CLINICAL RESEARCH
Prevention and epidemiology

Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study

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Aims	Statins reduce LDL cholesterol (LDL-C) and the risk of vascular events, but it remains uncertain whether there is clinically relevant genetic variation in their efficacy. This study of 18 705 individuals aims to identify genetic variants related to the lipid response to simvastatin and assess their impact on vascular risk response.
Methods and results	A genome-wide study of the LDL-C and apolipoprotein B (ApoB) response to 40 mg simvastatin daily was performed in 3895 participants in the Heart Protection Study, and the nine strongest associations were tested in 14 810 additional participants. Selected candidate genes were also tested in up to 18 705 individuals. There was 90% power to detect differences of 2.5% in LDL-C response (e.g. 42.5 vs. 40% reduction) in the genome-wide study and of 1% in the candidate gene study. None of the associations from the genome-wide study was replicated, and nor were significant associations found for 26 of 36 candidates tested. Novel lipid response associations with variants in *LPA*, *CELSR2/PSRC1/SORT1*, and *ABCC2* were found, as well as confirmatory evidence for published associations in *LPA*, *APOE*, and *SLCO1B1*. The largest and most significant effects were with *LPA* and *APOE*, but were only 2–3% per allele. Reductions in the risk of major vascular events during 5 years of statin therapy among 18 705 high-risk patients did not differ significantly across genotypes associated with the lipid response.
Conclusions	Common genetic variants do not appear to alter the lipid response to statin therapy by more than a few per cent, and there were similar large reductions in vascular risk with simvastatin irrespective of genotypes associated with the lipid response to simvastatin. Consequently, their value for informing clinical decisions related to maximizing statin efficacy appears to be limited.
Keywords	Pharmacogenetics • Statins • LDL-C • ApoB

Introduction

Statin therapy is a widely prescribed, well-tolerated, and effective approach to lowering blood levels of low-density lipoprotein cholesterol (LDL-C) and the risk of vascular events.[1] Standard statin regimens typically reduce LDL-C by ~40%,[2] and greater absolute reductions in LDL-C produce greater reductions in the risk of major vascular events.[1] The lipid response to statins is perceived to vary between individuals and to have genetic influences,[3] but reliable large-scale evidence of pharmacogenetic interactions and the impact on the risk response to statins is limited. Therefore, it remains unclear whether genetic variation is relevant to the effects and clinical management of statin therapy.

Genetic associations with the lipid response to statin therapy have been reported (for example with *APOE*, *SLCO1B1*, *LPA*, *PCSK9*, and *HMGCR*), but their effects have been relatively modest and most have been inconsistently replicated.[4–18] Furthermore, little is known about the impact of variants associated with lipid response on the reduction in vascular risk with statin therapy. The majority of previous studies of lipid response to statin have adopted a candidate-gene approach.[6–9,12–14,16] Hypothesis-free genome-wide investigations of the lipid response to statin have only been reported in a total of ∼10 000 individuals for LDL-C response and ∼3500 individuals for apolipoprotein B (ApoB) response.[4,5,15,18] The most convincing lipid response associations have been in genes with validated associations for statin-related adverse events or lipid levels.[19,20] In addition, genes related to statin pharmacokinetics and pharmacodynamics,[3,21] and coronary heart disease (CHD) risk[22,23] are plausible candidates for variation in response to statin therapy.

The aim of the present study was to investigate the associations of common genetic variants with response to statin therapy. It includes genome-wide association analyses of the LDL-C and ApoB responses to 40 mg simvastatin daily in 3895 participants in the Heart Protection Study and independent testing in a further 14 810 of the participants. The effects of selected candidate genes on the lipid response to statins were also assessed in up to 18 705 participants. Finally, the effects of variants that affected lipid response on the reductions in major vascular events produced by statin therapy were assessed among 18 705 genotyped patients randomly allocated simvastatin vs. placebo for an average of 5 years.

Methods

The design of the study is outlined in *Figure 1* and further details are provided below.

The Heart Protection Study

Between 1994 and 1997, 20 536 men and women aged 40–80 years were recruited from 69 collaborating hospitals in the UK (with ethics committee approval). Participants were eligible for inclusion if they had non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L (135 mg/dL) and either a previous diagnosis of coronary disease, ischaemic stroke, other occlusive disease of non-coronary arteries, diabetes mellitus, or (if men 65 years or older) treated hypertension. Patients were not on statin therapy at entry into the study. At the screening visit, all participants provided written consent and began a pre-randomization 'run-in' phase involving 4 weeks of placebo followed by 4–6 weeks of 40 mg simvastatin daily, after which fully compliant individuals were randomly allocated to 40 mg simvastatin daily or matching placebo for ∼5 years. A non-fasting blood sample was taken at screening (i.e. before starting any statin therapy) and at the end of run-in (i.e. while on 40 mg simvastatin daily). The pre-specified primary outcome for assessing the effect of statin therapy in different subgroups was the first occurrence after randomization of an incident major vascular event (defined as either non-fatal MI or coronary death, coronary or non-coronary revascularizations, or any stroke). Further details of the Heart Protection Study are reported elsewhere.[24,25]

Laboratory methods

In the central laboratory, Beckman autoanalysers used standard spectrophotometric enzymatic methods to measure total cholesterol and lipid fractions (including LDL-C directly) and immunoturbidimetric methods to measure ApoB. Coefficients of variation for lipid measurements were typically <5%.

Genotyping methods

Genome-wide study

A random selection of 4000 self-reported Caucasians with lipids and other biomarker measurements were selected, and genotypes measured using the Illumina 610K Quad panel. Genome-wide data were available for 3895 individuals after quality control exclusions including inadequate DNA, discrepant sex, repeated samples, and poor (<95%) genotyping success rate. Single nucleotide polymorphisms (SNPs) with <0.5% minor allele frequency, <95% call rate, or significant deviation from Hardy–Weinberg equilibrium ($P < 5 \times 10^{-7}$) were excluded, leaving a total of 546 210 SNPs for analysis. Single nucleotide polymorphisms from the genome-wide analysis were selected for independent testing if $P < 1 \times 10^{-5}$ for associations with either the LDL-C or the ApoB response to simvastatin therapy, or if $P < 5 \times 10^{-5}$ for both the LDL-C and ApoB responses. The SNPs selected from the genome-wide analysis were genotyped using custom I.PLEX panels in the remaining 14 810 participants in the Heart Protection Study with available DNA.

