



Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting

Editorial, see p 2102

BACKGROUND: Relative risk reduction with statin therapy has been consistent across nearly all subgroups studied to date. However, in analyses of 2 randomized controlled primary prevention trials (ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm] and JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin]), statin therapy led to a greater relative risk reduction among a subgroup at high genetic risk. Here, we aimed to confirm this observation in a third primary prevention randomized controlled trial. In addition, we assessed whether 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 [West of Scotland Coronary Prevention Study]; n=4910) and 2 observational cohort studies (CARDIA [Coronary Artery Risk Development in Young Adults] and BiImage; n=1154 and 4392, respectively). For each participant, we calculated a polygenic risk score derived from up to 57 common DNA sequence variants previously associated with coronary heart disease. We compared the relative efficacy of statin therapy in those at high genetic risk (top quintile of polygenic risk score) versus all others (WOSCOPS), as well as the association between the polygenic risk score and coronary artery calcification (CARDIA) and carotid artery plaque burden (BiImage).

RESULTS: Among WOSCOPS trial participants at high genetic risk, statin therapy was associated with a relative risk reduction of 44% (95% confidence interval [CI], 22–60; $P<0.001$), whereas in all others, the relative risk reduction was 24% (95% CI, 8–37; $P=0.004$) despite similar low-density lipoprotein 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 3 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 1.3% (95% CI, 0.6–1.9) in all others. Each 1-SD 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 coronary heart disease event.

CLINICAL TRIAL REGISTRATION: URL: <http://www.clinicaltrials.gov>. Unique identifiers: NCT00738725 (BiImage) and NCT00005130 (CARDIA). WOSCOPS was carried out and completed before the requirement for clinical trial registration.

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Clinical Perspective

What Is New?

- A recent analysis of primary prevention statin trials surprisingly suggested that those at high genetic risk for coronary heart disease derive greater relative benefit from statin therapy.
- We developed an expanded genetic risk score for coronary heart disease with 57 single-nucleotide polymorphisms to identify individuals at high genetic risk.
- We show in an independent study (WOSCOPS [West of Scotland Coronary Prevention Study]) that statin therapy was associated with a relative risk reduction of 44% for coronary heart disease among those at high genetic risk versus 24% among all others.
- In addition, 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 coronary heart disease event.

Coronary heart disease (CHD) is a complex, chronic disease responsible for ≈ 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 $\approx 20\%$ 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 were more efficacious in one subgroup than another, this might affect decisions on who is 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–single-nucleotide polymorphism (SNP) polygenic risk score for CHD, derived greater relative risk reduction from statin therapy compared with all others.⁵ In 2 primary prevention trials (ASCOT-LLA [Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm⁶] and JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin⁷]), 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 2 main goals: to test in a third statin trial whether 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 with all others and

to test whether a greater burden of subclinical coronary atherosclerosis is present in those at high genetic risk compared with 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 6595 men (age, 45–64 years) with hypercholesterolemia but without a history of myocardial infarction who were allocated to pravastatin 40 mg daily versus placebo to prevent coronary events. Genetic data were available for 4892 men. Long-term WOSCOPS results beyond the end of the study were included to assess the durable effects of primary preventive statin therapy by genetic risk. Results were also available from a prior analysis⁵ that included a subset of 6978 individuals with genetic data from ASCOT-LLA, a randomized trial of atorvastatin 10 mg daily versus placebo in those with hypertension but without cardiovascular disease, and 8769 individuals with genetic data from JUPITER, a randomized trial of rosuvastatin 20 mg daily versus placebo in those with no history of cardiovascular events but elevated C-reactive protein.

