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ORIGINAL ARTICLE
Lipids

A gene risk score using missense variants in *SLCO1B1* is associated with earlier onset statin intolerance

Margherita Bigossi [1,2], Cyrielle Maroteau [3], Adem Y Dawed [1], Alasdair Taylor[1], Sundararajan Srinivasan[1], Alaa' Lufti Melhem [1], Ewan R. Pearson [1], Roberto Pola [2], Colin N. A. Palmer [1] and Moneeza K. Siddiqui [1,*]

[1]Pat McPherson Centre for Pharmacogenetics & Pharmacogenomics, Division of Population Health & Genomics, School of Medicine, Ninewells Hospital & Medical School, University of Dundee, Dundee DD1 9SY, UK; [2]Section of Internal Medicine and Thromboembolic Diseases, Department of Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, L.go A. Gemelli 8, 00168 Rome, Italy; and [3]Human Genetics Centre of Excellence, Novo Nordisk Research Centre Oxford, Oxford OX3 7FZ, UK

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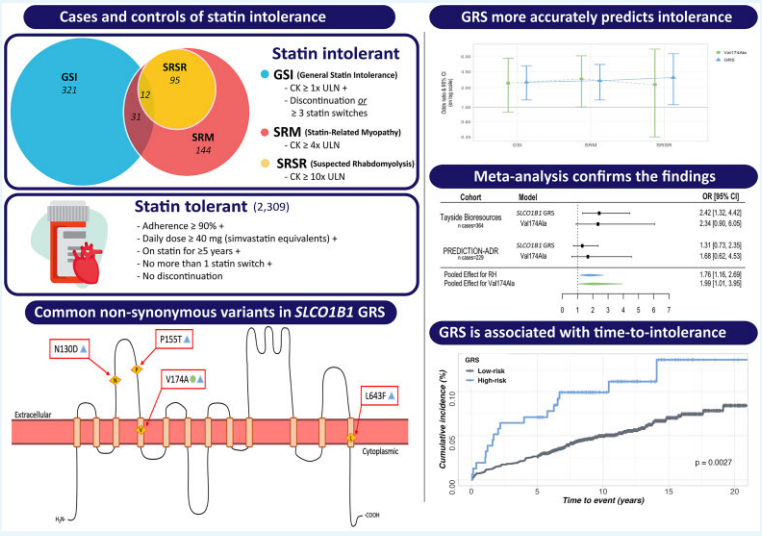
Background and aims The efficacy of statin therapy is hindered by intolerance to the therapy, leading to discontinuation. Variants in *SLCO1B1*, which encodes the hepatic transporter OATB1B1, influence statin pharmacokinetics, resulting in altered plasma concentrations of the drug and its metabolites. Current pharmacogenetic guidelines require sequencing of the *SLCO1B1* gene, which is more expensive and less accessible than genotyping. In this study, we aimed to develop an easy, clinically implementable functional gene risk score (GRS) of common variants in *SLCO1B1* to identify patients at risk of statin intolerance.

Methods and results A GRS was developed from four common variants in *SLCO1B1*. In statin users from Tayside, Scotland, UK, those with a high-risk GRS had increased odds across three phenotypes of statin intolerance [general statin intolerance (GSI): OR_{GSI} 2.42; 95% confidence interval (CI): 1.29–4.31, $P = 0.003$; statin-related myopathy: OR_{SRM} 2.51; 95% CI: 1.28–4.53, $P = 0.004$; statin-related suspected rhabdomyolysis: OR_{SRSR} 2.85; 95% CI: 1.03–6.65, $P = 0.02$]. In contrast, using the Val174Ala genotype alone or the recommended OATP1B1 functional phenotypes produced weaker and less reliable results. A meta-analysis with results from adjudicated cases of statin-induced myopathy in the PREDICTION-ADR Consortium confirmed these findings ($OR_{Val174Ala}$ 1.99; 95% CI: 1.01–3.95, $P = 0.048$; OR_{GRS} 1.76; 95% CI: 1.16–2.69, $P = 0.008$). For those requiring high-dose statin therapy, the high-risk GRS was more consistently associated with the time to onset of statin intolerance amongst the three phenotypes compared with Val174Ala (GSI: $HR_{Val174Ala}$ 2.49; 95% CI: 1.09–5.68, $P = 0.03$; HR_{GRS} 2.44; 95% CI: 1.46–4.08, $P < 0.001$). Finally, sequence kernel association testing confirmed that rare variants in *SLCO1B1* are associated with the risk of intolerance ($P = 0.02$).

Conclusion We provide evidence that a GRS based on four common *SLCO1B1* variants provides an easily implemented genetic tool that is more reliable than the current recommended practice in estimating the risk and predicting early-onset statin intolerance.

* Corresponding author. Tel: +44 138 238 3874, Email: m.k.siddiqui@dundee.ac.uk

Graphical Abstract



Schematic representation of the definition of cases and controls, common *SLCO1B1* variants included in the gene risk score (GRS), and findings from the study. The GRS, based on four common *SLCO1B1* variants, is more reliable than Val174Ala alone in estimating the risk and predicting early onset statin intolerance.