Candidate gene study

Single nucleotide polymorphisms in loci that had previously been associated with lipid response, statin pharmacokinetics or pharmacodynamics, statin-related side-effects, LDL-C levels, or CHD risk were selected for the candidate gene study.[4,5,12,15,18–23] Thirty-six candidate SNPs were custom genotyped including 33 SNPs using I.PLEX panels in the 14 810 individuals used for independent testing in the genome-wide study and a further 3 SNPs (rs4149056 and rs2306283 in *SLCO1B1* and rs4299376 in *ABCG5/8*) in previous experiments in the same individuals.[19,22] Data were also available for most of these variants from the genome-wide panel, yielding directly measured genotypes in up to 18 705 individuals. To allow for multiple comparisons, a threshold of $P < 0.001$ was taken to indicate statistical significance for these candidate SNPs. For completeness, the remaining literature-based candidate loci that were not selected for custom genotyping[4,5,12,15,18–23] were examined directly or in proxy SNPs[26] in the genome-wide data where possible.

Additional information

Quality control details and allele frequencies for SNPs selected for custom genotyping are shown separately for the genome-wide panel and custom genotyping data in the Supplementary material online, *Table S1*. The results for SNPs showing deviation from Hardy–Weinberg equilibrium (rs857252 and rs9982601) should be interpreted with caution. The minor allele was coded as the effect allele in all analyses and chromosomal positions were based on NCBI build 36.

Statistical methods

The proportional LDL-C or ApoB responses were defined by the changes in $\log_e$ lipid levels from the screening visit prior to starting statin therapy ('off-statin') to the randomization visit following 4–6 weeks on 40 mg simvastatin daily ('on-statin') in compliant individuals. Linear regression was used to estimate the associations between genetic variants and lipid response to statin. The additional per cent reduction per allele was calculated as $100 \times \exp(M) \times (1-\exp(\beta))$, where β is the regression estimate of the per allele effect on the change in the log lipid level and M is the overall mean change in the log lipid level. Percentage lipid reductions within comparison groups
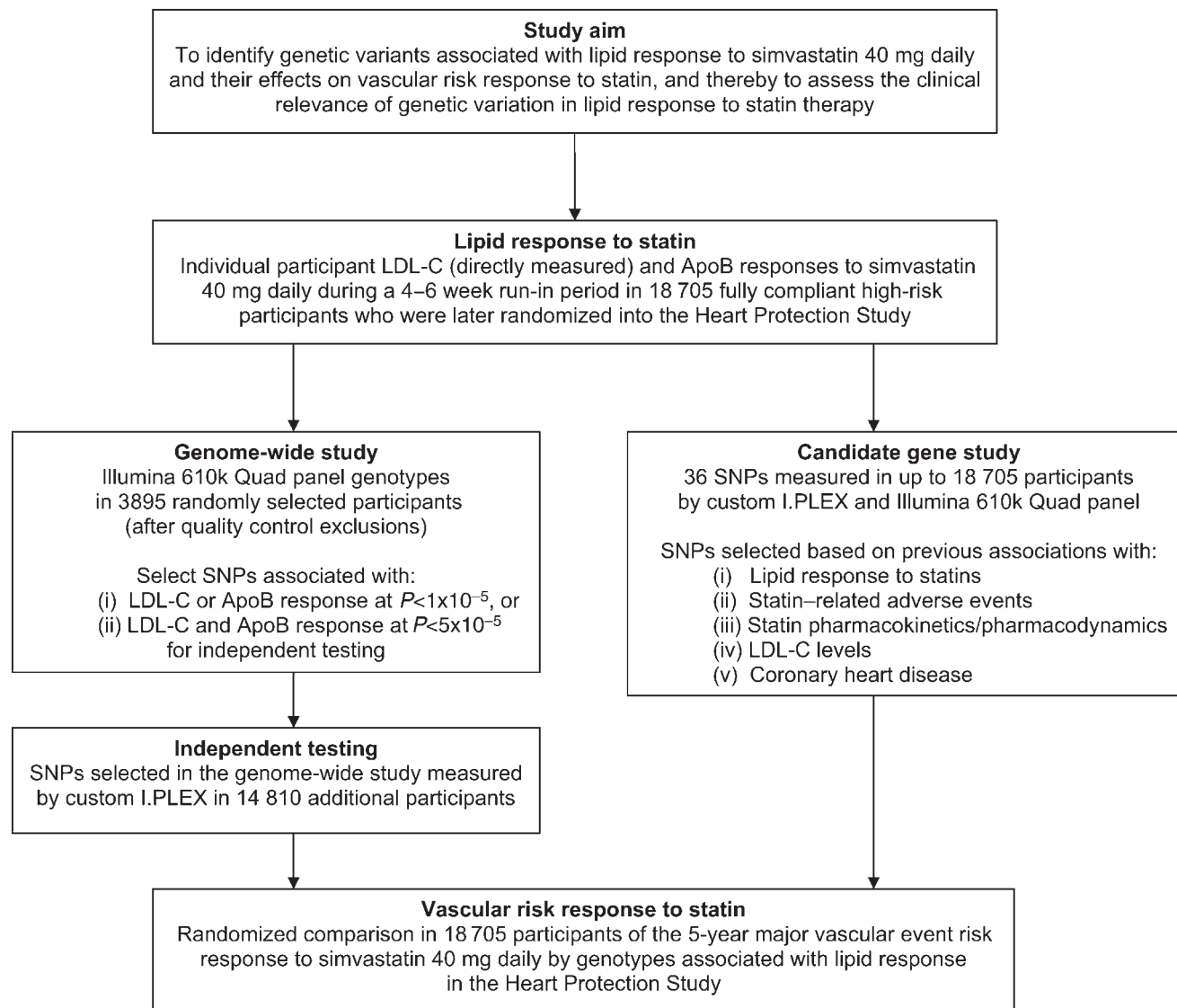
Figure 1 Study design outline.

were estimated as $100 \times (1-exp(M_g))$, where M_g denotes the mean change in the log lipid level within the group. Standard errors (SEs) were estimated from the 95% confidence intervals (CIs). Secondary analyses included estimating the associations with the absolute lipid response to statin and with off-statin lipid levels. Where appropriate, genotype scores summarizing the available information at a locus were calculated based on previously published methods or joint regression analyses. Lipid response estimates for candidate SNPs were calculated using all available genotype data from the different genotyping platforms (after quality control analyses showed no heterogeneity between the results). Cox proportional hazard models were used to estimate the effects of genotypes on the proportional risk response to simvastatin during the randomized phase of the Heart Protection Study. Differences in the proportions of events were used to estimate the absolute risk response to statin. All analyses were performed using PLINK (version 1.07) and SAS (version 9).