In 2 observational cohorts (CARDIA [Coronary Artery Risk Development in Young Adults] and BiImage), 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 2 vascular beds in those without clinical CHD. The CARDIA study (NCT00005130) is an observational study of cardiovascular risk factors in 5115 young adults (age, 18–30 years at baseline, 1989–1990) as previously described.^{10,11} Of these participants, 1154 individuals of European ancestry without CHD at baseline with available genetic data and coronary artery calcification (CAC) assessment at the 15-year follow-up were included in the analyses. The BiImage study (NCT00738725) is a multiethnic, observational study aimed at characterizing subclinical atherosclerosis in 6699 US adults (age, 55–80 years at baseline, 2008–2009) at risk for, but without, clinical atherosclerotic cardiovascular disease.^{12,13} Because current genome-wide association effect estimates for CHD are most robust in those of European ancestry,¹⁴ we focused on the 4929 individuals of European ancestry. Of those individuals, 4392 with both genetic data available and carotid plaque assessment were included in analyses. In WOSCOPS, CARDIA, and BiImage, 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 followed were in accordance with institutional guidelines.

Polygenic Risk Score

Genome-wide association analyses have identified 67 SNPs across the genome that are independently associated with CHD (Table 1 in the online-only Data Supplement).^{14–16} We

recently showed that an expanded set of SNPs compared with a polygenic risk score comprising 27 SNPs modestly improves risk discrimination.¹⁷ Fifty-seven of these variants were genotyped among WOSCOPS participants with the Illumina Metabochip¹⁸ and included in analyses. Thirteen variants were directly genotyped among CARDIA participants with the Affymetrix Human SNP Array 6.0 and another 25 proxy variants available through statistical imputation. CARDIA genotypes were downloaded from the National Institutes of Health dbGAP data repository (accession phs000613.version 1.p2). Fifty-nine variants were directly genotyped among Biomag participants with the Illumina HumanExome Beadchip¹⁹ and an additional 4 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 from 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, SD=1) was created per cohort (Figure 1 in the online-only Data Supplement).

Outcomes

The primary outcome for the WOSCOPS analysis was non-fatal myocardial infarction or death resulting from CHD.⁸ In WOSCOPS, we also studied change in LDL cholesterol from baseline; on-treatment LDL cholesterol was obtained 1 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 Biomag.²⁰ In the CARDIA study, CAC was assessed by ECG-gated electron beam computed tomography (Imatron C-150, GE Imatron, San Francisco, CA) or multidetector computed tomography (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 Biomag, carotid plaque was ascertained with the Philips iU22 carotid ultrasound system (Philips Healthcare, Bothell, WA) interpreted at the University of Copenhagen (Copenhagen, Denmark) as described previously.^{12,21} If carotid plaque was present on the basis of local carotid intima-media thickness, it was quantified with 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 whether polygenic risk score (per 1 SD and high genetic risk versus all others) associated with risk of developing incident nonfatal myocardial infarction or death caused by CHD. The models were adjusted for age, sex, diabetes mellitus status, smoking status, baseline LDL cholesterol, baseline high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication status, and family history of myocardial infarction

or stroke. Sex was not used as a covariate in WOSCOPS because all participants were male. Higher-order terms for polygenic risk score were not significantly associated with outcome, and the linear assumption was not violated. Next, we stratified participants into 2 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 (CI) 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 follows:

$$SE_{ARR} = \sqrt{\frac{\left(\frac{a}{n_1}\right)\left(1 - \frac{a}{n_1}\right)}{n_1} + \frac{\left(\frac{c}{n_2}\right)\left(1 - \frac{c}{n_2}\right)}{n_2}}$$

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 χ^2 test for heterogeneity was used to test the differences in absolute risk reduction from statins between those at high genetic risk and all others.

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 were combined by use of a fixed-effects meta-analysis. A χ^2 test for heterogeneity was used to compare the proportional risk reductions between the meta-analyzed effect estimates as previously described.²²

In 2 population-based cohort studies, we tested whether prevalent subclinical atherosclerosis differed between those at high genetic risk and 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 CARDIA. We determined whether 2 predictors (polygenic risk score as a continuous variable or a dichotomized high genetic risk versus all others) were associated with CAC using multivariate logistic regression in CARDIA. We similarly tested whether polygenic risk score was associated with prevalent carotid plaque in Biomag. The outcome variable was the natural log transformation of total bilateral carotid plaque plus 1. The models were adjusted for age, sex, diabetes mellitus status, smoking status, LDL cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication status, and family history of CHD.

