

Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials



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Summary

Background Genetic variants have been associated with the risk of coronary heart disease. In this study, we tested whether or not a composite of these variants could ascertain the risk of both incident and recurrent coronary heart disease events and identify those individuals who derive greater clinical benefit from statin therapy.

Methods A community-based cohort study (the Malmo Diet and Cancer Study) and four randomised controlled trials of both primary prevention (JUPITER and ASCOT) and secondary prevention (CARE and PROVE IT-TIMI 22) with statin therapy, comprising a total of 48 421 individuals and 3477 events, were included in these analyses. We studied the association of a genetic risk score based on 27 genetic variants with incident or recurrent coronary heart disease, adjusting for traditional clinical risk factors. We then investigated the relative and absolute risk reductions in coronary heart disease events with statin therapy stratified by genetic risk. We combined data from the different studies using a meta-analysis.

Findings When individuals were divided into low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) genetic risk categories, a significant gradient in risk for incident or recurrent coronary heart disease was shown. Compared with the low genetic risk category, the multivariable-adjusted hazard ratio for coronary heart disease for the intermediate genetic risk category was 1.34 (95% CI 1.22–1.47, $p < 0.0001$) and that for the high genetic risk category was 1.72 (1.55–1.92, $p < 0.0001$). In terms of the benefit of statin therapy in the four randomised trials, we noted a significant gradient ($p = 0.0277$) of increasing relative risk reductions across the low (13%), intermediate (29%), and high (48%) genetic risk categories. Similarly, we noted greater absolute risk reductions in those individuals in higher genetic risk categories ($p = 0.0101$), resulting in a roughly threefold decrease in the number needed to treat to prevent one coronary heart disease event in the primary prevention trials. Specifically, in the primary prevention trials, the number needed to treat to prevent one such event in 10 years was 66 in people at low genetic risk, 42 in those at intermediate genetic risk, and 25 in those at high genetic risk in JUPITER, and 57, 47, and 20, respectively, in ASCOT.

Interpretation A genetic risk score identified individuals at increased risk for both incident and recurrent coronary heart disease events. People with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy.

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Introduction

The risk of developing coronary heart disease depends on several factors that are related both to lifestyle and genetics. Heritable factors account for as much as 30–60% of the variation in risk,^{1,2} and large-scale studies have identified genetic variants associated with coronary heart disease at stringent levels of statistical significance.^{3,4} Previous studies have shown that an assessment of genetic risk burden based on several loci can identify individuals at increased risk for incident coronary heart disease in population-based epidemiological cohorts.^{5–12} Additionally, whereas some individual variants have been assessed in isolated studies for an association with recurrent events, an independent association between a multi-locus genetic risk score and recurrent coronary heart disease events has not been clearly shown.^{13–16}

The clinical benefit from treatments that reduce the likelihood of coronary heart disease events might vary by the degree of risk at baseline. As such, in addition to identifying risk, a genetic risk score consisting of fully studied coronary heart disease risk single-nucleotide polymorphisms (SNPs) might also characterise individuals who will receive the greatest clinical benefit from statin therapy. Such a finding would be of particular interest in the primary prevention setting. Therefore, our study had two main goals: first, to test if a multi-locus genetic risk score based on a combination of 27 loci might predict not only incident coronary heart disease in an epidemiological cohort but also incident or recurrent coronary heart disease events in a clinical trial setting; and second, to assess whether or not the clinical benefit of statin therapy varies by genetic risk score in four randomised controlled trials of statin therapy.

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Methods

Primary prevention populations

The baseline characteristics of the participants of each study are listed in appendix p 4. In brief, the Malmö Diet and Cancer Study (MDCS)¹⁷ is a community-based prospective epidemiological cohort of middle-aged (45–64 years old) individuals from southern Sweden. Genetic samples were available from 27817 people without documented coronary heart disease at baseline. JUPITER¹⁸ was a primary prevention trial that tested rosuvastatin 20 mg daily versus placebo in 17802 individuals with LDL cholesterol level lower than 3·37 mmol/L, high-sensitivity C-reactive protein of 2 mg/L or higher, and no known cardiovascular disease. Genetic samples were available in 8749 individuals for this analysis. Another primary prevention trial, ASCOT,¹⁹ tested the clinical benefit of different classes of antihypertensive therapy in 19342 high-risk individuals without documented coronary heart disease. The lipid-lowering group (ASCOT-LLA) randomly assigned individuals from the main trial with a total cholesterol

level of up to 6·5 mmol/L to either atorvastatin 10 mg daily or placebo. In total, 4219 individuals from ASCOT-LLA were included in the treatment-related analyses. Additionally, 2759 participants from the blood pressure-lowering group of ASCOT who were not receiving a statin drug were assessed in the non-treatment-related analyses.