Results

In the 18 705 genotyped participants, the mean off-statin and on-statin LDL-C levels during the pre-randomized phase were 3.37 and 1.98 mmol/L, respectively (*Table 1*). On average, compliance with 40 mg simvastatin daily for 4–6 weeks resulted in a 42.4% reduction in LDL-C and a 32.8% reduction in ApoB. In absolute terms, this corresponded to a 1.39 mmol/L reduction in LDL-C and 0.37 g/L reduction in ApoB. Additional characteristics are shown in the Supplementary material online, *Table S2*.

Lipid response to statin in the genome-wide association study

This genome-wide association study in 3895 individuals had 90% power to detect a 2.5% difference (e.g. 42.5 vs. 40%) in the LDL-C response in SNPs with 15% minor allele frequency and to detect even smaller differences in more common SNPs. The QQ plot of the association *P*-values did not indicate an excess of significant results compared with those expected by chance alone (Supplementary material online, *Figure S1*) and only nine SNPs passed the pre-defined threshold for independent testing (*Figure 2*). Of these, eight SNPs were successfully genotyped in an additional 14 810 individuals and the one (rs17510813) that failed genotyping was strongly correlated ($r^2 = 0.8$) with a SNP (rs17595975) that was successfully genotyped. None of these SNP associations was, however, confirmed in the independent data set (all $P > 0.05$; *Table 2*).

Lipid response to statin in literature-based candidate genes

Custom genotyping data were available for 36 SNPs in literature-based candidate genes[4,5,12,15,18–23] in up to 18 705 individuals. The study had 90% power to detect differences in the lipid response of <1% at $P < 0.001$ in SNPs with at least a 15% minor allele frequency (which is representative of the candidates selected). No significant associations were found for 26 of these SNPs (Supplementary material online, *Tables S3* and *S4*). The results for the 10 SNPs at five loci that did reach statistical significance ($P < 0.001$) after correction for multiple testing are shown in *Table 3*. These five loci are discussed below (in order of the statistical significance for the proportional LDL-C or ApoB response).

LPA locus

For two SNPs at the *LPA* locus, rs3798220 and rs10455872, there were 2.30% and 3.15% smaller proportional LDL-C reductions
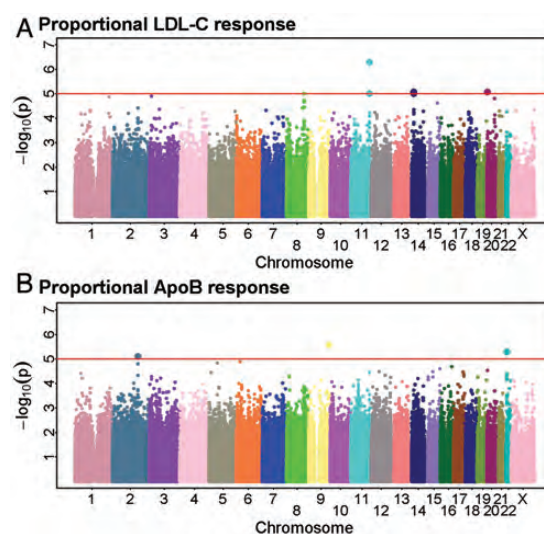
Figure 2 The genome-wide Manhattan plot of associations with proportional (*A*) LDL cholesterol response and (*B*) apolipoprotein B response to 40 mg simvastatin daily in 3895 individuals. Single nucleotide polymorphisms with $P < 1 \times 10^{-5}$ for either LDL cholesterol or apolipoprotein B response, or if $P < 5 \times 10^{-5}$ for both LDL cholesterol and apolipoprotein B response associations were selected for independent testing. A reference line has been plotted at $P = 1 \times 10^{-5}$.

Table 1 Mean (95% CI) lipid levels and lipid response in 18 705 genotyped participants

	Off-statin	On-statin	Response to 40 mg simvastatin daily	
			Proportional reduction	Absolute reduction
LDL-C (mmol/L)	3.37 (3.36, 3.38)	1.98 (1.97, 1.99)	42.4% (42.2, 42.6%)	1.39 (1.38, 1.40)
ApoB (g/L)	1.14 (1.14, 1.14)	0.77 (0.77, 0.78)	32.8% (32.6, 32.9%)	0.37 (0.36, 0.37)
HDL-C (mmol/L)	1.06 (1.06, 1.07)	1.05 (1.04, 1.05)	1.3% (1.1, 1.5%)	0.01 (0.01, 0.02)
ApoA$_1$ (g/L)	1.19 (1.19, 1.20)	1.22 (1.22, 1.22)	−2.0% (−2.2, −1.9%)	−0.02 (−0.03, −0.02)

Table 2 Proportional lipid response associations (per allele) for the top-hits from the genome-wide analyses that were selected for custom genotyping in independent samples[a]

