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

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Received 23 April 2012; revised 3 August 2012; accepted 18 September 2012; online publish-ahead-of-print 24 October 2012

See page 949 for the editorial comment on this article (doi:10.1093/eurheartj/ehs439)

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.
Impact of common genetic variation

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,21 and coronary heart disease (CHD) risk22,23 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 oxidative 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 immunoturbidometric 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 × 10−5) 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 × 10−5 for associations with either the LDL-C or the ApoB response to simvastatin therapy, or if P < 5 × 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.6–9,12–15,18–22 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 genotyping4,5,12,15,18–23 were examined directly or in proxy SNPs26 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 loge 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 × exp(M) × (1−exp(β)), 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
**Study aim**

To identify genetic variants associated with lipid response to simvastatin 40 mg daily and their effects on vascular risk response to statin, and thereby to assess the clinical relevance of genetic variation in lipid response to statin therapy.

**Lipid response to statin**

Individual participant LDL-C (directly measured) and ApoB responses to simvastatin 40 mg daily during a 4–6 week run-in period in 18 705 fully compliant high-risk participants who were later randomized into the Heart Protection Study.

**Genome-wide study**

Illumina 610k Quad panel genotypes in 3895 randomly selected participants (after quality control exclusions)

Select SNPs associated with:

(i) LDL-C or ApoB response at $P<1\times10^{-5}$, or
(ii) LDL-C and ApoB response at $P<5\times10^{-5}$ for independent testing

**Candidate gene study**

36 SNPs measured in up to 18 705 participants by custom I.PLEX and Illumina 610k Quad panel

SNPs selected based on previous associations with:

(i) Lipid response to statins
(ii) Statin-related adverse events
(iii) Statin pharmacokinetics/pharmacodynamics
(iv) LDL-C levels
(v) Coronary heart disease

**Independent testing**

SNPs selected in the genome-wide study measured by custom I.PLEX in 14 810 additional participants

**Vascular risk response to statin**

Randomized comparison in 18 705 participants of the 5-year major vascular event risk response to simvastatin 40 mg daily by genotypes associated with lipid response in the Heart Protection Study.

**Figure 1** Study design outline.
The genome-wide association study in 3895 individuals 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](https://academic.oup.com/eurheartj/article-abstract/34/13/982/484905/130824A005)
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

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Nearby gene(s)/locus</th>
<th>Effect/other allele</th>
<th>Genome-wide analysis</th>
<th>Independent testing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effect allele freq</td>
<td>n</td>
<td>Additional % reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C response</td>
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<td>2</td>
<td>XIRP2</td>
<td>C/T 0.16</td>
<td>3894</td>
<td>-1.58 (-2.39, -0.78)</td>
</tr>
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<td>rs3749004</td>
<td>2</td>
<td>XIRP2</td>
<td>G/A 0.11</td>
<td>3887</td>
<td>-1.96 (-2.91, -1.02)</td>
</tr>
<tr>
<td>rs7047055</td>
<td>9</td>
<td>MED27</td>
<td>T/C 0.49</td>
<td>3888</td>
<td>1.20 (0.62, 1.77)</td>
</tr>
<tr>
<td>rs9888300</td>
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<td>1q24</td>
<td>C/A 0.39</td>
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<td>1.50 (0.92, 2.07)</td>
</tr>
<tr>
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<tr>
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<td>-2.17 (-3.15, -1.20)</td>
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<tr>
<td>rs857252</td>
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<td>UBOX5/FASTKD5</td>
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<td>3891</td>
<td>-1.39 (-2.01, -0.77)</td>
</tr>
<tr>
<td>rs5759068</td>
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<td>ApoB response</td>
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<td>XIRP2</td>
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<td>XIRP2</td>
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</tr>
<tr>
<td>rs7047055</td>
<td>9</td>
<td>MED27</td>
<td>T/C 0.49</td>
<td>3888</td>
<td>1.17 (0.69, 1.66)</td>
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<tr>
<td>rs9888300</td>
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<td>1q24</td>
<td>C/A 0.39</td>
<td>3888</td>
<td>1.05 (0.53, 1.54)</td>
</tr>
<tr>
<td>rs10893006</td>
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<td>1q24</td>
<td>T/C 0.34</td>
<td>3849</td>
<td>0.92 (0.41, 1.43)</td>
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<td>T/C 0.12</td>
<td>3893</td>
<td>-1.31 (-2.08, -0.55)</td>
</tr>
<tr>
<td>rs17595975</td>
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<td>T/G 0.11</td>
<td>3873</td>
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<td>G/T 0.38</td>
<td>3891</td>
<td>-1.09 (-1.61, -0.58)</td>
</tr>
<tr>
<td>rs5759068</td>
<td>22</td>
<td>22q11</td>
<td>T/C 0.39</td>
<td>3872</td>
<td>-1.19 (-1.70, -0.67)</td>
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</tbody>
</table>

*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.

bThe 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%.

aLDL-C response

bApoB response
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 ($P < 0.001$)$^a$

