsets of individuals more likely to have clinical benefit from preventive strategies. We show that a 57-SNP polygenic risk score for CHD can identify individuals 1) at higher risk for developing a coronary event, 2) more likely to experience clinical benefit from preventive statin therapy, and 3) with a greater burden of subclinical atherosclerosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PERSPECTIVE

What is New?

- A recent analysis of primary prevention statin trials surprisingly suggested those at high genetic risk for coronary heart disease (CHD) derive greater relative benefit from statin therapy.
- We now developed an expanded genetic risk score for CHD with 57 SNPs to identify individuals at high genetic risk.
- We now show in an independent study (WOSCOPS) statin therapy was associated with a relative risk reduction of 44% for CHD among those at high genetic risk versus 24% among all others.
- Additionally, we observe that those at high genetic risk have an increased burden of atherosclerosis in both coronary and carotid arteries.

What Are the Clinical Implications?

- Stratifying by genetic risk may identify a subset of adults who have a greater burden of subclinical atherosclerosis and derive the greatest benefit from statin therapy to prevent a first CHD event.

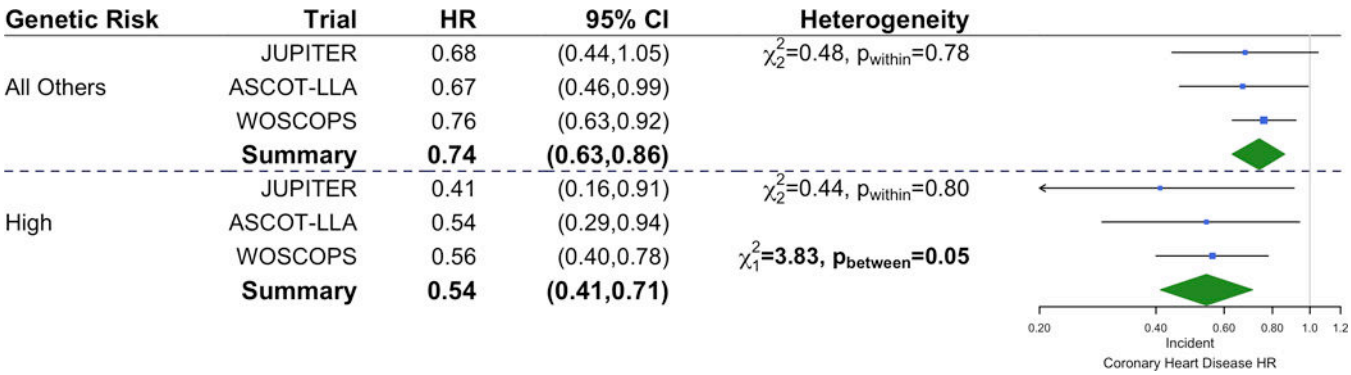

Figure 1. Incident Coronary Heart Disease Events by Statin Therapy and Genetic Risk Group in WOSCOPS

Nonfatal myocardial infarction or death from coronary heart disease rate by randomized treatment group and polygenic risk group in the WOSCOPS trial. Absolute events (and percentage) per individuals in each group is shown at the bottom of the bars. This represents 604 events over 64,031 total patient-years of follow up. The follow up period was 4.8 years (SD 0.7 years) within the trial for both placebo and statin groups, and out of trial was 8.1 years (SD 3.4 years) in the placebo group and 8.4 years (SD 3.0 years) in the statin-treated group.