Keywords Pharmacogenomics • *SLCO1B1* • Statins • Adverse drug reactions • Precision medicine • Musculoskeletal symptoms

Introduction

Statins are the cornerstone of lipid-lowering therapy, showing great efficacy in reducing cholesterol levels and the incidence of cardiovascular events. Evidence from multiple randomized clinical trials (RCTs) and meta-analyses shows that statin therapy reduces major cardiovascular events (MACE) by ∼22% for each mmol/L reduction in LDL-cholesterol (LDL-C), and total mortality by ∼10% >5 years. Adverse drug reactions (ADRs) to statins in clinical trials were rare, presenting in only ∼5% of cases.[1] Despite this favourable safety profile, in routine care settings, nearly one in five patients on statin therapy discontinues the drug due to reported side effects.[2] Musculoskeletal symptoms are the most common ADRs: ranging from muscle pain or weakness associated with increased creatinine kinase (CK) levels (i.e. myalgia and myopathy) to rapid and life-threatening muscle breakdown (i.e. rhabdomyolysis). These symptoms are the primary cause of poor compliance with statin therapy, accounting for an estimated 25% relative risk increase in the rate of first-onset cardiovascular events.[3]

The causal mechanisms of these side effects are not fully understood; however, there is evidence of a correlation with systemic exposure to statins and their metabolites. Key proteins in the pharmacokinetics of statins are those responsible for their absorption, distribution, metabolism, and excretion. The most extensively studied protein in relation to statin intolerance is the hepatic uptake transporter OATP1B1 (solute carrier organic anion transporter family member 1B1). Missense variants in the encoding gene, *SLCO1B1*, are associated with altered function of the transporter, impacting the systemic concentration of statins and their metabolites and thereby affecting the risk of statin intolerance.

The strongest evidence exists for a common reduced function variant, rs4149056: Val174Ala. Homozygous carriers of the minor C allele at rs4149056 show increased plasma concentrations of statins by as much as 221% in *in vitro* studies, and an increase in the odds of myopathy by 3- to 17-fold in post-hoc analyses of RCTs.[4–10] Less clinical evidence exists for the effects of other *SLCO1B1* variants. In a recent GWAS of simvastatin metabolites by Mykkänen *et al.*, two increased function variants (rs11045819: Pro155Thr and rs34671512: Leu643Phe) were independently associated with a 32% and 36% per allele decrease in systemic exposure to simvastatin acid, respectively.[11] Another common variant associated with functional alteration of the transporter is rs2306283: Asn130Asp. Partially controversial evidence exists for this variant, with studies finding either increased function.[12–15] or no change in the functionality of the transporter.[16–20] These pharmacokinetic findings support the hypothesis that there are variants in *SLCO1B1*, which independently affect OATP1B1 function and, in turn, ADRs.

While statins are used by >10% of the adult populations in the United Kingdom (UK), genetic precision medicine to avoid ADR in the prescribing of statins is not routine.[21–23] In this study, we use large cohorts to develop three validated definitions of statin intolerance using combinations of poor adherence to therapy and elevated enzyme levels. We then develop a clinically implementable functional gene risk score (GRS) of statin intolerance, including all four common missense variants of *SLCO1B1*. We test the comparative ability of the GRS and Val174Ala in identifying statin users at risk of statin intolerance and early onset of statin intolerance. Finally, we use whole-exome sequencing to estimate the association of rare variants in *SLCO1B1* with clinically adjudicated cases of statin-induced myopathy.

Methods

The study was approved by the ethics committees at each study centre. At recruitment, all participants provided written informed consent for their data to be used for research purposes. The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and all applicable regulatory requirements.

This paper has been reported according to the STREGA (STrengthening the REporting of Genetic Association Studies) guidelines.

Discovery cohort: Tayside bioresource

This case-control study population was derived from two bioresources: GoDARTS (Genetics of Diabetes Audit and Research in Tayside Scotland) and SHARE (Scottish Health Research Register and Biobank), which are part of the Tayside Bioresource, University of Dundee.[24,25] Details on recruitment, data collection, linkage, and biobanking have been described in detail previously.[24,25] These bioresources contain electronic health records, genetic data, laboratory information and community prescribing records with longitudinal follow-up from a total of 15 378 statin users of white European descent. These bioresources have been previously used to make discoveries in the pharmacogenetics of statins, blood pressure medications, and anti-diabetic drugs.[26–30]

A statin user was defined as an individual with two or more prescriptions of a statin. Historical prescriptions of statins include simvastatin, atorvastatin, rosuvastatin, cerivastatin, pravastatin, and fluvastatin. Data were available from January 1999 to December 2020.

Phenotypes of statin intolerance

Prescribing patterns and laboratory testing data were used to establish phenotypes of statin intolerance. Statin types, average daily dose, statin switching, discontinuation, and percentage of daily coverage were computed from prescribing records. The use of prescribing patterns to identify statin intolerance has been described previously.[28] CK test measurements from outpatient or inpatient settings were collected. CK tests from high-dependency units (emergency rooms, cardiac care, stroke, trauma units, or surgical wards) were excluded. The upper limit of normal (ULN) for usable test results was set at 120 IU/L for women and 180 IU/L for men, based on criteria used and described previously.[31] The highest CK test results while on statin per individual were used to define intolerance. Three phenotypes of increasing severity of intolerance were defined in order to assess a biological gradient of genetic effect.

General statin intolerance. Cases of general statin intolerance (GSI) were defined as users with at least one CK measurement above the ULN while on statin therapy, associated with either three or more switches in statin drug or premature discontinuation of treatment (defined as interruption of treatment 9 months from the date of death or from the study ending date, whichever came first). The definition of GSI has been published as part of the discovery of the role of the *LILRB5* variant in statin intolerance.[28]

Statin-related myopathy and statin-related suspected rhabdomyolysis. Cases of statin-related myopathy (SRM) were defined as users with at least one CK measurement 4 times above the ULN while on statin therapy. Statin users with at least one CK measurement 10 times above the ULN were considered to be possible cases of statin-related rhabdomyolysis (SRSR).