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Nearby gene(s)/locus</th>
<th>$n$</th>
<th>Effect/other allele</th>
<th>Effect allele freq</th>
<th>LDL-C response Additional % reduction$^b$ (95% CI)</th>
<th>$P$-value</th>
<th>ApoB response Additional % reduction$^b$ (95% CI)</th>
<th>$P$-value</th>
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<tr>
<td>rs646776</td>
<td>1</td>
<td>CELSR2/PSRC1/SORT1</td>
<td>18 289</td>
<td>C/T</td>
<td>0.21</td>
<td>0.47 (0.13, 0.80) 6.7 x 10$^{-3}$</td>
<td>0.76 (0.47, 1.05) 2.4 x 10$^{-2}$</td>
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<tr>
<td>rs3798220</td>
<td>6</td>
<td>LPA</td>
<td>14 472</td>
<td>C/T</td>
<td>0.02</td>
<td>-2.30 (-3.47, -1.15) 7.1 x 10$^{-5}$</td>
<td>-2.09 (-3.09, -1.11) 2.5 x 10$^{-5}$</td>
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<td></td>
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<tr>
<td>rs10455872</td>
<td>6</td>
<td>LPA</td>
<td>14 462</td>
<td>G/A</td>
<td>0.09</td>
<td>-3.15 (-3.74, -2.58) 8.1 x 10$^{-28}$</td>
<td>-2.86 (-3.35, -2.36) 6.5 x 10$^{-31}$</td>
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<td>rs2002042</td>
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<td>ABC2</td>
<td>18 027</td>
<td>T/C</td>
<td>0.25</td>
<td>0.65 (0.33, 0.97) 8.2 x 10$^{-5}$</td>
<td>0.56 (0.28, 0.83) 7.5 x 10$^{-5}$</td>
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<tr>
<td>rs11045819</td>
<td>12</td>
<td>SLCO1B1</td>
<td>14 338</td>
<td>A/C</td>
<td>0.16</td>
<td>0.92 (0.49, 1.34) 2.4 x 10$^{-5}$</td>
<td>0.66 (0.29, 1.02) 4.3 x 10$^{-4}$</td>
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<tr>
<td>rs4149056</td>
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<td>SLCO1B1</td>
<td>16 867</td>
<td>C/T</td>
<td>0.15</td>
<td>-1.15 (-1.57, -0.74) 5.0 x 10$^{-8}$</td>
<td>-0.96 (-1.31, -0.60) 1.0 x 10$^{-7}$</td>
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<tr>
<td>rs4803750</td>
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<td>APOE Cluster</td>
<td>18 326</td>
<td>G/A</td>
<td>0.07</td>
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<td>1.21 (0.75, 1.66) 2.6 x 10$^{-7}$</td>
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<td>APOE Cluster</td>
<td>18 265</td>
<td>G/A</td>
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<td>-0.77 (-1.12, -0.42) 1.3 x 10$^{-5}$</td>
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<td>2.55 (1.98, 3.11) 4.8 x 10$^{-18}$</td>
<td>2.84 (2.35, 3.32) 4.9 x 10$^{-29}$</td>
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<td>APOE Cluster</td>
<td>14 388</td>
<td>G/A</td>
<td>0.18</td>
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<td>-0.91 (-1.27, -0.55) 5.7 x 10$^{-7}$</td>
<td></td>
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</tr>
</tbody>
</table>

$^a$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). 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 e2 SNP) and rs4420638 (an approximate proxy for the rs429358 e4 SNP; $r^2 \sim 0.7$) contributed independent information. The rs7412 T allele (e2) was strongly associated with off-statin LDL-C levels, with a 0.55 mmol/L lower mean LDL-C per variant (Figure 3). Consequesntly, 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 (e4 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 APOA1, ZNF259, LIPC, ABC1, 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 ($P < 0.01$; Supplementary material online, Tables S3 and S4), and there were suggestive associations with SNPs in or near APOB and ABC1 ($P < 0.01$; 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 (HMGCWR, rs2231142 (ABCG2), rs9367897 (a direct proxy for rs6924995; MYLIP), and rs1627770 (ALG10))—were not confirmed in the present study (Supplementary material online, Tables S3–S5).
Table 1: 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.

![Table and Figure](https://academic.oup.com/eurheartj/article-abstract/34/13/982/484905)

**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. 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. 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.

### Table: Gene/locus (SNP) Simvastatin allocated Placebo allocated Hazard ratio (95% CI) Proportional risk reduction (95% CI) Absolute risk reduction (95% CI)