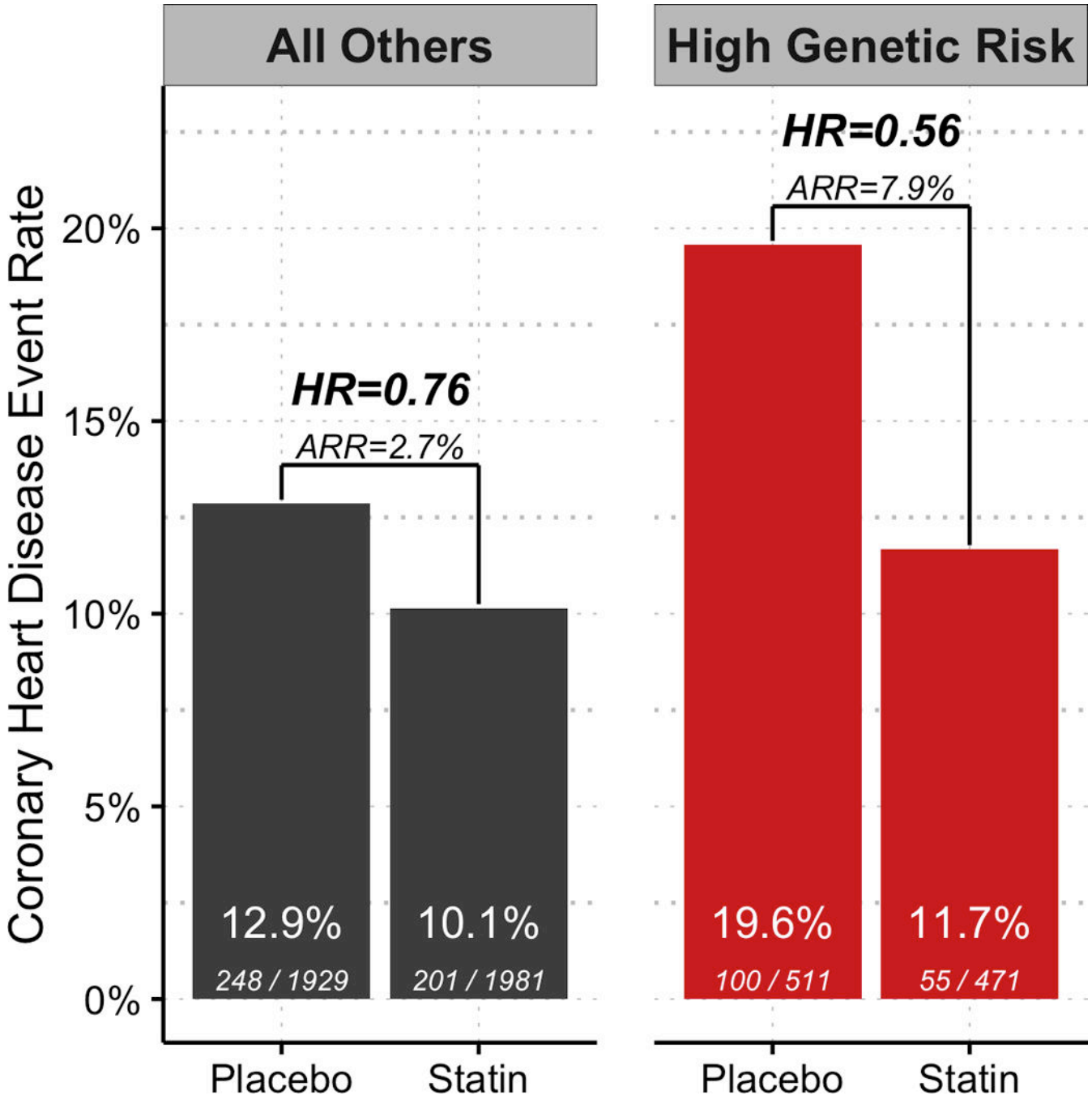

Figure 2. Forest Plot of Incident Coronary Heart Disease After Statin Therapy by Genetic Risk Group in Statin Primary Prevention Trials

The multi-variable adjusted hazard ratios of incident coronary heart disease after statin therapy by genetic risk group are presented for three primary prevention trials. Data from JUPITER and ASCOT-LLA were obtained from prior analyses.[5] Fixed effects meta-analysis was used to estimate the relative effect of statin therapy on incident coronary heart disease across trials for each genetic risk group (*P* for difference = 0.05). CI = confidence interval; HR = hazard ratio.