Secondary prevention populations

CARE²⁰ was a secondary prevention trial that investigated the clinical benefit of pravastatin 40 mg daily versus placebo in 4159 individuals with previous myocardial infarction who had total cholesterol level of up to 6·2 mmol/L and LDL cholesterol level between 3·0 and 4·5 mmol/L. Genetic samples were available for 2878 individuals in this study. Another secondary prevention trial, PROVE IT-TIMI 22, investigated the clinical benefit of moderate statin therapy (pravastatin 40 mg daily) versus intensive statin therapy (atorvastatin 80 mg daily) in 4162 patients after an acute coronary syndrome who had total cholesterol level of up to 6·2 mmol/L.²¹ A genetic substudy included 1999 individuals.

Genetic risk score

A genetic risk score was derived on the basis of 27 SNPs that were significantly associated with coronary heart disease at a genome-wide level in previous analyses (appendix p 2).²² Table 1 shows the loci, lead SNPs, published effect sizes, risk alleles, and risk allele frequency, with the specifics for each study provided in appendix p 5. Each individual participant received a score equal to the sum of the number of risk alleles for each SNP weighted by the log of the odds ratio reported with the SNP in the original report (appendix pp 13–16).

Outcomes

The outcome of interest was coronary heart disease, in view of the fact that the SNPs were originally reported to be associated with coronary events. We attempted to harmonise the definitions across studies based on the available endpoints. In JUPITER, ASCOT, and PROVE IT-TIMI 22, coronary heart disease was defined as a composite of coronary heart death, myocardial infarction, or unstable angina. In MDCS, coronary heart disease represented a composite of fatal or non-fatal myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention, and in CARE, coronary heart disease was coronary heart death or myocardial infarction.

Statistical analysis

We used Cox proportional hazard models to assess the risk of coronary heart disease for each quintile of genetic risk, in which we used the first quintile as the reference group; additionally, the risk for categories (low [quintile 1], intermediate [quintiles 2–4], and high [quintile 5]) and per 1 SD was calculated. These analyses

	Lead SNP	OR for coronary heart disease	Risk allele	Risk allele frequency
1p13.3 (SORT1)	rs646776	1.19	T	0.77
1p32.2 (PPAP2B)	rs17114036	1.17	A	0.92
1p32.3 (PCSK9)	rs11206510	1.15	T	0.82
1q41 (MIA3)	rs17465637	1.14	C	0.75
2q33.1 (WDR12)	rs6725887	1.17	C	0.13
3q22.3 (MRAS)	rs9818870	1.15	T	0.15
6p21.31 (ANKS1A)	rs17609940	1.07	G	0.79
6p24.1 (PHACTR1)	rs9349379	1.12	G	0.43
6q23.2 (TCF21)	rs12190287	1.08	C	0.63
6q25.3 (LPA)	rs3798220	1.47	C	0.01
6q25.3 (LPA)	rs10455872	1.70	G	0.07
7q32.2 (ZC3HC1)	rs11556924	1.09	C	0.64
9p21.3 (CDKN2A)	rs4977574	1.29	G	0.55
9q34.2 (ABO)	rs9411489	1.10	T	0.21
10q11.21 (CXCL12)	rs1746048	1.17	C	0.86
10q24.32 (CYP17A1)	rs12413409	1.12	G	0.90
11q23.3 (APOA5)	rs964184	1.13	G	0.13
12q24 (HNF1A)	rs2259816	1.08	T	0.35
12q24.12 (SH2B3)	rs3184504	1.13	T	0.48
13q34 (COL4A1)	rs4773144	1.07	G	0.41
14q32.2 (HHIPL1)	rs2895811	1.07	C	0.45
15q25.1 (ADAMTS7)	rs3825807	1.08	T	0.57
17p11.2 (RASD1)	rs12936587	1.07	G	0.53
17p13.3 (SMG6)	rs216172	1.07	C	0.64
17q21.32 (UBE2Z)	rs46522	1.06	T	0.48
19p13.2 (LDLR)	rs1122608	1.15	G	0.77
21q22.11 (KCNE2)	rs9982601	1.20	T	0.13

Risk allele frequency data are from the Malmö Diet and Cancer Study.¹⁷
SNP=single-nucleotide polymorphism. OR=odds ratio.