All tests were 2 tailed with a threshold of $\alpha = 0.05$. Statistical analyses were conducted in R version 3.2.1 (R Foundation, Vienna, Austria).

RESULTS

The mean length of follow-up for WOSCOPS participants in the trial was 4.8 years (SD, 0.7 years) for both the 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 are shown in Table 1 and by randomized treatment groups in Table II in the online-only Data Supplement. Individuals at high genetic risk (top quintile of polygenic risk scores) were more likely to report a family history of CHD (7% versus 5%; $P=0.004$) and were less likely to be current smokers (40% versus 45%; $P=0.006$) compared with 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 with the American College of Cardiology/American Heart Association pooled cohort equations) were similar across quintiles of polygenic risk score (Table III in the online-only Data Supplement).

Table 1. Characteristics of WOSCOPS (West of Scotland Coronary Prevention Study) Participants, by Genetic Risk Group

	High Genetic Risk (≥ 80 th Percentile Polygenic Risk Score) (n=979)	All Others (< 80 th Percentile Polygenic Risk Score) (n=3913)	P Value
Age, y	54.9 (5.5)	55.2 (5.5)	0.17
Male, %	100	100	...
Body mass index, kg/m ²	26.1 (3.1)	26.0 (3.2)	0.35
Family history of coronary heart disease, %	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, y	13.6 (2.8)	13.6 (2.7)	0.49
Follow-up during trial, y	4.9 (0.7)	4.8 (0.7)	0.17
Follow-up during trial, y	8.7 (2.6)	8.3 (2.5)	0.25

Values are presented as mean (SD) when appropriate. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

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 χ^2 tests.

Among those allocated to placebo, those at high genetic risk were at increased risk for a first CHD event (hazard ratio [HR], 1.62; 95% CI, 1.29–2.05; $P<0.001$) after adjustment for traditional cardiovascular risk factors (Table 2 and Figure II and Table IV in the online-only Data Supplement). Furthermore, among placebo-treated participants in WOSCOPS, a 1-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; $P<0.001$). The association of polygenic risk score with CHD did not vary between those with and those without a self-reported family history of CHD (P for interaction=0.47; Table V in the online-only Data Supplement). Mean baseline LDL cholesterol was 192 mg/dL (SD, 17.5 mg/dL) in the high genetic risk group and 192 mg/dL (SD, 17.3 mg/dL) among all others ($P=0.4$).

Among those at high genetic risk, statin therapy reduced the 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 and 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 to prevent 1 coronary event was 13 among participants at high genetic risk 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 with 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 3 studies combined, statin therapy reduced the 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 3 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 1.3% (95% CI, 0.6–1.9) in all others. This translates to a number needed to treat to prevent 1 coronary event of 28 (95% CI, 20–50) in the high genetic risk score group and 80 (95% CI, 52–175) in all others.

We tested whether 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 BiImage Study (ages 55–80 years) are presented in Table VI in the online-only Data Supplement. In CARDIA, for every 1-SD increase in polygenic risk score, the multivariable-adjusted odds ratio for CAC presence was 1.32 (95% CI, 1.04–1.68; $P=0.02$; Table 4).

Table 2. Incident Coronary Heart Disease Event Risk, Low-Density Lipoprotein Cholesterol Lowering, and Relative Risk Reduction of Coronary Heart Disease Across Quintiles of Polygenic Risk Score in WOSCOPS (West of Scotland Coronary Prevention Study)

