Supplemental Material

The Clinical Pharmacogenetics Implementation Consortium

(CPIC) guideline for SLC01B1, ABCG2, and CYP2C9 and statin-associated musculoskeletal symptoms

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CPIC guidelines for SLC01B1 and statin-induced myopathy- Supplement v3.0
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CPIC UPDATES

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on www.cpicpgx.org. Information will be reviewed and updated periodically on that website.

New to this guideline:

- Updated evidence reviews for SLCO1B1 (Table S1) and revised recommendation (Table 2)
- Addition of CYP2C9 and ABCG2 evidence reviews and recommendations (Tables S2 and S3 and Tables 3 and 4)
- Evidence reviews and recommendation for all statins (Tables S1-S3 and Tables 2-6)
- Addition of the Figure 1. SLCO1B1 recommendations with intensity and statin dose stratified by SLCO1B1 phenotype
- Evidence reviews for HMGC4 and CYP3A4/5 and all statins (Tables S4 and S5)
- Combined recommendations for SLCO1B1/ABCG2 and SLCO1B1/CYP2C9 (Tables 5 and 6)
- Implementation resources (gene and drug resource mappings, CDS alerts, allele definition, allele frequency, allele functionality, diplotype to phenotype tables have all been updated and reformatted and are now available at https://cpicpgx.org/guidelines/cpic-guideline-for-statins/

LITERATURE REVIEW

We searched the PubMed database (1966 to July 2021) using the following keyword strategies:

SLCO1B1: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (SLCO1B1 OR OATP1B1) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response OR reaction) NOT ("review"[Publication Type]) AND English[lang] AND ("2014/01/01"[PDAT] : "2021/07/20"[PDAT])

ABCG2: (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (ABCG2 OR BCRP) AND (myopathy CPIC guidelines for SLCO1B1 and statin-induced myopathy- Supplement v3.0
OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT (“review”[Publication Type]) AND English[lang]

**CYP2C9:** (fluvastatin) AND (CYP2C9)

**HMGCR:** (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (HMGCR) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT (“review”[Publication Type]) AND English[lang]

**CYP3A4/5:** (simvastatin OR rosuvastatin OR pravastatin OR pitavastatin OR atorvastatin OR fluvastatin OR lovastatin OR Caduet OR Vytorin) AND (CYP3A4 OR CYP3A5) AND (myopathy OR myalgia OR discontinuation OR tolerance OR pharmacokinetic OR efficacy OR LDL lowering OR reaction OR Rhabdomyolysis OR Myositis OR “Statin associated muscle symptoms” OR withdrawal OR intolerance OR hepatocyte uptake OR response) NOT (“review”[Publication Type]) AND English[lang]

Using these search terms, 1023 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between **SLCO1B1, ABCG2, CYP2C9, HMGCR, or CYP3A4/5** genotypes and statins pharmacokinetic parameters as well as clinical outcomes. Non-English manuscripts and reviews were excluded. Following the application of these inclusion and exclusion criteria, 197 publications were reviewed and included in the evidence table (Table S1 to S5).

**AVAILABLE GENETIC TEST OPTIONS**

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (1). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see **Allele Definition Table**, **Allele Functionality Table** and **Allele Frequency Table** [https://cpicpgx.org/guidelines/cpic-guideline-for-statins/] adhere to these CPIC guidelines for **SLCO1B1** and statin-induced myopathy- Supplement v3.0
allele nomenclature standards (1). Moreover, the **Allele Definition Table, Allele Functionality Table**, and **Allele Frequency Table** may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles. Furthermore, the Association for Molecular Pathology and College of American Pathologists have published a joint recommendation for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2C9* (2).

Commercially available genetic testing options change over time. Additional updated information can be found at the Genetic Testing Registry (GTR). The GTR provides a central location for voluntary submission of genetic test information by providers and is available at [http://www.ncbi.nlm.nih.gov/gtr/](http://www.ncbi.nlm.nih.gov/gtr/).