SNP	Chr	Nearby gene(s)/locus	Effect/other allele	Genome-wide analysis				Independent testing		
				Effect allele freq	n	Additional % reduction[b] (95% CI)	P-value	n	Additional % reduction[b] (95% CI)	P-value
LDL-C response										
rs10497323	2	*XIRP2*	C/T	0.16	3894	−1.58 (−2.39, −0.78)	9.9×10^{-5}	14 454	0.21 (−0.23, 0.65)	0.35
rs3749004	2	*XIRP2*	G/A	0.11	3887	−1.96 (−2.91, −1.02)	3.8×10^{-5}	14 371	0.23 (−0.29, 0.74)	0.39
rs7047055	9	*MED27*	T/C	0.49	3888	1.20 (0.62, 1.77)	5.3×10^{-5}	13 354	−0.16 (−0.49, 0.17)	0.34
rs9888300	11	*11q24*	C/A	0.39	3888	1.50 (0.92, 2.07)	5.3×10^{-7}	14 405	−0.11 (−0.44, 0.21)	0.49
rs10893006	11	*11q24*	T/C	0.34	3849	1.38 (0.77, 1.97)	9.9×10^{-6}	14 413	−0.07 (−0.40, 0.26)	0.67
rs17510813	14	*SRP54/FAM177A1*	T/C	0.12	3893	−2.07 (−3.00, −1.15)	8.4×10^{-6}			
rs17595975	14	*SRP54/FAM177A1*	T/G	0.11	3873	−2.17 (−3.15, −1.20)	9.8×10^{-6}	14 115	−0.19 (−0.71, 0.32)	0.47
rs857252	20	*UBOX5/FASTKD5*	G/T	0.38	3891	−1.39 (−2.01, −0.77)	8.6×10^{-6}	13 628	−0.07 (−0.41, 0.26)	0.67
rs5759068	22	*22q11*	T/C	0.39	3872	−1.25 (−1.87, −0.64)	5.4×10^{-5}	14 446	−0.16 (−0.49, 0.16)	0.33
ApoB response										
rs10497323	2	*XIRP2*	C/T	0.16	3894	−1.52 (−2.20, −0.85)	8.0×10^{-6}	14 454	0.03 (−0.35, 0.40)	0.89
rs3749004	2	*XIRP2*	G/A	0.11	3887	−1.62 (−2.41, −0.83)	4.7×10^{-5}	14 371	0.10 (−0.34, 0.54)	0.65
rs7047055	9	*MED27*	T/C	0.49	3888	1.17 (0.69, 1.66)	2.6×10^{-6}	13 354	−0.03 (−0.32, 0.25)	0.82
rs9888300	11	*11q24*	C/A	0.39	3888	1.05 (0.55, 1.54)	3.4×10^{-5}	14 405	−0.19 (−0.47, 0.09)	0.18
rs10893006	11	*11q24*	T/C	0.34	3849	0.92 (0.41, 1.43)	4.5×10^{-4}	14 413	−0.20 (−0.49, 0.08)	0.17
rs17510813	14	*SRP54/FAM177A1*	T/C	0.12	3893	−1.31 (−2.08, −0.55)	7.0×10^{-4}			
rs17595975	14	*SRP54/FAM177A1*	T/G	0.11	3873	−1.28 (−2.09, −0.48)	1.7×10^{-3}	14 115	−0.03 (−0.48, 0.41)	0.88
rs857252	20	*UBOX5/FASTKD5*	G/T	0.38	3891	−1.09 (−1.61, −0.58)	2.9×10^{-5}	13 628	−0.07 (−0.36, 0.21)	0.62
rs5759068	22	*22q11*	T/C	0.39	3872	−1.19 (−1.70, −0.67)	5.2×10^{-6}	14 446	−0.18 (−0.46, 0.10)	0.20

[a]Results are ordered by chromosomal position. SNPs from the genome-wide analysis were selected for custom genotyping in independent samples only if $P < 1 \times 10^{-5}$ for associations with either LDL-C or ApoB response, or if $P < 5 \times 10^{-5}$ for both LDL-C and ApoB response.

[b]The average proportional LDL-C reduction in response to simvastatin 40 mg daily was 42.36% and the average proportional reduction in ApoB was 32.76%.

Table 3 Proportional lipid response associations (per allele) for literature-based candidate single nucleotide polymorphisms that were selected for custom genotyping and that reached statistical significance ($P < 0.001$)[a]

SNP	Chr	Nearby gene(s)/locus	n	Effect/ other allele	Effect allele freq	LDL-C response		ApoB response	
						Additional % reduction[b] (95% CI)	P-value	Additional % reduction[b] (95% CI)	P-value
rs646776	1	CELSR2/PSRC1/ SORT1	18 289	C/T	0.21	0.47 (0.13, 0.80)	6.7×10^{-3}	0.76 (0.47, 1.05)	2.4×10^{-7}
rs3798220	6	LPA	14 472	C/T	0.02	−2.30 (−3.47, −1.15)	7.1×10^{-5}	−2.09 (−3.09, −1.11)	2.5×10^{-5}
rs10455872	6	LPA	14 462	G/A	0.09	−3.15 (−3.74, −2.58)	8.1×10^{-28}	−2.86 (−3.35, −2.36)	6.5×10^{-31}
rs2002042	10	ABCC2	18 027	T/C	0.25	0.65 (0.33, 0.97)	8.2×10^{-5}	0.56 (0.28, 0.83)	7.5×10^{-5}
rs11045819	12	SLCO1B1	14 338	A/C	0.16	0.92 (0.49, 1.34)	2.4×10^{-5}	0.66 (0.29, 1.02)	4.3×10^{-4}
rs4149056	12	SLCO1B1	16 867	C/T	0.15	−1.15 (−1.57, −0.74)	5.0×10^{-8}	−0.96 (−1.31, −0.60)	1.0×10^{-7}
rs4803750	19	APOE Cluster	18 326	G/A	0.07	1.22 (0.68, 1.74)	8.5×10^{-6}	1.21 (0.75, 1.66)	2.6×10^{-7}
rs2075650	19	APOE Cluster	18 265	G/A	0.14	−0.82 (−1.22, −0.41)	7.8×10^{-5}	−0.77 (−1.12, −0.42)	1.3×10^{-5}
rs7412	19	APOE Cluster	14 455	T/C	0.08	2.55 (1.98, 3.11)	4.8×10^{-18}	2.84 (2.35, 3.32)	4.9×10^{-29}
rs4420638	19	APOE Cluster	14 388	G/A	0.18	−0.96 (−1.38, −0.54)	6.4×10^{-6}	−0.91 (−1.27, −0.55)	5.7×10^{-7}

[a]Results are ordered by chromosomal position. Results for all literature-based candidate SNPs selected for custom genotyping are shown in Supplementary material online, *Table S3* and *S4*.
[b]The average proportional LDL-C reduction in response to simvastatin 40 mg daily was 42.36% and the average proportional reduction in ApoB was 32.76%.

with statin therapy per minor allele and similar effects on the ApoB response (*Table 3*). These two *LPA* SNPs were independent ($r^2 = 0.02$) and the sum of the minor alleles in the two SNPs was used to construct an *LPA* genotype score (as had been done previously for associations with coronary disease risk).[27] Higher *LPA* genotype scores were associated with smaller proportional lipid reductions but higher off-statin lipid levels, and with slightly smaller absolute lipid reductions (*Figure 3*).

APOE locus
Of the four genotyped SNPs in the *APOE* region, only rs7412 (the ε2 SNP) and rs4420638 (an approximate proxy for the rs429358 ε4 SNP; $r^2 \sim 0.7$)[28,29] contributed independent information. The rs7412 T allele (ε2) was strongly associated with off-statin LDL-C levels, with a 0.55 mmol/L lower mean LDL-C per variant (*Figure 3*). Consequently, despite being associated with a 2.5% larger proportional reduction in LDL-C with statin therapy, it was also associated with smaller absolute reductions. In contrast, the rs4420638 G allele (ε4 proxy) was associated with a 0.16 mmol/L higher off-statin LDL-C, a 1% smaller proportional reduction, and a slightly larger absolute reduction (*Table 3*, Supplementary material online, *Table S3*).