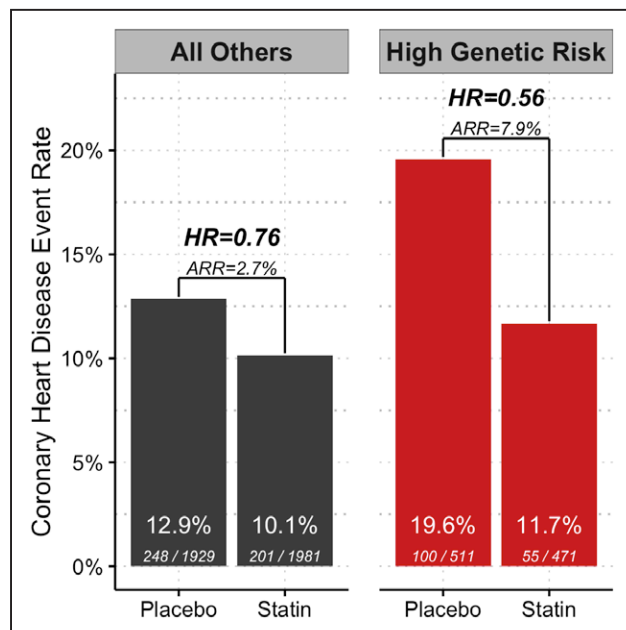
Polygenic Risk Score Quintile	Coronary Heart Disease Event Risk*		LDL Cholesterol Reduction After Statin, Mean (SD), mg/dL	Relative Risk Reduction With Statin Therapy Within Each Quintile of Polygenic Risk	
	Hazard Ratio (95% CI)	P Value		Hazard Ratio (95% CI)	P Value
1	...		-44.7 (1.8)	0.65 (0.44–0.97)	0.035
2	0.83 (0.57–1.20)	0.33	-44.8 (1.7)	1.00 (0.67–1.48)	0.99
3	1.22 (0.86–1.71)	0.26	-43.4 (1.8)	0.68 (0.48–0.97)	0.04
4	1.06 (0.74–1.51)	0.77	-43.7 (1.7)	0.77 (0.54–1.11)	0.16
5 (High)	1.66 (1.21–2.29)	0.0019	-42.5 (1.8)	0.56 (0.40–0.78)	<0.001

LDL indicates low-density lipoprotein. Values were adjusted for age, sex, diabetes mellitus status, smoking status, LDL cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication status, and family history of coronary heart disease.

*Placebo-treated participants.

In BiImage, for every 1-SD increase in polygenic risk score, there was a 9.7% increase (95% CI, 2.2–17.8; $P=0.01$) in carotid artery plaque burden. The median

carotid plaque burden among those at high genetic risk was 215 mm² (interquartile range, 52–618 mm²) compared with 208 mm² (interquartile range, 39–581 mm²) among all other participants ($P=0.02$; Tables VII and VIII in the online-only Data Supplement). Unlike this expanded 57-SNP score, we did not observe an association of a prior restricted 27-SNP score⁵ with carotid artery plaque burden (Table IX in the online-only Data Supplement).

**Figure 1. Incident coronary heart disease events by statin therapy and genetic risk group in WOSCOPS (West of Scotland Coronary Prevention Study).**

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

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 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 with all others. In addition, an expanded 57-SNP score was associated with subclinical atherosclerosis in 2 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 suggest that statins might confer greater relative risk reduction in 1 subgroup: those at high genetic risk. Across 3 primary prevention trials, those at high genetic risk have a nearly 3-fold lower number needed to treat to prevent 1 CHD event. In those at high genetic risk, the lower number needed to treat to prevent 1 CHD event is driven by both an elevated baseline rate of events (1.6-fold greater) and a greater relative risk reduction of events from statin therapy.

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 y of follow-up)								
All others	248	1929	12.9	201	1981	10.1	2.7	38
High	100	511	19.6	55	471	11.7	7.9	13
JUPITER (108 events, 2.4 y of follow-up)								
All others	53	3486	1.5	35	3483	1.0	0.5	200
High	14	864	1.6	6	878	0.7	0.9	112
ASCOT-LLA (149 events, 6.1 y of follow-up)								
All others	61	1619	3.8	45	1756	2.6	1.2	84
High	28	426	6.6	15	418	3.6	3.0	34

ARR indicates absolute risk reduction; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; NNT, number needed to treat with statin to prevent 1 event; and WOSCOPS, West of Scotland Coronary Prevention Study.