Statin tolerance. The definition of statin tolerance has been defined and used previously.[28] Briefly, controls were defined as statin users who had been on the drug for at least 5 years with adherence of at least 90% and a minimum average daily dose of 40 mg (calculated in simvastatin equivalents),[32] and had to have no recorded high CK measurement, no discontinuation, and no more than one switch in statin therapy.

Validation of phenotypes. These definitions of statin intolerance were validated against the outcome of MACE. Hazards of MACE were significantly higher for those with intolerance compared with statin-tolerant controls. GSI was associated with 1.39 times the hazards of MACE, while SRM and SRSR were associated with 2.18 and 3.06 times the hazards of MACE compared with statin tolerant controls. For details on MACE-free survival analysis see Supplementary methods (Supplementary material online, *Section S1*).

Genetic data for common variants

Genotype data for the four common *SLCO1B1* polymorphisms (rs4149056: Val174Ala, rs2306283: Asn130Asp, rs11045819: Pro155Thr, rs34671512: Leu643Phe) were available. Details on genotyping methods and quality control are available in Supplementary material online, *Section S2*.

Developing an SLCO1B1 gene risk score

We defined a functional GRS using the four common *SLCO1B1* variants (Val174Ala, Leu643Phe, Asn130Asp, and Pro155Thr). Based on functional characterization and pharmacokinetic studies,[27,33,34] we considered homozygous carriers of Val174Ala to have a high-risk GRS, irrespective of the presence of variants in other loci. Furthermore, we included in this category also those heterozygous for Val174Ala who were not carriers of any increased function variants (*Table 1*). All remaining diplotypes were categorized as low risk.

Testing the effect of the PharmVar-informed functional OATP1B1 phenotypes

Phamacogene Variation Consortium (PharmVar) characterizes the function of alleles in *SLCO1B1*. Following this, the Clinical Pharmacogenetics Implementation Consortium (CPIC) use a combination of these alleles providing diplotypes from which OATP1B1 function can be inferred.[33,35] Accordingly, we grouped our cohort into predicted OATP1B1 transporter functions: normal function, increased function, decreased function, and poor function. We then tested the association of these functional OATP1B1 phenotypes with our phenotypes of statin intolerance. Individuals with uncharacterized alleles, who fall into the 'indeterminate transporter function' group, were excluded from the analysis. Further details are available in Supplementary material online, *Section S3*.

Data source: PREDICTION-ADR and exome sequencing for rare variants

Whole exome sequencing was undertaken on 229 individuals clinically adjudicated as having statin-induced myopathy and 488 statin-tolerant controls as part of the PREDICTION-ADR consortium. Exome sequenced data from this study as well as case adjudication methods have previously been described in the context of discovery and validation of pharmacogenetic association studies.[28,29,36] Further details are available in Supplementary material online, *Section S4*.

Statistical methods

Common variants

Analyses in Tayside bioresource. Binary logistic regression was used to test the association between the functional GRS and the phenotypes of statin intolerance. Covariates associated with statin intolerance were used in the models, including sex, age, type of statin drug, average daily dosage, and concomitant drug therapy. The relative likelihood AIC statistics were used to compare the established Val174Ala model with the GRS model.[37] Cox proportional-hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of the GRS with intolerance-free survival stratified by dose. The likelihood ratio (LR) test was used to test the goodness of fit of the cox regression models with added genetic information (either Val174Ala or *SLCO1B1* GRS) compared with the underlying clinical model.

Meta-analysis with PREDICTION-ADR

The association between *SLCO1B1* (both Val174Ala and the GRS) and clinically adjudicated cases of statin-induced myopathy was tested using a binary logistic regression model adjusted for age and sex. Findings from

Table 1 Definition of the *SLCO1B1* gene risk score from the four common missense variants

	Val174Ala (rs4149056T > C)	Leu643Phe (rs34671512A > C)	Asn130Asp (rs2306283A > G)	Pro155Thr (rs11045819C > A)
High-risk	CC	X	X	X
High-risk	CT	AA	AA	CC
Low-risk	All remaining allele combinations			

Individuals with a high-risk SLCO1B1 gene risk score (GRS) were classified as being either homozygous for the deleterious Val174Ala variant or heterozygous for the same variant and not carrying protective variants in the other loci. All remaining allele combinations were categorized as low risk. X indicates either allele at the locus.