SLCO1B1 locus
The rs11045819 and rs4149056 SNPs each showed 1% differences per allele in the proportional lipid reduction (*Table 3*), and rs12372157 and rs2306283 showed smaller effects (Supplementary material online, *Tables S3* and *S4*). All four of these SNPs contributed independent information and *SLCO1B1* genotype scores were calculated using the joint regression coefficients for the proportional LDL-C and ApoB responses. Higher scores were associated with smaller proportional lipid reductions per tertile (*Figure 3*) and, since the score was not associated with differences

in off-statin lipid levels, higher scores were also associated with smaller absolute lipid reductions.

CELSR2/PSRC1/SORT1 locus
The rs646776 C allele was associated with a 0.47% larger proportional LDL-C reduction and 0.76% larger ApoB reduction (*Figure 3*). However, it was also strongly associated with lower off-statin lipid levels, and the net effect was smaller absolute reductions.

ABCC2 locus
The rs2002042 T allele was associated with a 0.65% larger proportional LDL-C reduction and 0.56% larger ApoB reduction and, since it was not associated with off-statin lipid levels, was associated with slightly larger absolute reductions in the lipid response.

Other literature-based candidate single nucleotide polymorphisms
Suggestive associations (unadjusted $P < 0.01$) with proportional lipid response were also seen with SNPs in *APOA5/ZNF259*, *LIPC*, *ABCB1*, *PON1*, and *CETP* (Supplementary material online, *Tables S3−S5*). In secondary analyses of the absolute lipid response, SNPs in or near *LDLR*, *CETP*, and *LIPC* were significantly associated ($P < 0.001$; Supplementary material online, *Tables S3* and *S4*), and there were suggestive associations with SNPs in or near *APOB* and *ABCB1* ($P < 0.01$; Supplementary material online, *Table S5*). These associations with an absolute lipid response corresponded to trends in off-statin lipid levels (Supplementary material online, *Tables S3−S5*). Other SNPs previously associated with the lipid response—such as rs10474433 (*HMGCR*), rs2231142 (*ABCG2*), rs9367897 (a direct proxy for rs6924995; *MYLIP*), and rs1627770 (*ALG10*)[5,15,18,30] were not confirmed in the present study (Supplementary material online, *Tables S3−S5*).

Gene/locus (SNP)	N	LDL–C (mmol/L)			ApoB (g/L)		
		Mean off–statin (SE)	Per cent reduction (SE)	Absolute reduction (SE)	Mean off–statin (SE)	Per cent reduction (SE)	Absolute reduction (SE)
LPA score							
0 variants	11480	3.36 (0.008)	43.2% (0.1%)	1.41 (0.006)	1.13 (0.002)	33.5% (0.1%)	0.372 (0.002)
1 variant	2794	3.43 (0.015)	40.0% (0.3%)	1.34 (0.012)	1.17 (0.004)	30.6% (0.2%)	0.351 (0.003)
2 variants	185	3.56 (0.060)	37.5% (1.1%)	1.28 (0.047)	1.22 (0.017)	28.7% (0.9%)	0.342 (0.012)
Per variant effect (SE)		*0.08 (0.015)*	*−3.11 (0.27)*	*−0.069 (0.012)*	*0.04 (0.004)*	*−2.82 (0.23)*	*−0.020 (0.003)*
		P=1.1x10⁻⁷	*P=4.4x10⁻³²*	*P=7.8x10⁻⁹*	*P=7.2x10⁻¹⁹*	*P=1.0x10⁻³⁵*	*P=6.0x10⁻¹⁰*
APOE (rs7412)							
0 ε2 variants	12305	3.45 (0.007)	42.1% (0.1%)	1.42 (0.006)	1.16 (0.002)	32.5% (0.1%)	0.370 (0.002)
1 ε2 variant	2060	2.96 (0.016)	44.6% (0.3%)	1.28 (0.014)	1.04 (0.005)	35.0% (0.3%)	0.357 (0.004)
2 ε2 variants	90	1.80 (0.056)	48.1% (1.3%)	0.85 (0.066)	0.80 (0.025)	40.9% (1.1%)	0.324 (0.018)
Per ε2 variant effect (SE)		*−0.55 (0.017)*	*2.55 (0.29)*	*−0.159 (0.014)*	*−0.13 (0.005)*	*2.84 (0.25)*	*−0.014 (0.004)*
		P=2.1x10⁻²¹⁵	*P=4.8x10⁻¹⁸*	*P=2.7x10⁻³⁰*	*P=6.0x10⁻¹⁵⁴*	*P=4.9x10⁻²⁹*	*P=1.1x10⁻⁴*
SLCO1B1 score							
Lower third	3686	3.38 (0.013)	43.3% (0.2%)	1.42 (0.010)	1.14 (0.004)	33.4% (0.2%)	0.373 (0.003)
Middle third	4322	3.35 (0.012)	42.6% (0.2%)	1.39 (0.010)	1.13 (0.003)	32.9% (0.2%)	0.365 (0.003)
Upper third	4059	3.39 (0.013)	41.5% (0.2%)	1.37 (0.010)	1.14 (0.004)	32.0% (0.2%)	0.359 (0.003)
Per group effect (SE)		*0.00 (0.009)*	*−0.88 (0.16)*	*−0.025 (0.007)*	*0.00 (0.003)*	*−0.69 (0.14)*	*−0.007 (0.002)*
		P=0.62	*P=2.6x10⁻⁸*	*P=4.9x10⁻⁴*	*P=0.34*	*P=2.4x10⁻⁷*	*P=3.1x10⁻⁴*
CELSR2/PSRC1/SORT1 (rs646776)							
TT	11305	3.41 (0.008)	42.1% (0.1%)	1.40 (0.006)	1.16 (0.002)	32.4% (0.1%)	0.366 (0.002)
CT	6137	3.31 (0.010)	42.6% (0.2%)	1.37 (0.008)	1.12 (0.003)	33.2% (0.1%)	0.363 (0.002)
CC	847	3.17 (0.026)	43.0% (0.5%)	1.32 (0.022)	1.08 (0.007)	34.0% (0.4%)	0.357 (0.006)
Per C allele effect (SE)		*−0.11 (0.010)*	*0.47 (0.17)*	*−0.031 (0.008)*	*−0.04 (0.003)*	*0.76 (0.15)*	*−0.004 (0.002)*
		P=6.1x10⁻²⁸	*P=6.7x10⁻³*	*P=9.5x10⁻⁵*	*P=3.9x10⁻⁴¹*	*P=2.4x10⁻⁷*	*P=0.08*
ABCC2 (rs2002042)							
CC	10212	3.37 (0.008)	42.0% (0.1%)	1.37 (0.006)	1.14 (0.002)	32.4% (0.1%)	0.361 (0.002)
TC	6668	3.37 (0.010)	42.8% (0.2%)	1.40 (0.008)	1.14 (0.003)	33.1% (0.1%)	0.370 (0.002)
TT	1147	3.36 (0.024)	43.1% (0.4%)	1.41 (0.019)	1.14 (0.007)	33.4% (0.3%)	0.373 (0.005)
Per T allele effect (SE)		*0.00 (0.010)*	*0.65 (0.16)*	*0.024 (0.008)*	*0.00 (0.003)*	*0.56 (0.14)*	*0.007 (0.002)*
		P=0.84	*P=8.2x10⁻⁵*	*P=1.9x10⁻³*	*P=0.56*	*P=7.5x10⁻⁵*	*P=5.9x10⁻⁴*