**LINKING GENETIC VARIABILITY TO VARIABILITY IN DRUG-RELATED PHENOTYPES**

*SLCO1B1*. Both SLCO1B1 decreased and poor function phenotypes are associated with increased exposure for most statins, with greater effects of poor function phenotypes. Effects on exposure also vary by statin type (**Figure S1**). Therefore, the risk of SAMS varies based on statin type and statin dose. For simvastatin, the evidence linking SAMS to *SLCO1B1* rs4149056 (c.521T>C) is of high quality, and this association has been reproduced in retrospective studies of randomized trials and clinical practice-based cohorts (**Table S1**). This variant is present in several *SLCO1B1* star alleles including the relatively common *SLCO1B1* *5* and *15* alleles. Although the association of rs4149056 with myopathy varies by statin, there is evidence supporting the role of *SLCO1B1* variants in the systemic clearance of all statins (3) (**Table S1**). Pasanen *et al.* determined that homozygous carriers of the C allele at rs4149056 (CC genotype) had substantially greater exposure to the active simvastatin acid (AUC_{0-12}) than subjects homozygous for the ancestral T allele (4). In single-dose studies (**Figure S1**), the observed plasma AUCs of active simvastatin acid, pitavastatin, atorvastatin, pravastatin and rosuvastatin have been 221%, 162-191%, 144%, 57-130% and 62-117% higher, respectively in rs4149056
CC homozygotes than in rs4149056 TT homozygotes (Figure S1). Thus, the recommendations in this guideline (for SLCO1B1, ABCG2 and CYP2C9) are based on both pharmacokinetic evidence and when available clinical evidence supporting increased risk of SAMS (see Supplemental Material for further detail). Further, we make note in this guideline when therapeutic recommendations are based solely on the basis of pharmacokinetic data due to the absence of clinical toxicity data related to SAMS (Figure 1).

Genotype at rs4149056 may also alter the desired lipid-lowering efficacy of statins (Table S1). Because rs4149056 influences hepatic uptake of statins, the C allele (e.g., SLCO1B1*5 and *15) has opposite effects on toxicity and efficacy as the presence of the minor allele attenuates the LDL-cholesterol lowering effect (because hepatic HMGCR is the rate limiting step for de novo cholesterol biosynthesis). Carriers of the rs4149056 C allele experience lesser LDL-cholesterol reduction when taking simvastatin (5-8) but one report suggests this may be due to poor drug adherence (9). As anticipated from the pharmacokinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin (10-12), rosuvastatin (13, 14), and pitavastatin (15-19). Even for simvastatin, however, the change in LDL-cholesterol level due to rs4149056 is small (<10 mg/dl) (5), and there is no evidence that this variant impacts vascular events (20). As such, our recommendations are primarily based on this variant’s effects on PK and SAMS, rather than the relationship between rs4149056 and efficacy on lowering LDL or risk of cardiovascular events.

ABCG2. ABCG2 decreased and poor function phenotypes are associated with increased exposure to rosuvastatin, with greater exposure for the poor function phenotypes (Table S2). In particular, rosuvastatin levels (AUC and C_{max}) may be doubled in individuals with poor function phenotypes (21). Based on the observed increase in exposure, the risk for myopathy would also be expected to be increased (22). Nonetheless, there is only a single study directly assessing myopathy due to rosuvastatin use in individuals with decreased or poor function phenotypes which did not show any significant effect on myopathy (23). However, for efficacy, the JUPITER Trial showed an increase in lipid lowering effects of rosuvastatin in individuals with decreased and poor function phenotypes (24). Dosing based on genotype for rosuvastatin must necessarily include other considerations such as liver or renal function and ancestry (Table 3). The higher levels of rosuvastatin observed in individuals of Asian ancestry have been attributed
to higher allele frequencies of the reduced function \(ABCG2\) polymorphism, c.421G>A (rs2231142) (25); however, other factors may contribute to higher rosuvastatin levels in Asians (26). The effect of the \(ABCG2\) polymorphism, rs2231142 (c.421C>A), has also been studied for its association with pharmacokinetic, toxicity or efficacy with other statins, such as atorvastatin, pitavastatin, fluvastatin and lovastatin (Table S2). Except for fluvastatin, in which a single study showed a clear association of rs2231142 with exposure, the evidence for association of \(ABCG2\) genetic variants with exposure, response or toxicity to other statins is considered weak to moderate primarily because of small sample sizes or variation in results among studies (Table S2).