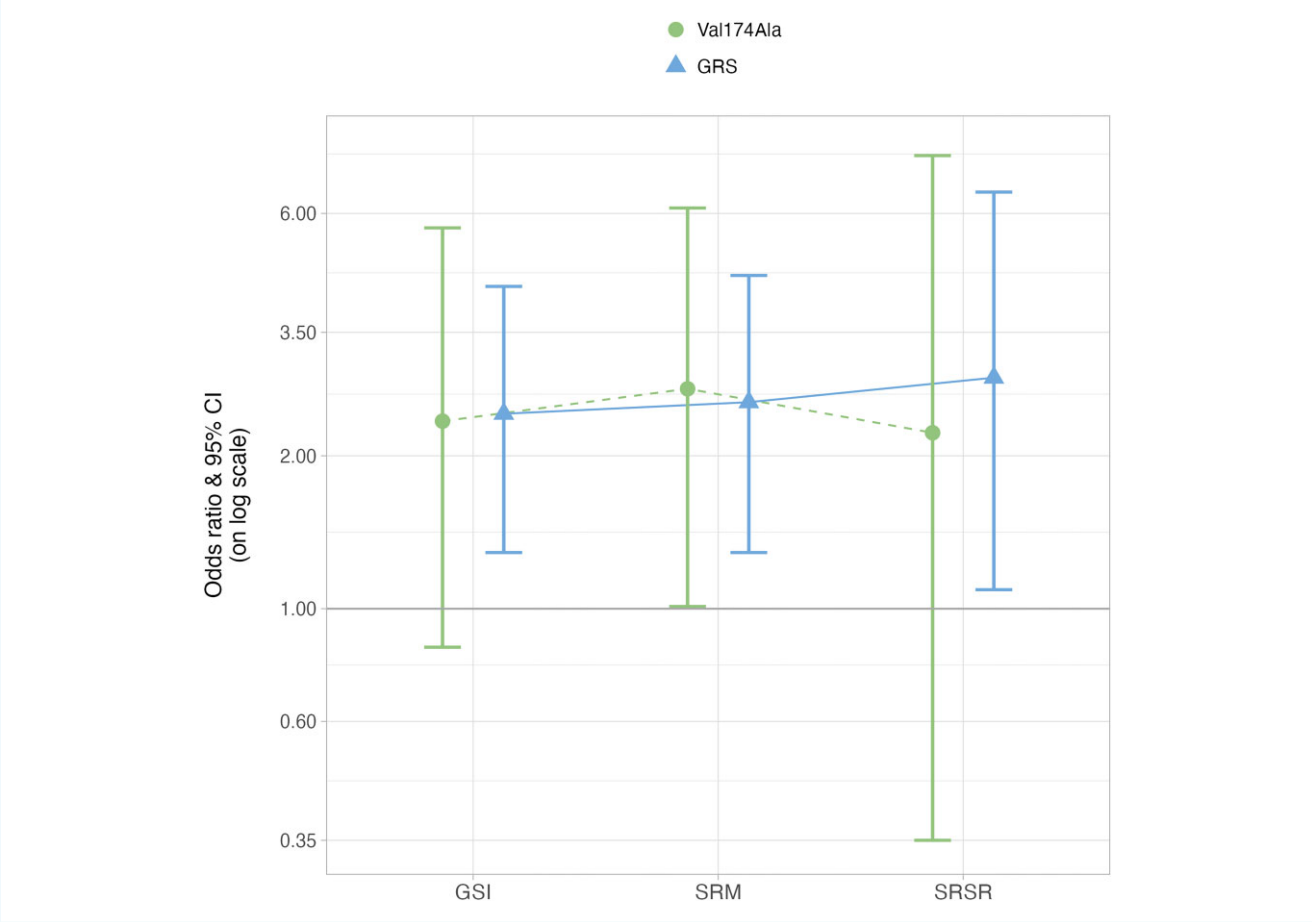


Figure 1 Models adjusted for age, sex, previous cardiovascular events, interacting medications, statin type, and statin dose. GSI, general statin intolerance; CI, confidence interval; SRM, statin-related myopathy; SRSR, statin-related suspected rhabdomyolysis.

these analyses were used to perform fixed-effects meta-analyses with results from the Tayside Bioresources. Since the three phenotype groups from Tayside Bioresources contain overlapping individuals, only one of them could be selected for the meta-analysis. The GSI phenotype was selected as it had the largest number of cases. The two meta-analyses were performed using the metafor package in R, and results are presented in a combined forest plot.

Rare variants Using exome sequencing data, we performed first a single variant analysis using PLINK/Seq (http://atgu.mgh.harvard.edu/plinkseq/) and then a gene-based association for rare variants [mean allele frequency (MAF) ≤1%] using the Optimal Unified Test (SKAT-O). SKAT-O, a test combining the strengths of the burden test and non-burden sequence kernel association testing (SKAT), is robust to the proportion of rare variants that are causal and to the directions of the causal variant effects (relative to other tests).[38] Here we tested the association of *SLCO1B1* rare variants with clinically adjudicated statin-induced myopathy. Methods for sequencing and rare variant analysis have been described in detail previously.[29]

Results

Study population

From 15 378 statin users, a total of ~174 000 person-years of statin use were available. In the study population, ~4% of statin users met