35% 40% 45% 50%
Percent reduction (95% CI)

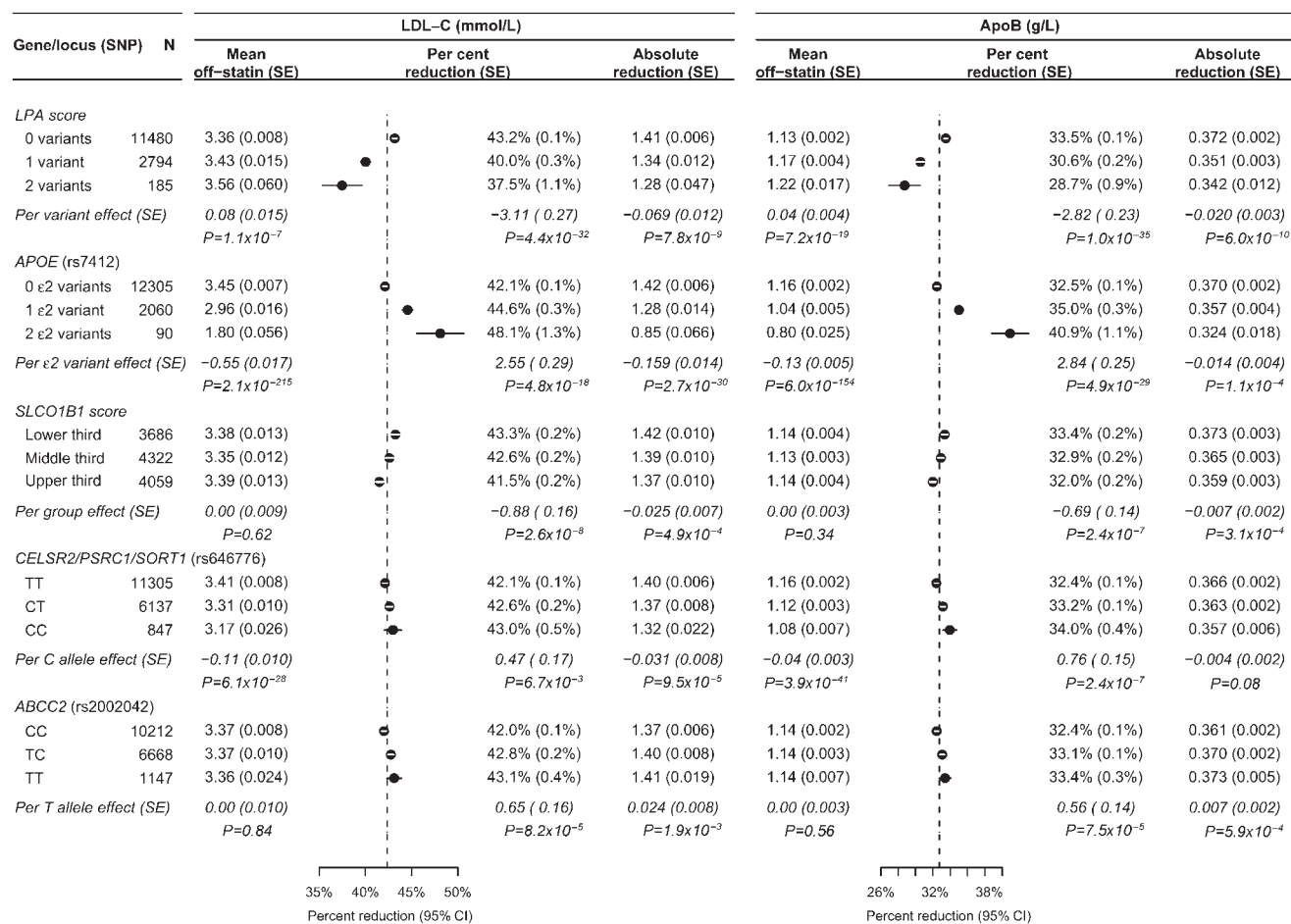26% 32% 38%
Percent reduction (95% CI)

Figure 3 Lipid and lipid response associations with literature-based candidate loci that were significantly associated ($P < 0.001$) with the proportional lipid response. Estimated effects and standard errors are shown. Per cent reductions and 95% confidence intervals by genotype are plotted and the average response in all genotyped participants is shown by a dashed line. The *SLCO1B1* score was calculated by joint regression on rs4149056, rs11045819, rs12372157, and rs2306283. The regression coefficients (per additional effect allele) were 0.013, −0.018, 0.015, −0.010, respectively, for the proportional LDL cholesterol response, and 0.011, −0.010, 0.010, −0.008, respectively, for the proportional apolipoprotein B response.

Vascular risk response to statin by genotype

On average during the 5-year randomized treatment period in the Heart Protection Study, there was a 1.0 mmol/L reduction in LDL-C between participants allocated 40 mg simvastatin daily vs. placebo.[25] In the genotyped participants, random allocation to 40 mg simvastatin daily reduced the proportional 5-year risk of major vascular events by 23.3% (95% CI: 18.5–27.8%) and the absolute risk by 5.2% (95% CI: 4.0–6.4%; *Figure 4*). There were no statistically significant differences in either the proportional or the absolute reductions in major vascular events by genotype at any of the loci that were associated with proportional lipid response (*Figure 4*). However, some of these variants were associated with differences in the underlying risk of major vascular events (e.g. placebo group risk of 27.5% in *LPA* carriers vs. 24.2% in non-carriers) and with differences, albeit non-significant, in the absolute risk reductions (e.g. 6.5% in *LPA* carriers vs. 4.3% in non-carriers).