**CYP2C9.** Genetic variations in \(CYP2C9\) are associated with increased exposure to fluvastatin (Table S3), but the pharmacokinetics or pharmacodynamics of other statins are not affected. To date, studies have focused on two alleles, \(CYP2C9*2\) (decreased function) and \(CYP2C9*3\) (no function). Hirvensalo et al. showed that for fluvastatin the AUC was 25% and 75% greater per copy of the \(CYP2C9*2\) and \(CYP2C9*3\) variant allele, respectively. Additionally, \(CYP2C9*2\) and \(CYP2C9*3\) alleles are associated with increased risk of fluvastatin-induced adverse effects, including liver toxicity and SAMS. However, the evidence supporting increased risk of myopathy in carriers of decreased or poor function alleles of \(CYP2C9\) is of moderate quality and mainly based on the pharmacokinetic evidence. Genetic variation in \(CYP2C9\) has not been associated with fluvastatin lipid-lowering response.

**CYP3A4 and CYP3A5.** To date, studies have focused on two alleles, \(CYP3A4*1B\) (a promoter variant) and \(CYP3A5*3\) (harboring a common intronic variant causing a splice defect which leads to truncated inactive \(CYP3A5\) protein). While neither variant has been shown to predict myopathy while on atorvastatin, Wilke et al. describe an association for these variants with the severity of muscle damage in a small cohort of 68 patients who reported myalgias while taking atorvastatin (27). Although significant, the effect size was modest. For patients with myalgias on atorvastatin, the median CK level was 321 units/L in carriers of the \(CYP3A4*1B\) allele, vs 246 units/L in non-carriers (adjusted p = 0.059), and the median CK level was 318 units/L in carriers of the \(CYP3A5*3\) allele, vs 246 units/L in non-carriers (adjusted p = 0.010).
CYP3A4 and CYP3A5 genes are located on chromosome 7, at a locus that also contains two pseudogenes, and CYP3A7 which is predominantly expressed in utero (28). Functionally, the CYP3A4 and CYP3A5 enzymes have a high degree of overlap in their substrate specificity (biological redundancy), and there is wide patient-to-patient variability (more than 10-fold variation) in their expression in adults. While CYP3A4*1B and CYP3A5*3 are in strong linkage disequilibrium (D’ >0.8), the CYP3A5*3 allele is thought to be the causal variant driving the association between this locus and CK elevation during atorvastatin therapy. Because this variant only predicts the severity of how high the CK may go, it does not predict who will develop SAMS, and thus, the association may not be clinically actionable. There are additional published studies (see Table S5), but the overall strength of evidence for CYP3A4/5 and statin response was rated as weak. Therefore, the current guideline does not make any recommendations regarding CYP3A4/5 genotype at this time.

HMGCR. HMGCR encodes for HMG-CoA reductase, the target of statins. Variations in HMGCR (e.g., rs1724484A>T and rs17238540T>G) have been shown to be associated with LDL-c response (see Table S4) but with very limited and weak data to support. Thus, the current guideline does not make recommendation regarding HMGCR and statin lipid response.