<table>
<thead>
<tr>
<th>Gene/locus (SNP)</th>
<th>Simvastatin allocated</th>
<th>Placebo allocated</th>
<th>Hazard ratio (95% CI)</th>
<th>Proportional risk reduction (95% CI)</th>
<th>Absolute risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPA genotype</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Non-carrier (0 variant alleles)</td>
<td>1131/5697 (19.9%)</td>
<td>1398/5783 (24.2%)</td>
<td>20.2% (13.7–26.2%)</td>
<td>4.3% (2.8–5.8%)</td>
<td></td>
</tr>
<tr>
<td>Carrier (1+ variant alleles)</td>
<td>320/1523 (21.0%)</td>
<td>400/1456 (27.5%)</td>
<td>27.6% (16.2–37.5%)</td>
<td>6.5% (3.4–9.5%)</td>
<td></td>
</tr>
<tr>
<td>APOE (rs7412)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>e2 variant non-carrier</td>
<td>1246/6118 (20.4%)</td>
<td>1558/6187 (25.2%)</td>
<td>21.8% (15.7–27.4%)</td>
<td>4.8% (3.3–6.3%)</td>
<td></td>
</tr>
<tr>
<td>e2 variant carrier</td>
<td>206/1104 (18.7%)</td>
<td>236/1046 (22.6%)</td>
<td>19.8% (3.4–33.5%)</td>
<td>3.9% (0.5–7.3%)</td>
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<tr>
<td>SLCO1B1 score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lower third</td>
<td>377/1841 (20.5%)</td>
<td>472/1849 (25.6%)</td>
<td>22.8% (11.6–32.6%)</td>
<td>5.1% (2.4–7.8%)</td>
<td></td>
</tr>
<tr>
<td>Middle third</td>
<td>415/2154 (19.3%)</td>
<td>525/2168 (24.2%)</td>
<td>23.0% (12.4–32.3%)</td>
<td>4.9% (2.5–7.4%)</td>
<td></td>
</tr>
<tr>
<td>Upper third</td>
<td>417/2026 (20.8%)</td>
<td>534/2033 (26.3%)</td>
<td>24.5% (14.2–33.6%)</td>
<td>5.7% (3.1–8.3%)</td>
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</tr>
<tr>
<td>CELSR2/PSRC1/SORT1 (rs646776)</td>
<td>1168/5667 (20.6%)</td>
<td>1451/5638 (25.7%)</td>
<td>22.3% (16.1–28.1%)</td>
<td>5.1% (3.6–5.7%)</td>
<td></td>
</tr>
<tr>
<td>C allele non-carrier (TT)</td>
<td>675/3461 (19.5%)</td>
<td>875/3523 (24.8%)</td>
<td>24.8% (16.9–32.0%)</td>
<td>5.3% (3.4–7.3%)</td>
<td></td>
</tr>
<tr>
<td>CELSR2/PSRC1/SORT1 (rs646776)</td>
<td>1168/5667 (20.6%)</td>
<td>1451/5638 (25.7%)</td>
<td>22.3% (16.1–28.1%)</td>
<td>5.1% (3.6–5.7%)</td>
<td></td>
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<tr>
<td>C allele non-carrier (CT)</td>
<td>1023/5046 (20.3%)</td>
<td>1348/5166 (26.1%)</td>
<td>25.1% (18.6–31.0%)</td>
<td>5.8% (4.2–7.5%)</td>
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<tr>
<td>C allele non-carrier (CC)</td>
<td>792/3953 (20.9%)</td>
<td>945/3882 (24.5%)</td>
<td>20.8% (13.0–27.9%)</td>
<td>4.4% (2.6–6.3%)</td>
<td></td>
</tr>
<tr>
<td>All genotyped participants</td>
<td>1885/9347 (20.2%)</td>
<td>2376/9358 (25.4%)</td>
<td>23.3% (18.5–27.8%)</td>
<td>5.2% (4.0–6.4%)</td>
<td></td>
</tr>
</tbody>
</table>

**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). 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. 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). 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. Some genes found to be associated with higher LDL-C levels (e.g. APOE) have been associated with higher risks of cardiovascular disease. 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. In the present randomized trial, despite the small differences in absolute 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. Previous studies have reported an association of rs10455872 in LPA with the lipid response to statin therapy, 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. 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, 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 have been associated with small differences in the lipid response to statin therapy in both the present study (SLCO1B1 and ABCG2) and previous reports (e.g. SLCO1B1, ABCG2, and ABCB1). 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. 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 ABCG2 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. 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. 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 percent. 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

Supplementary material is available at European Heart Journal online.

Acknowledgements

The Heart Protection Study was designed and conducted by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) at the University of Oxford. This genetic study of the lipid response to statin therapy was designed, analysed, and interpreted by the CTSU and genotyping was done by the Centre National de Génotypage (CNG), Evry. The most important acknowledgements are to the participants in the study, to the Steering Committee and to the collaborators.25 We also gratefully acknowledge the staff of the Wolfson laboratories in CTSU for their help with processing, storage and retrieval of blood samples.

Funding

The Heart Protection Study (ISRCTN48489393) was supported by the UK Medical Research Council, British Heart Foundation, Merck & Co (manufacturers of simvastatin), and Roche Vitamins Ltd (manufacturers of vitamins). Genotyping was supported by a grant to Oxford University and CNG from Merck & Co. J.C.H. acknowledges support from the British Heart Foundation Centre of Research Excellence, Oxford (RE/08/004). The funders had no role in the design of the study, in the data collection or in the decision to submit the results for publication. The CTSU has a policy of not accepting honoraria or other payments from the pharmaceutical industry, except for reimbursement of costs to participate in scientific meetings.

Conflict of interest: The University of Oxford has been granted a patent for a genetic variant related to statin-induced myopathy.

References


Impact of common genetic variation

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