Discussion

The present study identified associations with the lipid response to simvastatin for SNPs in three genes—*LPA*, *CELSR2/PSRC1*/SORT1, and *ABCC2*—that had not been reported previously. It also provided confirmation for independent SNP associations at the *LPA*, *APOE*, and *SLCO1B1* loci that had previously been reported to be associated with the lipid response to other statins.[5,15,18] The 10 variants associated with lipid response in the present study were in LDL-related genes, the *LPA* gene and statin pharmacokinetic genes, and all of them had small effects on the lipid response (0.5–3.0% per allele). Given these findings, it seems unlikely that there are common variants that alter the lipid response to statin therapy by more than a few per cent. This large randomized study also found no significant associations of these variants with the proportional or absolute risk reductions produced by simvastatin therapy, suggesting that the clinical relevance of these variants for guiding statin therapy may be limited.
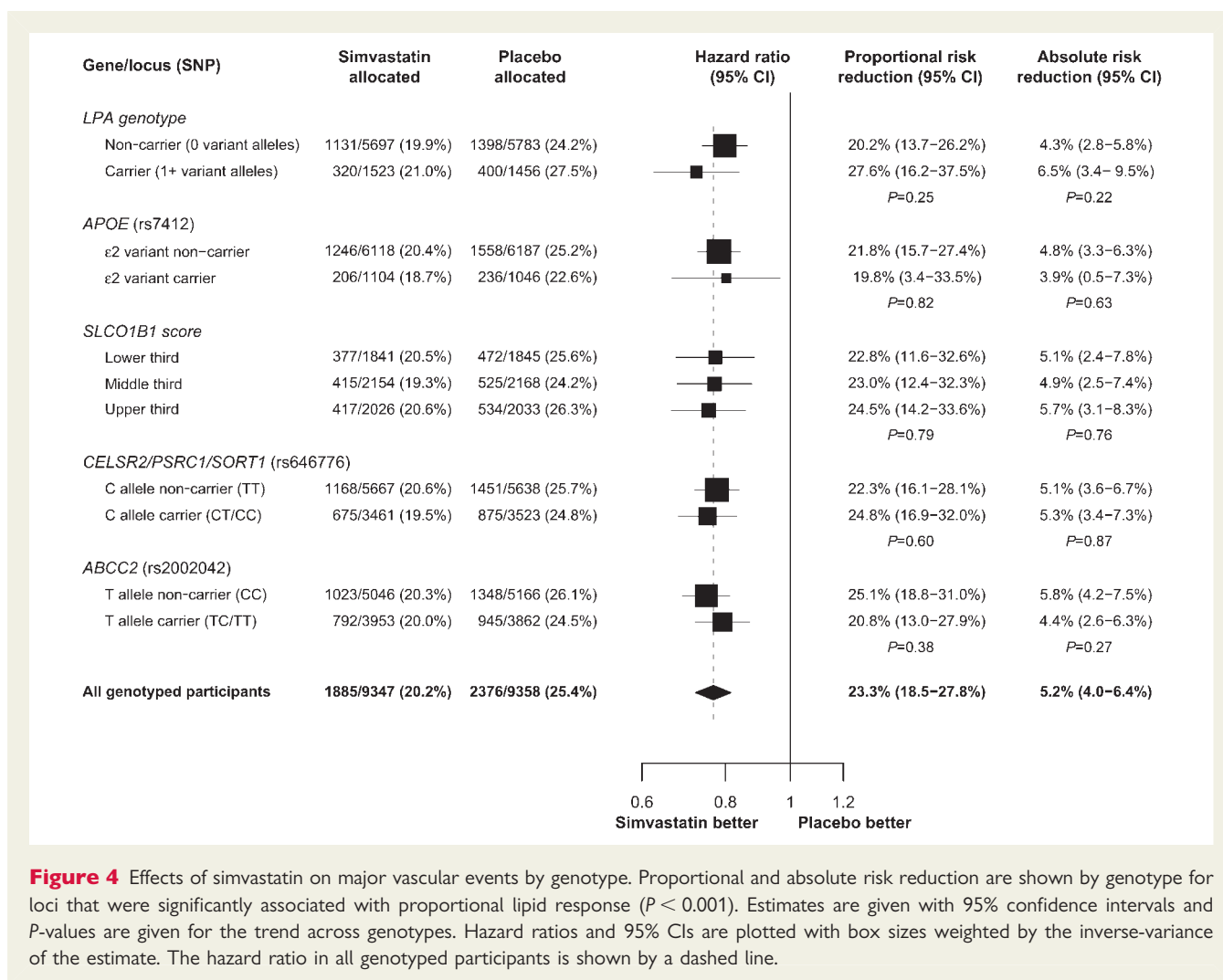
Gene/locus (SNP)	Simvastatin allocated	Placebo allocated	Hazard ratio (95% CI)	Proportional risk reduction (95% CI)	Absolute risk reduction (95% CI)
LPA genotype					
Non-carrier (0 variant alleles)	1131/5697 (19.9%)	1398/5783 (24.2%)		20.2% (13.7–26.2%)	4.3% (2.8–5.8%)
Carrier (1+ variant alleles)	320/1523 (21.0%)	400/1456 (27.5%)		27.6% (16.2–37.5%)	6.5% (3.4–9.5%)
				P=0.25	*P*=0.22
APOE (rs7412)					
ε2 variant non-carrier	1246/6118 (20.4%)	1558/6187 (25.2%)		21.8% (15.7–27.4%)	4.8% (3.3–6.3%)
ε2 variant carrier	206/1104 (18.7%)	236/1046 (22.6%)		19.8% (3.4–33.5%)	3.9% (0.5–7.3%)
				P=0.82	*P*=0.63
SLCO1B1 score					
Lower third	377/1841 (20.5%)	472/1845 (25.6%)		22.8% (11.6–32.6%)	5.1% (2.4–7.8%)
Middle third	415/2154 (19.3%)	525/2168 (24.2%)		23.0% (12.4–32.3%)	4.9% (2.5–7.4%)
Upper third	417/2026 (20.6%)	534/2033 (26.3%)		24.5% (14.2–33.6%)	5.7% (3.1–8.3%)
				P=0.79	*P*=0.76
CELSR2/PSRC1/SORT1 (rs646776)					
C allele non-carrier (TT)	1168/5667 (20.6%)	1451/5638 (25.7%)		22.3% (16.1–28.1%)	5.1% (3.6–6.7%)
C allele carrier (CT/CC)	675/3461 (19.5%)	875/3523 (24.8%)		24.8% (16.9–32.0%)	5.3% (3.4–7.3%)
				P=0.60	*P*=0.87
ABCC2 (rs2002042)					
T allele non-carrier (CC)	1023/5046 (20.3%)	1348/5166 (26.1%)		25.1% (18.8–31.0%)	5.8% (4.2–7.5%)
T allele carrier (TC/TT)	792/3953 (20.0%)	945/3862 (24.5%)		20.8% (13.0–27.9%)	4.4% (2.6–6.3%)
				P=0.38	*P*=0.27
All genotyped participants	1885/9347 (20.2%)	2376/9358 (25.4%)		23.3% (18.5–27.8%)	5.2% (4.0–6.4%)

```
        0.6      0.8    1    1.2
     Simvastatin better   Placebo better
```