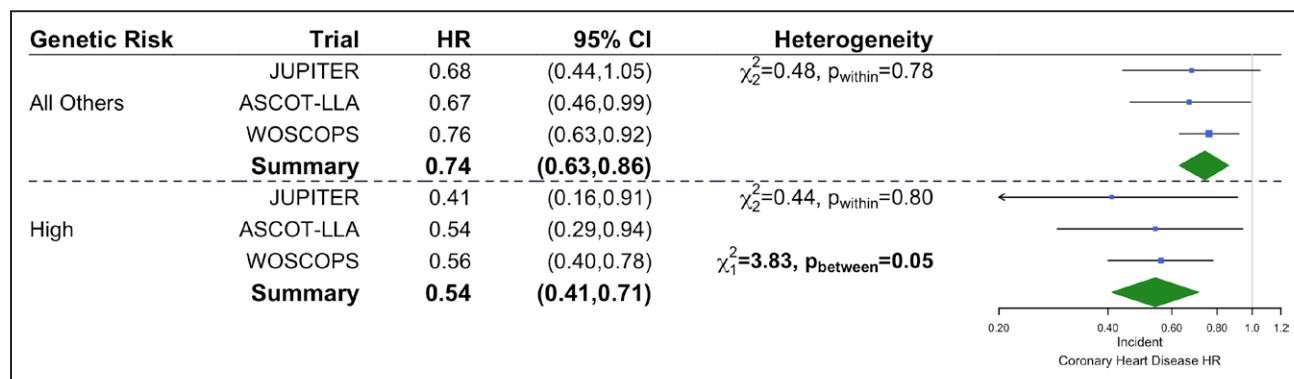
JUPITER and ASCOT-LLA data are from Mega et al.⁵

Large-scale genetic association analyses have expanded the number of SNPs associated with CHD.^{14,16} Compared with 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 bur-

den of subclinical atherosclerosis. An increased number of CHD variants is linked to subclinical atherosclerosis in 2 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 BiImage.²⁷ We now extend these findings to a low-risk, young cohort of essentially statin-ineligible individuals.

Both CAC and carotid plaque are strong predictors of CHD events independently 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} Noncoding genomic variants at 9p21 and 6p24 are strongly associated with both CAC and

**Figure 2. Forest plot of incident coronary heart disease after statin therapy by genetic risk group in statin primary prevention trials.**

The multivariable-adjusted hazard ratios (HRs) of incident coronary heart disease after statin therapy by genetic risk group are presented for 3 primary prevention trials. Data from JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm) 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 indicates confidence interval; HR, hazard ratio; and WOSCOPS, West of Scotland Coronary Prevention Study.

Table 4. Coronary Artery Calcification Burden, by Polygenic Risk Score Quintile in CARDIA (Coronary Artery Risk Development in Young Adults)

Polygenic Risk Score Quintile	CAC>1%, %	CAC >0*	
		OR (95% CI)	P Value
1	8.7	1	
2	12.1	2.08 (0.89–4.83)	0.09
3	10.9	2.08 (0.87–4.98)	0.10
4	14.3	3.02 (1.31–7.00)	0.01
5 (High)	15.6	2.51 (1.08–5.85)	0.04

CAC indicates coronary artery calcification. Values were adjusted for age, sex, diabetes mellitus status, smoking status, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication status, and family history of coronary heart disease.

*Relative to quintile 1.

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 (Biolmage)²⁷ and a younger cohort with a paucity of traditional risk factors (CARDIA). This indicates that lifelong exposure to CHD risk alleles predisposes to the development of both 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 and atherosclerosis imaging markers to refine decision making for the 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 lifestyle²⁷ can modify high genetic risk, and we now demonstrate that statin therapy also may modify risk. Overall, these data may contribute to the conversation about statin eligibility in the primary prevention setting. At present, statin eligibility is determined from 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 sizable proportions of statin-ineligible patients. Furthermore, disclosure of genetic risk may motivate greater adherence to statin therapy.³⁷

Our analyses have potential limitations. First, the entry criteria in the 3 randomized controlled trials were different, and the trials had 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, crossover occurring after the termination of the trial would likely bias results to the null. Last, the polygenic risk score captures common genetic variation, but ≈ 1 in 200 individuals is affected by a monogenic disease, namely familial hypercholesterolemia, that markedly increases the 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 at higher risk for developing a coronary event, more likely to experience clinical benefit from preventive statin therapy, and with a greater burden of subclinical atherosclerosis.

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FOOTNOTES

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