Table 1

Characteristics of WOSCOPS Participants by Genetic Risk Group

	High Genetic Risk (≥80th percentile polygenic risk score) (n = 979)	All Others (<80th percentile polygenic risk score) (n = 3,913)	*P*
Age, years	54.9 (5.5)	55.2 (5.5)	0.17
Male, %	100	100	-
BMI, kg/m^2	26.1 (3.1)	26.0 (3.2)	0.35
Family history of CHD, %	7	5	0.004
Smoking, %	40	45	0.006
Diabetes mellitus, %	1	1	0.61
Systolic blood pressure, mmHg	135.6 (17.1)	135.5 (17.3)	0.95
Antihypertensive therapy, %	15	14	0.38
Total cholesterol, mg/dl	272 (22.9)	272 (22.6)	0.74
LDL cholesterol, mg/dl	192 (17.5)	192 (17.3)	0.20
HDL cholesterol, mg/dl	44 (9.5)	44 (9.4)	0.41
Triglycerides, mg/dl	160 (70.0)	160 (66.8)	0.92
Statin, %	48	51	0.11
Follow Up, years	13.6 (2.8)	13.6 (2.7)	0.49
Follow Up within trial, years	4.9 (0.7)	4.8 (0.7)	0.17
Follow Up after trial, years	8.7 (2.6)	8.3 (2.5)	0.25

Values are presented as mean (standard deviation) or %. High genetic risk is defined as the top quintile of polygenic risk score. Differences between continuous variables were tested with Student t-tests and categorical variables with chi-square tests.

BMI = body-mass index; CHD = coronary heart disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2

Incident CHD event risk, LDL cholesterol lowering and relative risk reduction of CHD across quintiles of polygenic risk score in WOSCOPS

Polygenic risk score quintile	CHD event risk* HR (95% CI, *P*)	LDL cholesterol reduction after statin mean mg/dl (SD)	Relative risk reduction with statin therapy within each quintile of polygenic risk HR (95% CI, *P*)
Q1	–	−44.7 (1.8)	0.65 (0.44–0.97, *P*=0.035)
Q2	0.83 (0.57–1.20, *P*=0.33)	−44.8 (1.7)	1.00 (0.67–1.48, *P*=0.99)
Q3	1.22 (0.86–1.71, *P*=0.26)	−43.4 (1.8)	0.68 (0.48–0.97, *P*=0.04)
Q4	1.06 (0.74–1.51, *P*=0.77)	−43.7 (1.7)	0.77 (0.54–1.11, *P*=0.16)
Q5 (High)	1.66 (1.21–2.29, *P*=0.0019)	−42.5 (1.8)	0.56 (0.40–0.78, *P*<0.001)

Adjusted for age, sex, diabetes mellitus status, smoking status, LDL cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication status, and family history of CHD.

CHD = coronary heart disease; CI = confidence interval; HR = hazard ratio; Q = quintile

*Placebo-treated participants

Table 3

Coronary heart disease event rates by genetic risk and treatment allocation

Trial / Polygenic risk score subgroup	Placebo			Statin Treated			ARR (%)	NNT
	Events (n)	Individuals (n)	Event rate (%)	Events (n)	Individuals (n)	Event rate (%)		
WOSCOPS (604 events, 8.1 years of follow-up)								
All Others	248	1,929	12.9%	201	1,981	10.1%	2.7%	38
High	100	511	19.6%	55	471	11.7%	7.9%	13
JUPITER (108 events, 2.4 years of follow-up)								
All Others	53	3,486	1.5%	35	3,483	1.0%	0.5%	200
High	14	864	1.6%	6	878	0.7%	0.9%	112
ASCOT-LLA (149 events, 6.1 years of follow-up)								
All Others	61	1,619	3.8%	45	1,756	2.6%	1.2%	84
High	28	426	6.6%	15	418	3.6%	3.0%	34

ARR = absolute risk reduction; NNT = number needed to treat with statin to prevent one event.

JUPITER and ASCOT-LLA data from Mega J*, Stitziel NO*, et al. *Lancet*. 2015[5] *Denotes equal contribution

Table 4

CAC burden by polygenic risk score quintile in CARDIA

Polygenic risk score quintile	CAC > 0 %	CAC > 0 OR (95% CI, *P*) *
Q1	8.7	1
Q2	12.1	2.08 (0.89–4.83, *P* =0.09)
Q3	10.9	2.08 (0.87–4.98, *P* =0.10)
Q4	14.3	3.02 (1.31–7.00, *P* =0.01)
Q5 (High)	15.6	2.51 (1.08–5.85, *P* =0.04)

* Relative to Q1. Adjusted for age, sex, diabetes mellitus status, smoking status, LDL cholesterol, HDL cholesterol, systolic blood pressure, antihypertensive medication status, and family history of CHD

CAC = coronary artery calcification; CHD = coronary heart disease; CI = confidence interval HR = hazard ratio; PCE = Pooled Cohorts Equation; PRS = polygenic risk score; Q = quintile