Table 1: Components of the genetic risk score, listed by locus

	Low genetic risk category	Intermediate genetic risk category	High genetic risk category	p value (intermediate vs low)	p value (high vs low)
Primary prevention populations					
Malmo Diet and Cancer Study	1.00	1.30 (1.17–1.44)	1.70 (1.51–1.91)	2×10^{-6}	2×10^{-18}
JUPITER	1.00	1.23 (0.61–2.44)	1.32 (0.58–2.98)	0.56	0.51
ASCOT	1.00	1.58 (1.06–2.34)	2.10 (1.35–3.25)	0.0236	0.0009
Meta-analysis	1.00	1.31 (1.19–1.45)	1.72 (1.53–1.92)	<0.0001	<0.0001
Secondary prevention populations					
CARE	1.00	1.52 (0.99–2.33)	1.67 (1.01–2.76)	0.0575	0.0482
PROVE IT-TIMI 22	1.00	1.87 (1.11–3.16)	2.04 (1.10–3.79)	0.0190	0.0239
Meta-analysis	1.00	1.65 (1.19–2.30)	1.81 (1.22–2.67)	0.0030	0.0029

Data are adjusted hazard ratios (95% CI), unless otherwise indicated. These analyses were done in participants in the Malmo Diet and Cancer Study, and in those in the placebo groups (in JUPITER, ASCOT, and CARE) or the lower-intensity statin treatment group (in PROVE IT-TIMI 22).

Table 2: Risk of coronary heart disease across genetic risk score categories, by study

were done on participants in MDCS, and in the placebo or lower-intensity statin treatment groups of the applicable trials. The models were adjusted for age, sex, diabetes status, smoking, race (if applicable), family history of coronary heart disease, HDL cholesterol, LDL cholesterol, and hypertension. In a meta-analysis, the estimates were combined from each study by use of a random-effects model to account for possible differences in study populations. We assessed heterogeneity across studies and types of studies, and analyses were stratified on the basis of the primary and secondary prevention populations.

The treatment-specific analyses were done in the JUPITER, ASCOT, CARE, and PROVE IT-TIMI 22 trials. The effect of statin versus placebo (or high-intensity versus moderate-intensity statin in the case of PROVE IT-TIMI 22) was assessed, and the number of events and event rates in the statin and placebo groups were analysed on the basis of the genetic risk score quintiles and aforementioned categories. Hazard ratios and 95% CIs were generated, and absolute risk reductions were calculated. For the primary prevention trials (JUPITER and ASCOT), we extrapolated 10-year event rates and calculated the numbers needed to treat for each study.

We combined the relative risk ratios for the benefit of statin therapy within each genetic risk score category across the trials using meta-analytical techniques, with separate analyses for the primary and secondary prevention populations. We assessed the resulting meta-analysis risk ratios across the genetic risk score categories with meta-regression. In terms of absolute risk reductions with statins, within each trial and within each genetic risk score category, the absolute risk difference for statin versus placebo and corresponding standard errors and 95% CIs were generated. Notably, the fact that the trials had populations with different absolute event rates (owing to varying degrees of cardiovascular risk and different durations of follow-up) precluded us from obtaining a clinically interpretable result by merely combining the raw absolute risk

differences across the four trials. Therefore, to normalise across the trials, we applied a scaling factor to the data (see appendix p 3 for further details). Then, within the data from each trial, meta-regression was done across the genetic risk score categories to establish how the relative magnitude of absolute risk reduction with statin therapy varied by genetic risk score category. We then undertook meta-analysis in which we combined the regression coefficients from the four trials, again stratified by primary and secondary prevention populations.

Role of the funding source

For this analysis, the funders of the individual clinical trials had no role in the analysis or interpretation of the data, or writing of the report. Investigators associated with each study had access to the data, and JLM, NOS, SK, and MSS were responsible for the final decision to submit for publication.