LEVELS OF EVIDENCE
The evidence summarized in Supplemental Table S1-S3 is graded using a scale modified slightly from Valdes et al. (29)

High: Evidence includes consistent results from well-designed, well-conducted studies.
Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.
Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.
STRENGTH OF DOSING RECOMMENDATIONS

CPIC’s dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data (Supplemental Tables S1-S3) as well as on some existing disease-specific consensus guidelines (30). Some of the factors that are considered in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for statins, *in vivo* pharmacokinetic and pharmacodynamic data for statins, *in vitro* enzyme/transporter activity of expressed wild-type or variant-containing gene, *in vitro* enzyme activity from tissues isolated from individuals of known genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of protein stability.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just four categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (31):

**Strong** recommendation for the statement: “The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.”

**Moderate** recommendation for the statement: “There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.”

**Optional** recommendation for the statement: “The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.”

**No recommendation:** “There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.”

OTHER CONSIDERATIONS

**Drug-drug interactions.** Between 1998 and 2001, more than forty cases of muscle toxicity associated with the use of cerivastatin were found to be fatal. Many of these occurred within the context of gemfibrozil, a drug that strongly inhibits the cytochrome P450 (CYP) 2C8-catalyzed biotransformation of cerivastatin and also inhibits membrane transport and phase II conjugation of statins (32, 33).
The biological disposition of each statin differs on a drug-by-drug basis. Some statins undergo extensive phase I oxidation (atorvastatin, fluvastatin, lovastatin, and simvastatin), others do not (pitavastatin, pravastatin, and rosuvastatin). CYP3A4 inhibitors (e.g., azole antifungals, protease inhibitors, amiodarone, and many calcium channel blockers) increase risk of myopathy for statins metabolized by CYP3A4/5 (e.g., simvastatin, lovastatin and atorvastatin) (34).

Many statins also undergo additional modification through phase II conjugation by enzymes of the UDP-glucuronosyltransferase-1 (UGT1) family. This process can be altered by concomitant administration of fibric acids (35). Gemfibrozil, a fibric acid derivative, alters pharmacokinetic parameters of a variety of statins. By inhibiting the glucuronidation and membrane transport of simvastatin hydroxy-acids, gemfibrozil increases systemic exposure to active simvastatin acid (36) placing patients at increased risk for developing myopathy. Because of interactions such as these, all the statin package labels recommend reducing the dose of statins in patients using concomitant medications known to alter its pharmacokinetics.

**The Role of Ancestry.** There is some evidence that Asian Americans are one of three important groups with an elevated risk/benefit ratio for use of some statins compared to other ancestry groups; the other important groups were patients on cyclosporine (CSA)/immune suppression and patients with severe kidney failure) (37-43). Geographic differences in allele frequency for \( SLCO1B1 \) rs4149056 (c.521T>C) do not appear to contribute to this sensitivity in Asians (44). For rosuvastatin, this difference appears to be at least partly attributable to variability in efflux transporters such as \( ABCG2 \), as well as gene-gene and gene-environment interactions not yet defined (45). For simvastatin, ancestry-dependent differences in \( SLCO1B1 \) variant frequency carry an undefined impact on outcome.

**Other Limitations.** The pharmacokinetic predictors of SAMS are well understood (5, 36, 46-61). Pharmacodynamic predictors have been less well characterized. Although the cellular mechanism linking statins to skeletal muscle damage still remains somewhat obscured, the weight of the evidence suggests that statin-mediated reduction in the levels of critical cholesterol
precursors (i.e., isoprenoids) can lead to mitochondrial dysfunction, and programmed cell death (62-65). While inherited variability in the prenylation of key mitochondrial oxygen transport proteins may drive a subclinical form of myopathy that becomes overtly manifest after exposure to statin, there is only limited evidence supporting the clinical utility of genotyping pharmacodynamic variants.

Because rs4149056 (c.521T>C) can be inherited in combination with other SLCO1B1 variants that carry a protective effect, the C allele should not be assumed to confer risk with 100% certainty. Like all drug-gene-outcome relationships reviewed by CPIC, it is anticipated that these guidelines will be updated as more variants (both common and rare) are increasingly characterized, e.g., through deep re-sequencing.