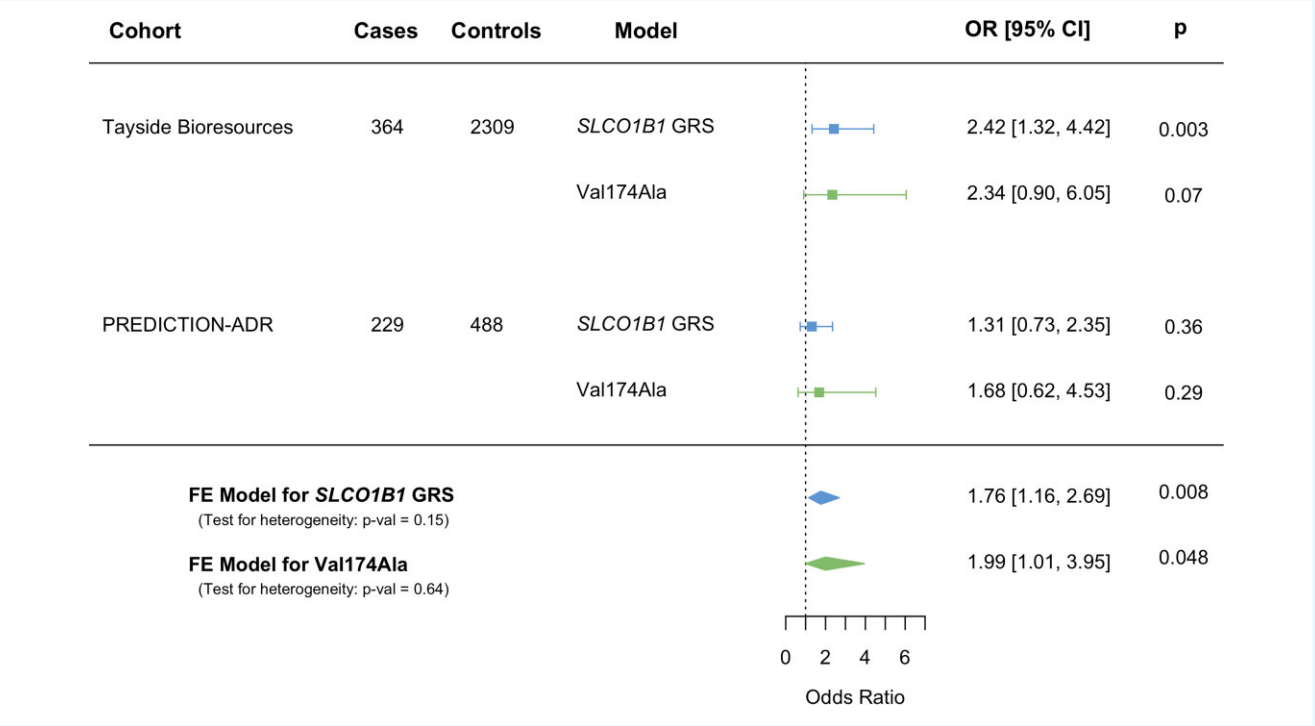


Figure 2 Forest plot showing combined results from a fixed-effects meta-analysis of the association between *SLCO1B1* GRS and Val174Ala to statin intolerance in Tayside Bioresources and PREDICTION-ADR Consortium. GRS, gene risk score.

the criteria for at least one phenotype of intolerance. Most were cases of GSI ($n = 364$, 2.4%), followed by cases of SRM ($n = 282$, 1.8%). As expected, cases of SRSR were the least common ($n = 107$, 0.7%). A total of 2309 (15%) statin users met all criteria defining statin-tolerant individuals and were used as controls. Baseline characteristics of cases and controls are presented in Supplementary material online, *Table S4*. Details on the frequency of statin intolerance among the genetic risk categories (GRS and Val174Ala) are available in Supplementary material online, *Table S5*.

Common variants

SLCO1B1 GRS is more robustly associated with incidence of statin intolerance compared with val174ala across all definitions

Individuals with a high GRS had increased odds of GSI, SRM, and SRSR when compared with those with a low GRS (GSI: OR 2.42; 95% CI: 1.29–4.31, $P = 0.003$; SRM: OR 2.51; 95% CI: 1.28–4.53, $P = 0.004$; SRSR: OR 2.85; 95% CI: 1.03–6.65, $P = 0.02$). In contrast, using the Val174Ala genotype alone produced weaker results. When compared with those with the Val174X genotypes, individuals homozygous for Val174Ala had significantly increased odds of SRM, but not of GSI or SRSR (GSI: OR 2.34; 95% CI: 0.84–5.62, $P = 0.07$; SRM: OR 2.71; 95% CI: 1.01–6.15, $P = 0.02$; SRSR: OR 2.22; 95% CI: 0.35–7.8, $P = 0.2$) (*Figure 1*, and corresponding table in Supplementary material online, *Table S6*). The AIC criteria for non-nested model selection strongly favoured the GRS as the best-fit between the two models (Supplementary material online, *Table S7*).

Meta-analysis shows the SLCO1B1 GRS provides more reliable estimates of ADRs

PREDICTION-ADR exome sequenced samples were selected based on clinically adjudicated definition of statin-induced myopathy and sex and age-matched to statin-tolerant controls. A meta-analysis between PREDICTION-ADR and Tayside Bioresources shows that the GRS model produces a more precise estimate of statin intolerance ($OR_{meta\text{-}analysis}$ 1.76; 95% CI: 1.16–2.69, $P = 0.008$) than the Val174Ala genotype alone ($OR_{meta\text{-}analysis}$ 1.99; 95% CI: 1.01–3.95, $P = 0.048$) (*Figure 2*).

PharmVar-informed functional OATP1B1 phenotypes do not consistently identify those at risk

In our cohort, ~66% (10 171) had a normal function phenotype, 27% (4131) had a decreased function phenotype, 4% (603) had an 'increased function' phenotype, and 2.5% (394) had a 'poor function' phenotype. Less than 1% (79) of our cohort had uncharacterized alleles and were excluded from the analysis (Supplementary material online, *Section S3*).

When compared with those with normal OATP1B1 function, individuals with poor OATP1B1 function had higher odds of GSI (2.98; 95% CI: 1.06–7.21, $P = 0.024$) and SRM (3.17; 95% CI: 1.17–7.26, $P = 0.012$), but not of SRSR (2.67; 95% CI: 0.42–9.63, $P = 0.20$). None of the other OATP1B1 functional phenotypes were significantly associated with statin intolerance (*Table 2*).

The SLCO1B1 GRS is more reliably associated with intolerance-free survival

The genetic effect of *SLCO1B1* on statin intolerance has previously been shown to be dose-dependent, consistent with the pharmacokinetic implications of the underlying causal mechanism. We therefore studied the hazards of statin intolerance by stratifying individuals by dose (<40 mg or ≥40 mg of simvastatin or equivalent dose of another statin).