Results

Higher genetic risk scores were associated with a raised risk of coronary heart disease, independent of established clinical predictors. Specifically, when evaluating participants in low (quintile 1), intermediate (quintiles 2–4), and high (quintile 5) genetic risk score categories, a gradient of risk for coronary heart disease was evident in the studies (table 2). When the data from the primary prevention cohorts were combined, the multivariable-adjusted hazard ratios (HRs) for incident coronary heart disease compared with the low genetic risk category were 1.31 (95% CI 1.19–1.45, $p < 0.0001$) for the intermediate genetic risk category and 1.72 (1.53–1.92, $p < 0.0001$) for the high genetic risk category (table 2). Similarly, the multivariable-adjusted HRs for recurrent coronary heart disease in the secondary prevention cohorts were 1.65 (1.19–2.30, $p = 0.0030$) for the intermediate genetic risk category and 1.81 (1.22–2.67, $p = 0.0029$) for the high genetic risk category (table 2). Overall, the multivariable-adjusted HRs were 1.34 (95% CI 1.22–1.47, $p < 0.0001$)

and 1.72 (1.55–1.92, $p < 0.0001$), respectively (figure 1). Data for individual quintiles 1–5 were similar (see appendix pp 6–7).

Baseline LDL cholesterol and HDL cholesterol levels were similar across genetic risk score categories within each trial, as were the absolute and percentage changes with statin therapy (appendix pp 8–10). Analyses were done to investigate the clinical benefit of statin therapy across genetic risk score. The benefit of statin versus placebo in the primary and secondary prevention trials with a total of 806 events is presented across genetic risk score categories in table 3 and genetic risk score quintiles in appendix pp 11–12. The relative risk reductions were 34% in low, 32% in intermediate, and 50% in high genetic risk score categories in the primary prevention trials, and 3% in low, 28% in intermediate, and 47% in high genetic

risk score categories in the secondary prevention trials. When the data were combined, the gradient of relative risk reductions with statin therapy across low, intermediate, and high genetic risk score categories were 13%, 29%, and 48%, respectively (p value for trend = 0.0277, figure 2).

Similarly, in terms of the absolute risk reductions, a graded increase in the benefit of statin therapy across the genetic risk score categories (from low risk to high risk) was evident in both the primary prevention trials (JUPITER and ASCOT) and the secondary prevention trials (CARE and PROVE IT-TIMI 22; table 3, figure 3). Correspondingly, the number needed to treat to reduce coronary heart disease events with statin therapy differed depending on genetic risk score. With a focus on the primary prevention trials, in JUPITER, the number needed to treat to prevent one coronary event in 10 years was 66 for those individuals with a low genetic risk score, 42 for those with an intermediate score, and 25 for those with a high score. In ASCOT, the number needed to treat to prevent one coronary heart disease event in 10 years was 57, 47, and 20, respectively, across the three genetic risk score categories.

Calculation of the difference in absolute risk reduction in each trial as a function of genetic risk score category and combination of the data from the trials showed a consistent and significant gradient, with greater absolute risk reductions recorded in those individuals in higher genetic risk score categories ($p = 0.0101$, appendix p 17). The regression coefficient of 0.71 indicates that for each 1% absolute risk reduction achieved with statin therapy in the intermediate genetic risk category, a 1.71% absolute

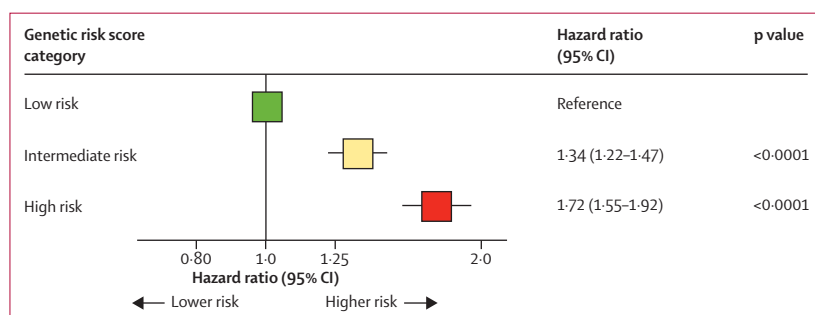


Figure 1: Summary of risk of coronary heart disease across genetic risk score categories in primary and secondary prevention populations

The boxes indicate the point estimates and the horizontal lines are 95% CIs.