In the interim, a clear limitation is that rare and de novo variants are often not tested for within currently available genotyping tests, if discovered, it may be unclear how to act upon such results. Yet, rare exonic variants in SLCO1B1 have been shown to have clinical impact (e.g., methotrexate clearance) (66). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a c.521 C allele, and a c.521TT genotype at rs4149056 does not necessarily imply the absence of other potentially function-altering variant(s) in SLCO1B1. Allele and variant function are available on PharmVar.org as well as CPIC’s SLCO1B1 Allele Functionality Table (67, 68).

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN EHR WITH CDS

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (69-73). See https://cpicpgx.org/guidelines/cpic-guideline-for-statins/ for resources to support the adoption of CPIC guidelines within an EHR. Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating the use of SLCO1B1, ABCG2 and CYP2C9 genotype results to guide statin use in an EHR.
Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (74, 75). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (Table 1, main manuscript). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the “person level” rather than at the date-centric “encounter level”. Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (69, 76).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/cpic-guideline-for-statins/).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC provides gene-drug specific tables that offer guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for drugs relevant to the CPIC guideline (see https://cpicpgx.org/guidelines/cpic-guideline-for-statins/).
FIGURE S1. PHARMACOKINETIC IMPACT OF RS4149056 GENOTYPE FOR SEVERAL STATINS. Effect of the SLCO1B1 c.521T>C variant (rs4149056) on plasma exposure (i.e., area under the concentration-time curve) for different statins, CC vs TT. This summary figure represents a composite of single-dose data from the following references: Pasanen et al (4), Ieiri et al (18), Lee et al. (77), Niemi et al (78), Pasanen et al (79), Choi et al (80), Deng et al (17), Ho et al (81).
Portions of this figure have been reproduced from reference (82) (Niemi et al) with permission from the author (MN), the publisher, the American Society for Pharmacology and Experimental Therapeutics (ASPET), and Pharmacological Reviews.
# TABLE S1. EVIDENCE LINKING SLCO1B1 GENOTYPE WITH STATIN PHENOTYPE