Val174Ala genotype and *SLCO1B1* risk score showed non-significant HRs for all phenotypes of statin intolerance in individuals on a lower dose (Supplementary material online, *Section S5*).

Table 2 Association of functional OATP1B1 phenotypes with phenotypes of statin intolerance

Genotype-determined phenotype of OATP1B1 transporter	GSI	SRM	SRSR
Increased function	0.79 (0.24–2.00), $P = 0.63$	0.85 (0.20–2.39), $P = 0.79$	1.29 (0.20–4.55), $P = 0.73$
Normal function	—	—	—
Decreased function	1.29 (0.86–1.93), $P = 0.21$	1.38 (0.86–2.18), $P = 0.17$	1.22 (0.56–2.48), $P = 0.60$
Poor function	2.98 (1.06–7.21), $P = 0.024$	3.17 (1.17–7.26), $P = 0.012$	2.67 (0.42–9.63), $P = 0.20$

Association of functional OATP1B1 phenotypes according to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines with phenotypes of statin intolerance in all statin users. All models adjusted for age, gender, previous cardiovascular events, statin type, and statin dose.
GSI, general statin intolerance; SRM, statin-related myopathy; SRSR, statin-related suspected rhabdomyolysis.

In individuals on higher statin doses (≥40 mg), for all phenotypes of statin intolerance, the GRS provided more robust estimates of time to onset of intolerance. Notably, the GRS model was able to detect an association with time to onset of SRSR 2.89 (95% CI: 1.17–7.14, $P = 0.02$), whereas the Val174Ala variant alone was unable to do so. Using the LR test, we tested the fit of the models including either Val174Ala alone or the *SLCO1B1* GRS to the clinical model and determined that the addition of the *SLCO1B1* GRS significantly improves the fit of the clinical model across all three phenotypes of intolerance in SRM ($P = 0.0025$, $P = 0.002$, and $P = 0.020$ for GSI, SRM, and SRSR, respectively), whereas the addition of Val174Ala does so only for SRM ($P = 0.08$, $P = 0.023$, and $P = 0.24$ for GSI, SRM, and SRSR, respectively) (*Table 3*).

Unadjusted Kaplan–Meier curves show the cumulative risk of GSI, SRM, and SRSR according to *SLCO1B1* GRS (*Figure 3*). Adjusted HRs and LR tests for both genetic models are presented in *Table 3*.

Rare variants in *SLCO1B1* are associated with statin-induced myopathy

Using data from the PREDICTION-ADR consortium with 229 exome-sequenced clinically adjusted cases of SRM and 488 controls, we assessed the potential role of rare variants. Five rare variants in *SLCO1B1* passed quality control. Their association with SRM is represented in Supplementary material online, *Table S9*. To analyse the burden of these variants, accounting simultaneously for risk-increasing and risk-decreasing variants, we performed SKAT-O analyses. These variants were found to be significantly associated with statin-induced myopathy ($P = 0.02$).

Discussion

Summary of main findings

We provide compelling evidence from >15 000 statin-treated individuals that a simple functional GRS, which includes four common *SLCO1B1* variants, has a more robust association with three validated phenotypes of statin intolerance compared with the Val174Ala variant alone. We confirm the comparative advantage of this GRS compared with Val174Ala using AIC model selection criteria and a meta-analysis across our cohort and PREDICTION-ADR.

Moreover, for those requiring high-dose statin therapy, we observe a stronger association between the GRS and the time to onset of all three phenotypes of statin intolerance compared with Val174Ala.

While rare variants in *SLCO1B1* have an effect on statin intolerance, this effect is likely modest due to sample size and therefore not actionable given the evidence available.

Limitations

A limitation of this study is the lack of direct phenotype replication. Statin intolerance is a complex secondary phenotype and is challenging to define when using real-world epidemiological data. This is because it requires genomic and biochemical data alongside prescribing records and/or physicians' notes. These factors limit the cohorts in which the clinical phenotype of statin intolerance can be defined. Indeed, replicating our phenotype of statin intolerance in other cohorts was a challenge (Supplementary material online, *Section S6*).

While the lack of extensive replication is a limitation, our observations are consistent with expected biological effects given the established pharmacological association between OATP1B1 and statin pharmacokinetics and are therefore less likely to be a result of type 1 error. Furthermore, they are consistent with and build upon recent evidence on *SLCO1B1* variants to characterize OATP1B1 function and consequences for statin ADRs.

Another consideration is the exclusion of rare variants from the GRS. Rare variants are likely to have penetrant effects on the functional activity of the OATP1B1 transporter. However, the development of a polygenic risk score combining common and rare variants is less applicable in clinical practice since rare variants can be reliably detected only in sequenced data, which are not as readily available. Rare variants tend to be causal and act independently; however, given the frequency of statin intolerance, this is unlikely to be driven by rare variants. Furthermore, the effect observed for rare variants was modest. Taking these factors into consideration for population-level pharmacogenetic testing, we decided to focus on common variants.

Strengths

A strength of the findings was that the *SLCO1B1* GRS has a biological gradient of increasing effect sizes with increasing severity of statin intolerance phenotypes, especially amongst simvastatin users. This biological gradient was observed for both incidence of statin intolerance as well as time to onset of intolerance; no biological gradient was observed for Val174Ala or for the functional *SLCO1B1* phenotypes.