	Events (n), control group	Individuals (n), control group	Event rate, control group (%)	Events (n), statin group	Individuals (n), statin group	Event rate, statin group (%)	HR	ARR (%)
Primary prevention populations								
JUPITER (108 events, 2.37 years of follow-up, 20 612 person-years of follow-up)								
Low genetic risk	10	865	1.16%	7	878	0.80%	0.68	0.36%
Intermediate genetic risk	43	2621	1.64%	28	2605	1.07%	0.68	0.57%
High genetic risk	14	864	1.62%	6	878	0.68%	0.41	0.94%
ASCOT (149 events, 6.07 years of follow-up, 25 609 person-years of follow-up)								
Low genetic risk	13	432	3.00%	8	412	1.94%	0.64	1.06%
Intermediate genetic risk	48	1187	4.04%	37	1344	2.75%	0.68	1.29%
High genetic risk	28	426	6.57%	15	418	3.59%	0.54	2.98%
Secondary prevention populations								
CARE (320 events, 4.94 years of follow-up, 13 623 person-years of follow-up)								
Low genetic risk	26	278	9.35%	22	297	7.41%	0.79	1.94%
Intermediate genetic risk	119	877	13.57%	92	850	10.82%	0.79	2.75%
High genetic risk	38	277	13.72%	23	299	7.69%	0.54	6.03%
PROVE IT-TIMI 22* (229 events, 2.03 years of follow-up, 3769 person-years of follow-up)								
Low genetic risk	20	213	9.39%	21	186	11.29%	1.24	−1.90%
Intermediate genetic risk	88	605	14.55%	55	595	9.24%	0.63	5.31%
High genetic risk	28	188	14.89%	17	212	8.02%	0.51	6.87%

HR=hazard ratio. ARR=absolute risk reduction. *In PROVE IT-TIMI 22, the control group is moderate-intensity statin therapy (pravastatin 40 mg) and the statin group is high-intensity statin therapy (atorvastatin 80 mg).

Table 3: Risk of coronary heart disease associated with statin therapy across genetic risk score categories

risk reduction would be expected to be seen in the high genetic risk category and a 0·29% absolute risk reduction in the low genetic risk category.

Discussion

Large-scale genetic association studies have identified several genetic variants that are individually associated with the risk of coronary heart disease. When combined into a 27-variant risk score, our multivariable-adjusted analyses showed that these variants could identify people at increased risk of coronary heart disease events, including incident coronary heart disease in primary prevention populations and recurrent coronary heart disease events in secondary prevention populations. Furthermore, when compared with people at low genetic risk, those with the highest genetic risk scores derived greater relative risk reduction and absolute risk reduction with statin therapy. Notably, in the primary prevention trials we found a roughly threefold difference between the low and high genetic risk score groups in the number needed to treat to prevent one coronary heart disease event.

Clinical, biochemical, and imaging parameters have been used to stratify cardiovascular risk and potentially to tailor therapy.²³ Our present analysis suggests that genetics might also have such a role. Previous data for genetic variants predicting recurrent coronary heart disease events independent of traditional risk factors are inconclusive,^{13–16} which is perhaps a result of varying definitions of prevalent coronary heart disease (eg, angina *vs* documented myocardial infarction) and inclusion of less specific outcomes (eg, non-cardiovascular death) in a composite endpoint. In terms of treatment options, the decision to prescribe any drug depends on weighing up of several factors, including efficacy, safety, and cost. In the case of statins, substantial relative risk reductions in major cardiovascular outcomes have been shown across the range of primary and secondary prevention.²⁴ Absolute risk reductions can depend on the risk profile of the population, but even in individuals at low risk of coronary heart disease, statins offer clinical benefit.²⁵

Nonetheless, debate continues about the use of statins in people at lower risk of coronary heart disease events, especially in primary prevention populations,²⁶ which is driven by concerns about safety and cost-effectiveness in an extremely broad population. For that reason, an understanding of the absolute risk reductions achieved with statin therapy in different subgroups could be useful in some circumstances. Moreover, lifetime risk of coronary heart disease is now receiving increased attention, and information about genetic risk could be obtained early in life.²⁷ As such, discussions have taken place about whether or not statin therapy could be considered at an earlier stage in people who do not currently meet practice guidelines, but who might still be at raised risk of coronary heart events. To define the best