Figure 4 Effects of simvastatin on major vascular events by genotype. Proportional and absolute risk reduction are shown by genotype for loci that were significantly associated with proportional lipid response (*P* < 0.001). Estimates are given with 95% confidence intervals and *P*-values are given for the trend across genotypes. Hazard ratios and 95% CIs are plotted with box sizes weighted by the inverse-variance of the estimate. The hazard ratio in all genotyped participants is shown by a dashed line.

LDL-related genes

Several genes (including *APOE*, *CELSR2/PSRC1/SORT1*, and *LDLR*) have previously been associated in genome-wide studies with moderately large effects on off-statin LDL-C levels (>0.1 mmol/L per allele).[20] In the present study, some variants were found to be associated with small, but significant, differences in the proportional lipid response to statin therapy (<3% per allele compared with the overall 42% LDL-C reduction). In each case, the variant was also associated with differences in off-statin LDL-C levels, such that some of the variants produced larger proportional lipid responses. A number of studies have reported effects of these and other LDL-related genes (including *APOE*, *LDLR*, *HMGCR*, and *PCSK9*) on the lipid response to statins.[4–6,8,9,12–16,18] However, some of those studies described the effects only after adjustment for the off-statin LDL-C level (without allowance for the effects of measurement error).[8,9,12,15,16] Given the observed effects of these variants on off-statin LDL-C levels, such adjustments may account for between-study differences in the reported effects of statin therapy on the proportional lipid response.[18,31] Some genes found to be associated with higher LDL-C levels (e.g. *APOE*) have been associated with higher risks of cardiovascular disease.[20] Similarly, in the present study, the effects of these LDL-related genotypes on off-statin LDL-C levels were directionally consistent with their effects on absolute risk in the placebo arm. Large-scale meta-analyses of randomized trials have established that the reduction in the risk of major vascular events with statin therapy is related to the absolute reduction in LDL-C across a wide range of pre-treatment LDL-C levels.[1] In the present randomized trial, despite the small differences in absolute risk and absolute LDL-C reduction associated with some of these variants, simvastatin therapy produced large and significant reductions in vascular risk irrespective of genotype (*Figure 4*).

LPA genotype

Levels of the LDL-like particle lipoprotein(a) [Lp(a)] are largely determined by the *LPA* gene.[32] Previous studies have reported an association of rs10455872 in *LPA* with the lipid response to statin therapy,[5,18] and the present study not only confirms it but has also identified an association with an independent SNP (rs3798220). Assays of LDL-C and ApoB typically include contributions from both LDL and Lp(a) particles, but statin therapy does not reduce the number or cholesterol content of Lp(a) particles.[33] *LPA* variant carriers have higher Lp(a) levels and a greater proportion of their measured LDL-C resides in Lp(a) particles which is not amenable to the effects of statins. Hence, studies with direct measures of Lp(a) molar levels and Lp(a)-cholesterol content are needed to clarify the impact of *LPA* genotype on the lipid response to statin therapy. In the present large randomized trial, the proportional reductions in major vascular events with statin therapy were not significantly different between *LPA* carriers and non-carriers, and remained significant in all *LPA* genotype groups (*Figure 4*). The *LPA* genotype has previously been associated with cardiovascular risk,[5,27] and *LPA* carriers in the present study were at a higher absolute risk of major vascular events than non-carriers. However, although the absolute reduction in risk with statin therapy appeared to be bigger among *LPA* carriers, this difference was also not statistically significant.

Statin pharmacokinetic genes

Several genes that have been implicated in pharmacokinetic pathways[3] have been associated with small differences in the lipid response to statin therapy in both the present study (*SLCO1B1* and *ABCC2*) and previous reports (e.g. *SLCO1B1*, *ABCG2*, and *ABCB1*).[5,12,16] The *SLCO1B1* rs4149056 variant is associated with a weaker lipid response to statin therapy, impaired hepatic uptake, higher blood levels of statins, and a substantially higher risk of myopathy.[19] The increase in myopathy risk seen with this variant in patients on simvastatin makes knowledge of this genotype of potential value in guiding statin choice (especially if other risk factors for myopathy are present). In the present study, however, the *SLCO1B1* and other gene variants involved in statin pharmacokinetics only had small effects (<1% per allele) on the lipid response to statin therapy and, even in combination, the four *SLCO1B1* SNPs and one *ABCC2* SNP only explained <0.5% of the variance in response. Consequently, their value for informing clinical decisions related to maximizing statin efficacy would seem to be limited.

Limitations

The present large study of the lipid response to simvastatin therapy was undertaken in a fully compliant population with individual-level response measurements. But, since only one off-statin and one on-statin lipid measurement was available for all of the participants, it was not possible to adjust the effects of genetic variants on the lipid response for off-statin lipid levels without introducing bias due to measurement error.[18,31] Instead, the observed associations with off-statin lipid levels were considered in the interpretation of the results. These findings are broadly consistent with those from previously reported studies after taking into account differences in genotyping platforms (e.g. the variants that were measured), analytical approaches (in particular, adjustment for off-statin lipid levels) and chance.[5,15,18] The present analyses had 90% power to detect common variants associated with differences of 2.5% in the LDL-C response (e.g. 42.5 vs. 40% reduction) in the genome-wide study and of 1% in the candidate gene study. With 4261 major vascular events among genotyped patients randomized between simvastatin vs. placebo for 5 years, this is the largest single study of the effects of genetic variants on the risk and lipid reductions produced by statin therapy. However, many more events (perhaps through collaborative meta-analyses of several trials) would be needed for genome-wide investigation of variation in the risk response to statins.

Conclusion

Common genetic variants do not appear to alter the lipid response to statin therapy by more than a few per cent. Statin therapy produces substantial proportional reductions in the risks of major vascular events, and these reductions were not found to be materially altered by genetic variants that influence lipid response. These findings support the current policy of basing decisions about the use of statin therapy, and its intensity, chiefly on an individual's estimated risk of having a major vascular event.

Supplementary material

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