In a subgroup analysis, we find that our GRS is associated with the risk of general intolerance in both simvastatin and atorvastatin users, while no effect was observed for Val174Ala (Supplementary material online, *Section S7*). Despite pharmacokinetic evidence,[9,33] the association between Val174Ala and atorvastatin-induced myopathy has been detected only by pooling results from several association studies.[39–42] That our GRS was significantly associated with intolerance also in atorvastatin users, despite a relatively small sample size (especially when compared with the statistical power of a meta-analysis), is a demonstration of the biological specificity of the effect.

Another strength of this study lies in the definition of the phenotypes of intolerance. Validation against the outcome of cardiovascular events ensures the robustness of the phenotypes of intolerance.[28] Particular attention was paid to the development of the control phenotype. To properly identify statin tolerant individuals, strict criteria based on laboratory and prescribing patterns were followed. Furthermore, the use of real-world longitudinal data from Tayside Bioresources meant that the median on-statin follow-up time was 11 (±6) years, almost 4 times the average follow-up time in clinical trials.

A final strength of this study is the meta-analysis with PREDICTION-ADR, which was performed in clinically adjudicated

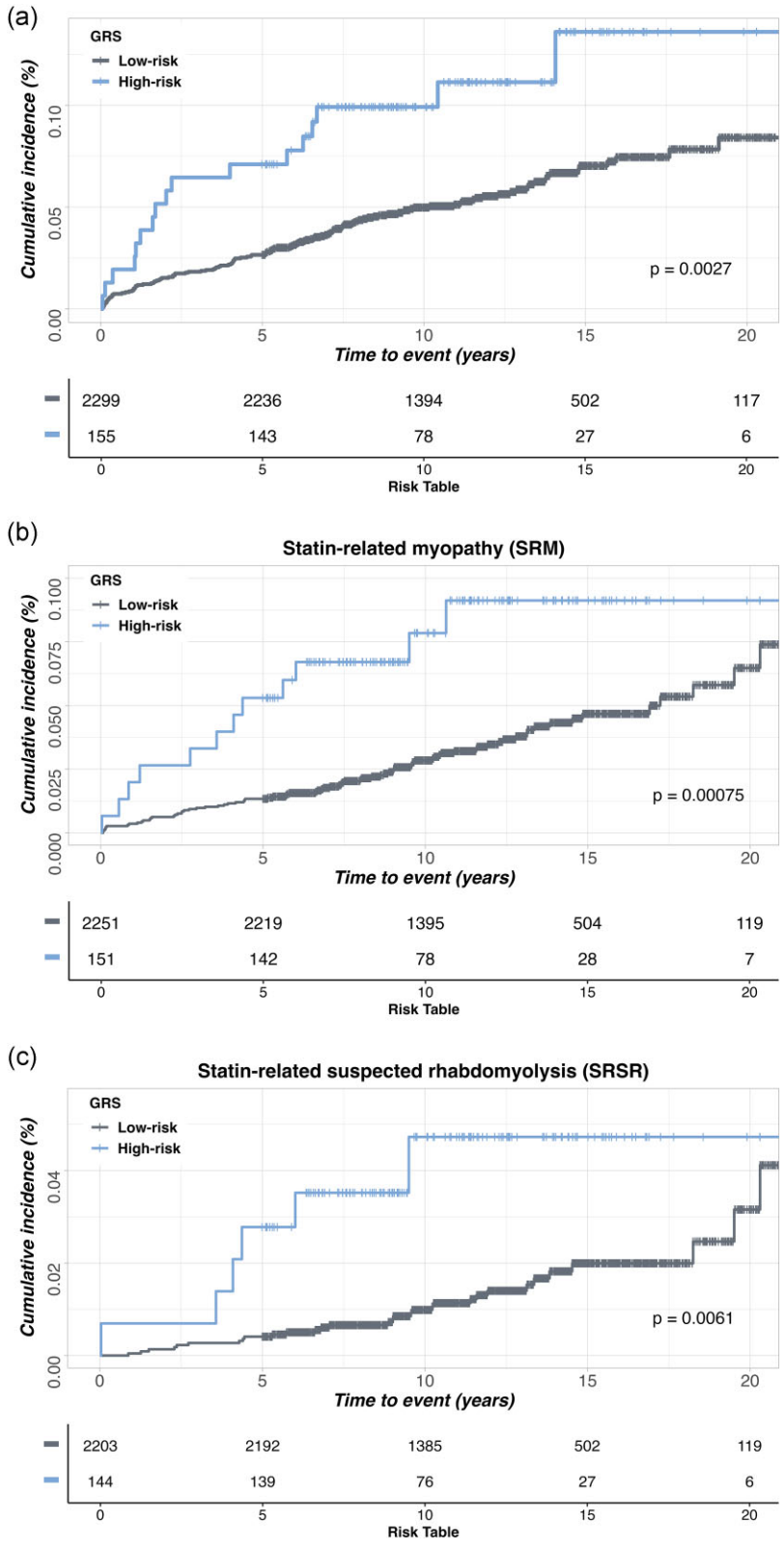


Figure 3 Unadjusted Kaplan–Meier curves and risk tables for cumulative incidence of (*a*) general statin intolerance, (*b*) statin-related myopathy, and (*c*) statin-related suspected rhabdomyolysis in individuals on an equivalent simvastatin dose ≥40 mg, according to the gene risk score (GRS) (blue: high-risk GRS; grey: low-risk GRS). Using likelihood ratio tests, the fit of the genetic models (either Val174Ala or *SLCO1B1* GRS) was compared with the clinical model, showing that the addition of the *SLCO1B1* GRS, and not Val174Ala, resulted in a statistically significant improvement (*Table 3*).