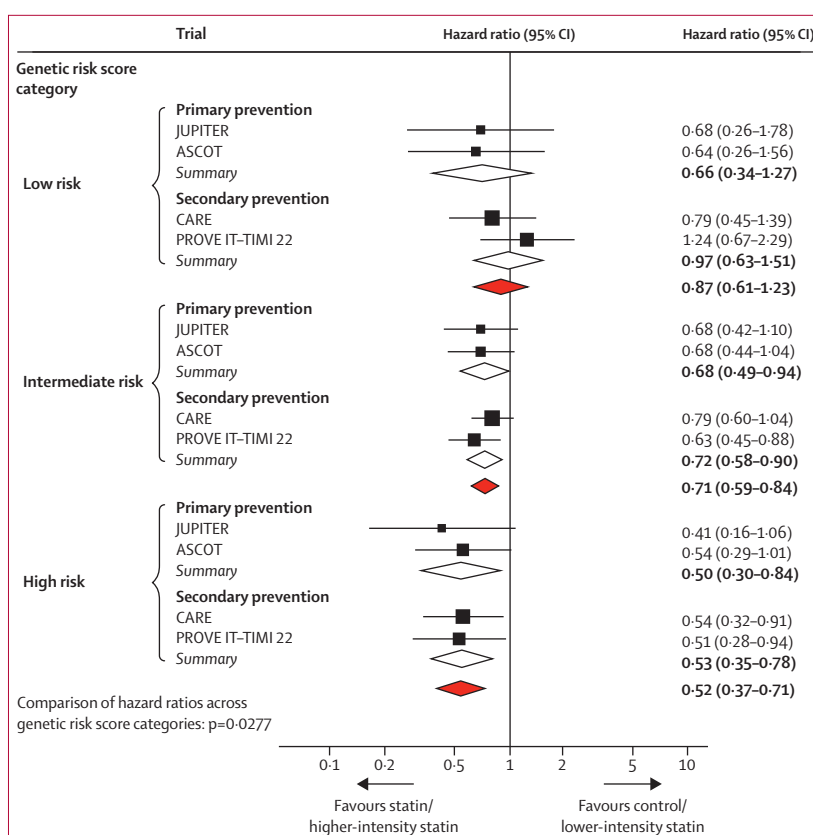


Figure 2: Hazard ratios for coronary heart disease with statin therapy across genetic risk score categories
The boxes indicate the point estimates, and the size of each box represents the weight of a trial's data within that subgroup. The horizontal lines are the 95% CIs. The diamonds provide summary data. In PROVE IT-TIMI 22, the control group is moderate-intensity statin therapy (pravastatin 40 mg) and the statin group is high-intensity statin therapy (atorvastatin 80 mg).

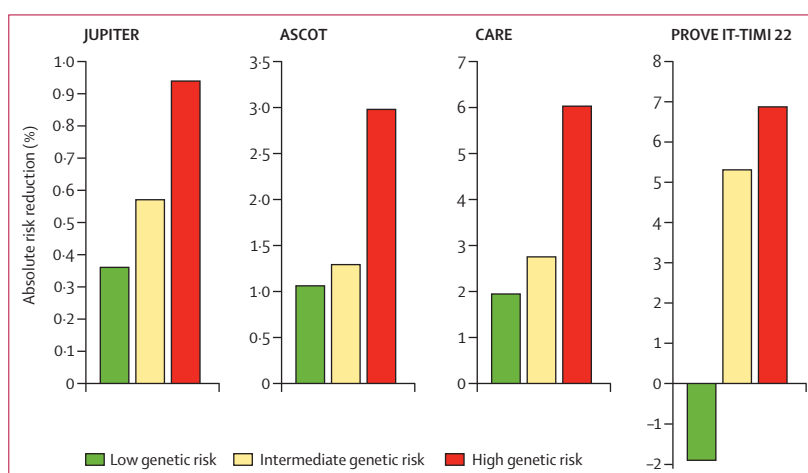


Figure 3: Absolute risk reductions of coronary heart disease events with statin therapy across genetic risk score categories

In PROVE IT-TIMI 22, the control group is moderate-intensity statin therapy (pravastatin 40 mg) and the statin group is high-intensity statin therapy (atorvastatin 80 mg).

approach to maximise the benefit of statin therapy in such a population is a complex challenge that needs further study. A genetic risk score offers a unique

Panel: Research in context**Systematic review**

We searched PubMed for original research relevant to this analysis published in English within the past 30 years. We used the following combination of keywords: "genetic", "risk score", and "coronary disease", and identified studies that describe the association of genetic variants and the risk of coronary heart disease, including several analyses examining the prognostic significance of several genetic variants, although these studies were largely confined to epidemiological cohorts and prediction of first manifestation of coronary heart disease. We also searched for "genetic", "risk score", "coronary disease", and "statins" without identifying studies that directly tested this specific concept. Therefore, in the present study we aimed to test whether or not a multi-locus genetic risk score predicts not only incident coronary heart disease in an epidemiological cohort but also recurrent coronary heart disease events in a clinical trial setting; and to assess whether or not the clinical benefit of statin therapy varies by genetic risk score.

Interpretation

A genetic risk score was derived based on 27 single-nucleotide polymorphisms that have been significantly associated with coronary heart disease at a genome-wide level in previous analyses. First, in an epidemiological cohort, people with a high genetic risk score were shown to have an increased risk of coronary heart disease, even after adjustment for established clinical predictors. We then assessed the association between the genetic risk score and coronary heart disease in primary and secondary prevention trials of statin therapy, and validated a gradient of risk for incident and recurrent coronary heart disease. In terms of the benefit of statin therapy, we tested the genetic risk score in four clinical trials and identified a significant gradient of increasing relative risk reduction across the low, intermediate, and high genetic risk categories. Similarly, in each trial, greater absolute risk reductions were recorded in those individuals in higher genetic risk categories, resulting in a roughly threefold decrease in the number needed to treat in the primary prevention trials. Therefore, genetics could help in the selection of populations for clinical trials that, so enriched, would be better positioned to test the clinical benefit of early initiation of statin therapy. Moreover, in situations in which optimisation of the number needed to treat is relevant, genetics could provide useful information.

perspective into future risk and could help in the selection of populations for clinical trials that, so enriched, would be better positioned to test the clinical benefit of early initiation of statin therapy in primary prevention; specifically, the role of statin therapy in people with apparently low clinical risk but with high genetic risk could be tested.²⁸

Previous analyses have assessed genetics and coronary heart disease events in the setting of statin therapy.^{29–40} However, such approaches have been limited by either examination of only one SNP, the use of SNPs whose association with coronary heart disease has not been well validated, not testing the SNP in a randomised trial of statin therapy, or not consistently validating any observed interactions. By contrast, our present analysis used a multi-locus genetic risk score comprised of well-validated coronary heart disease-risk SNPs and tested the score in four randomised controlled trials of statin therapy.

Our analyses have some potential limitations. First, data from several studies were used in this analysis, and each study has its own entry criteria, treatment allocation, and duration of follow-up. As such, the hazards

associated with the genetic risk categories differed somewhat, with the genetic-based risk in JUPITER apparently the lowest, which was possibly related to the patient population or the lower event rates than the other studies. However, the fact that we had access to data from a large community cohort study (MDCS), in addition to primary and secondary prevention clinical trials, allowed us to test the generalisability of the genetic risk score across various populations. Second, the numbers needed to treat were calculated by extrapolation of the effect of statin therapy during a 10-year period, and the treatment effect could vary over time. Nonetheless, studies of statin therapy suggest quite a linear long-term association with coronary event reduction.⁴¹ Third, these analyses were done within completed clinical trials, and the genetic risk score was not used specifically as an enrolment criterion. Dedicated clinical trials using a genetic risk score to triage statin therapy would add further to the knowledge base. Fourth, although we focused on the ability of genetics to offer insight into the risk of coronary heart disease and benefit of statin therapy, optimum tailoring of therapy might need a combination of several factors. Fifth, the present analysis focuses on genetic variants that were associated with the risk of coronary heart disease. Other variants have been described that are associated with LDL cholesterol levels. However, these variants mainly affect baseline LDL cholesterol, which is already routinely measured. Moreover, as previous studies show, they have little effect on the change in LDL cholesterol with statins or the clinical response to statin therapy.^{42,43} Therefore, our present analyses do not explore such variants unless they previously showed an association with coronary heart disease. Nonetheless, such a line of inquiry might also be informative. Finally, the gradient of relative risk reduction across genetic risk score categories in the present study was unexpected. Data from other studies suggest that patients with more versus less coronary heart disease risk SNPs have more extensive atherosclerosis,⁸ and thus, patients with a higher burden of these SNPs might well experience a greater benefit with statin therapy because more plaques are present that can be stabilised. However, this idea merits further study to elucidate the underlying mechanisms.