Table 3 Hazards of Val174Ala and *SLCO1B1* gene risk score to 20-year intolerance-free survival in individuals on higher equivalent doses (≥40 mg)

	Val174Ala (CC vs. CT + TT): HR (95% CI) *P*-value	LR test (clinical model + Val174Ala) χ^2 (df) *P*-value	*SLCO1B1* GRS (high- vs. low-risk): HR (95% CI) *P*-value	LR test (clinical model + *SLCO1B1* GRS) χ^2 (df) *P*-value
GSI ($n = 2454$)	2.49 (1.09–5.68) $P = 0.03$	χ^2 (1) = 3.05 $P = 0.08$	2.44 (1.46–4.08) $P < 0.001$	χ^2 (1) = 9.1481 **$P = 0.0025$**
SRM ($n = 2402$)	3.01 (1.31–6.94) $P = 0.01$	χ^2 (1) = 5.18 **$P = 0.023$**	2.51 (1.38–4.58) $P = 0.003$	χ^2 (1) = 8.96 **$P = 0.002$**
SRSR ($n = 2347$)	2.64 (0.63–11.1) $P = 0.2$	χ^2 (1) = 1.40 $P = 0.24$	2.89 (1.17–7.14) $P = 0.02$	χ^2 (1) = 5.35 **$P = 0.020$**

All models adjusted for age, gender, previous cardiovascular events, statin type, and statin dose.
CI, confidence interval; GRS, gene risk score; GSI, general statin intolerance; HR, hazard ratios; LR test, likelihood ratio test; SRS, statin-related myopathy; SRSR, statin-related suspected rhabdomyolysis. Bold values denote statistical significance at $P < 0.05$ threshold.

cases of statin-induced myopathy and using exome sequencing data. This confirmed our finding of a more robust association of statin intolerance with the functional GRS compared with Val174Ala.

Generalizability

In our study cohort, simvastatin and atorvastatin were the main drugs prescribed at the start of statin therapy (63% and 20%, respectively). While this limits the generalizability of our findings to other statins, it also reflects real-world prescription practices, particularly in the UK.

Replicating these findings in a RCT would provide the best quality evidence for clinical implementation; however, it would be challenging and expensive to run. Recruit-by-genotype pharmacokinetic studies would be a cost-effective alternative able to provide indirect biological evidence of these findings.

The study was conducted in a population of white European descent, which undoubtedly impacts the generalizability of our findings to other ancestries. Using UK Biobank genetic data and self-reported ethnicity, we observed that white Europeans were most likely to carry the high-risk GRS (%), followed by Chinese and South Asians (%). The lowest frequency was found in those of African (%) and Caribbean (%) descent (Supplementary material online, *Figure S6*).

Interpretation

Mechanistically, the association between *SLCO1B1* variants and the risk of myopathy seems straightforward. Decreased function variants disrupt the expression of the OATP1B1 transporter, leading to increased plasma concentrations of the drug and, in turn, a higher likelihood of adverse effects at the musculoskeletal level.

This research provides new evidence to support the now-established utility of pharmacogenetic testing to reduce the development of ADRs.[43] Our aim was to develop a functional GRS that would be easy to implement in clinical practice. Current recommendations for pharmacogenetic-guided statin treatment require sequencing of the *SLCO1B1* gene. Sequencing is comparatively more expensive and less available than genotyping, and therefore less likely to be used clinically. By choosing to select four common variants, we have sought to develop an attainable and reliable pharmacogenetic tool to identify patients at risk of statin intolerance. Interestingly, among those with low genetic risk, 24% carried one copy of Val174Ala. This means that testing for Val174Ala alone would misclassify around a fourth of statin users as being at higher risk than they really are.

Our group has previously shown an association between a missense variant in the leukocyte immunoglobulin-like receptor subfamily B5 gene, *LILRB5*, and statin intolerance, which has since been confirmed.[28,41] When we stratified the GRS effect by *LILRB5* genotype, we observed increased odds of intolerance, with a gradient for increasingly severe phenotypes of intolerance (2.5–4 times higher odds) (Supplementary material online, *Section S8*). Taken together, these findings highlight the potential for precision cardiovascular therapies using pharmacogenetic testing.

Conclusion

In this study, we show that a simple GRS using four common *SLCO1B1* variants is at least as reliable as the current recommended practice in estimating the risk and early onset of statin intolerance.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Conflict of interest: All authors declare that they have no conflicts of interest.

Author contributions

M.B. and M.S. contributed to the conception and design of the study. M.B. performed the data cleaning and statistical analysis. C.M., A.D., A.T., S.S., A.M., E.P., R.P., and C.P. assisted with data curation, interpretation, and critical revision of the manuscript. M.B. and M.S. wrote the first draft of the manuscript and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Data availability

GoDARTS and SHARE data are available subject to approval by the Tayside data access committee and can be made by contacting the corresponding author. PREDICTION-ADR data are available subject to approval and can be made by contacting the corresponding author. UK Biobank data are available via application directly to the UK Biobank, https://www.ukbiobank.ac.uk

Ethics statement

GoDARTS and SHARE studies were reviewed and approved by Tayside Medical Ethics Committee 053/04 and East of Scotland Ethics Committee NHS REC 13/ES/0020.

Multiple EU Research Ethics Committees (Tayside, Scotland; North West England, UK; and Sefton, UK) approved the PREDICTION-ADR study.

UK Biobank has approval from the North West Multi-Centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval, REC reference: 21/NW/0157, IRAS project ID: 299116.

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