In conclusion, our study showed that a genetic risk score identified individuals at increased risk of coronary heart disease across primary and secondary prevention populations. Furthermore, people with high genetic risk scores had the largest relative and absolute risk reductions with statin therapy. In situations in which optimisation of the number needed to treat is relevant, such as in the primary prevention setting, approaches that involve genetics could prove useful.

Contributors

JLM, NOS, SK, and MSS contributed to the study design, data analysis, data interpretation, and writing of the report. JGS, DIC, MC, JJD, FN, CH, CPC, FS, NP, PS, PMR, EB, and OM contributed to the study

design, data analysis, and data interpretation of either the present analysis or the associated clinical trials, and they each reviewed or revised the report.

Declaration of interests

JLM has received research grant support through Brigham and Women's Hospital from Bristol-Myers Squibb and Sankyo during the study; grant support through Brigham and Women's Hospital from Janssen, Bayer, Bristol-Myers Squibb/Sanofi, Daiichi Sankyo, and AstraZeneca outside the submitted work; and personal fees from Janssen, American Genomics, and Boehringer Ingelheim outside the submitted work. NOS has received grants from the National Institutes of Health during the study; and personal fees from American Genomics outside the submitted work. DIC has received research support for genetic analysis in the JUPITER population from AstraZeneca. MC has received non-financial support (as a member of the board) from Genomics England. JJD is employed at Quest Diagnostics, a company that offers tests for cardiovascular disease, and has received personal fees from Quest Diagnostics outside the submitted work. CH is employed at Pfizer, and has received personal fees from Pfizer outside the submitted work. CPC has received research grant support through Brigham and Women's Hospital from Accumetrics, Arisaph, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, Regeneron, Sanofi, and Takeda; personal fees from Accumetrics, CSL Behring, Essentialis, Merck, Regeneron, Sanofi, Takeda, Bristol-Myers Squibb, Lipimedix, and Pfizer; and has been on the advisory board for Bristol-Myers Squibb, Lipimedix, and Pfizer, outside the submitted work. FS has received grants from Bristol-Myers Squibb during the study, and has received consultation on a legal case from Pfizer, outside the submitted work. NP has received personal fees from Pfizer, and grants from Servier, Pfizer, and Amgen outside the submitted work. PS has received grant support through Imperial College London from Pfizer, and personal fees (honoraria) from Pfizer for lectures outside the submitted work. PMR has received research grants through Brigham and Women's Hospital from AstraZeneca and Amgen. Outside the submitted work, he has received grants through the Brigham and Women's Hospital from Novartis and Pfizer, and is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. EB has received grants through Brigham and Women's Hospital from Merck and Bristol-Myers Squibb and uncompensated consultancies and lectures from Merck, related to the submitted work. Outside the submitted work, he has received grants from Daiichi Sankyo, Duke University, AstraZeneca, GlaxoSmithKline, Johnson and Johnson, and Sanofi Aventis; personal fees for consultancies from Genzyme, The Medicines Company, and Sanofi-Aventis; and personal fees for lectures from Menari International, Medscape, Bayer, and Daiichi Sankyo. SK has received grants from the National Institutes of Health during the conduct of the study; research grant support from Merck and Celera, outside the submitted work; and personal fees from Catabasis, Regeneron, Amgen, Amarin, and Eli Lilly outside the submitted work. MSS has received research grant support through Brigham and Women's Hospital from Abbott Laboratories, Accumetrics, Amgen, AstraZeneca, AstraZeneca-Bristol-Myers Squibb Alliance, BRAHMS, Bristol-Myers Squibb-Sanofi-Aventis Joint Venture, Critical Diagnostics, Daiichi-Sankyo, diaDexus, Eisai, Genzyme, GlaxoSmithKline, Intarcia, Merck, Nanosphere, Ortho-Clinical Diagnostics, Roche Diagnostics, Sanofi-Aventis, Singulex, and Takeda; and has acted as a consultant for Aegerion, Amgen, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo/Eli Lilly, GlaxoSmithKline, Intarcia, Merck, MyoKardia, Pfizer, Sanofi-Aventis, Vertex, Zeus, Cubist, and Quest Diagnostics. JGS, FN, and OM declare no competing interests.

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