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major Findings</th>
<th>References</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin</strong></td>
<td><strong>In vitro</strong> SLCO1B1 is the major atorvastatin uptake transporter. The average contribution to atorvastatin uptake was $SLCO1B1 &gt; SLCO1B3 &gt;&gt; OATP2B1 &gt; NTCP$.</td>
<td>Vildhede, <em>et al.</em> (2014) (83)</td>
<td>Weak</td>
</tr>
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<td></td>
<td><strong>In vitro</strong> $SLCO1B1$ rs4149056 (c.521T&gt;C, *5) reduces atorvastatin transport activity by decreasing OATP1B1 function due to sorting errors in transporter localization</td>
<td>Kameyama, <em>et al.</em> (2005) (84)</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td><strong>Clinical</strong> $SLCO1B1$ rs4149056 (c.521T&gt;C) C allele is not significantly associated with an increased risk of atorvastatin-induced liver tox.</td>
<td>Fukunaga, <em>et al.</em> (2016) (98)</td>
<td>Weak</td>
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<tr>
<td>Clinical</td>
<td>The <strong>SLCO1B1</strong> rs4149056 (c.521T&gt;C) is associated with higher likelihood of dose decrease or switching during statin therapy.</td>
<td>de Keyser, <em>et al.</em> (2014) (113)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In vitro</td>
<td><strong>SLCO1B1</strong> rs2306283 (c.388A&gt;G, *1b) did not alter the activity of OATP1B1 significantly.</td>
<td>Kameyama, <em>et al.</em> (2005) (84)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>SLCO1B1</strong> rs2306283 (c.388A&gt;G) is not significantly associated with risk of myotoxicity in individuals that received atorvastatin.</td>
<td>Liu, <em>et al.</em> (2017) (91) Du, <em>et al.</em> (2018) (93)</td>
<td>Moderate</td>
</tr>
<tr>
<td>FLAVASTATIN</td>
<td><strong>Clinical</strong></td>
<td>Presence of the <em>SLCO1B1</em>/*14 allele is associated with enhanced lipid-lowering efficacy for fluvastatin.</td>
<td>Du, <em>et al.</em> (2018) (93)</td>
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<tr>
<td><strong>Clinical</strong></td>
<td>The <em>SLCO1B1</em> rs4149056 (c.521T&gt;C) C variant is associated with decreased lipid-lowering response to fluvastatin.</td>
<td>Couvert, <em>et al.</em> (2008) (115)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>In vitro</strong></td>
<td>The uptake of fluvastatin was not influenced by <em>SLCO1B1 rs4149056</em> (c.521T&gt;C) at concentrations &gt;1 uM</td>
<td>Deng, <em>et al.</em> (2008) (117)</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>In vitro</strong></td>
<td>The <em>SLCO1B1</em> rs4149056 (c.521T&gt;C) C variant is associated with reduced uptake of both fluvastatin enantiomers (3R,5S-fluvastatin and 3S,5R-fluvastatin).</td>
<td>Hirvensalo, <em>et al.</em> (2019) (119)</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Fluvastatin PK did not differ between subjects with different <em>SLCO1B1 rs4149056</em> (c.521T&gt;C) genotypes.</td>
<td>Niemi, <em>et al.</em> (2006) (120)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td><em>SLCO1B1</em> rs2306283 (c.388A&gt;G) is not significantly associated with lipid-lowering response to fluvastatin.</td>
<td>Couvert, <em>et al.</em> (2008) (115)</td>
<td>Weak</td>
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<tr>
<th>LOVASTATIN</th>
<th><strong>Clinical</strong></th>
<th><em>SLCO1B1</em> rs4149056 (c.521T&gt;C) C allele is associated with an increased concentration of lovastatin acid but have no significant effect on lovastatin lactone.</th>
<th>Tornio, <em>et al.</em> (2015) (122)</th>
<th>Weak</th>
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<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td><em>SLCO1B1</em> rs2306283 (c.388A&gt;G) is not associated with concentration of lovastatin acid and lovastatin lactone.</td>
<td>Tornio, <em>et al.</em> (2015) (122)</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td><em>SLCO1B1</em> rs4149056 (c.521T&gt;C) C allele is associated with an increased risk of statin-induced myopathy + rhabdomyolysis.</td>
<td>Lu, <em>et al.</em> (2021)(124)</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

| PITAVASTATIN | **Clinical** | *SLCO1B1* SNP rs4149056 (c.521T>C) did not affect the lipid-lowering efficacy of pitavastatin. | Yang, *et al.* (2010) (125) | Moderate |
| Clinical | **SLCO1B1** rs4149056 (c.521T>C) C allele is associated with an increased AUC and decreased clearance of pitavastatin. | Chung, *et al.* (2005) (126)  
Oh, *et al.* (2013) (128)  
Mori, *et al.* (2019) (95) | High |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Clinical</td>
<td><strong>SLCO1B1</strong> SNP rs2306283 (c.388A&gt;G) did not affect the lipid-lowering efficacy of pitavastatin.</td>
<td>Yang, <em>et al.</em> (2010) (125)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td>Pitavastatin AUC and Cmax increased for carriers of the <strong>SLCO1B1</strong> rs2306283 (c.388A&gt;G) polymorphism.</td>
<td>Wen, <em>et al.</em> (2010) (130)</td>
<td>Weak</td>
</tr>
</tbody>
</table>
| **Simvastatin** | *In vitro* | **SLCO1B1** rs4149056 (c.521T>C) is the key SNP determining the functional properties of **SLCO1B1***5, *15 allelic proteins and that decreased activities of these variant proteins are mainly caused by a sorting error produced by this SNP. Reduced transport function for **SLCO1B1***15 as compared with *1a. | Iwai, *et al.* (2004) (131)  
Kameyama, *et al.* (2005) (84)  
| Clinical | **SLCO1B1** rs4149056 (c.521T>C) C allele is associated with an increased risk of simvastatin-induced myopathy. | Link, *et al.* (2008) (133)  
Liu, *et al.* (2017) (91)  
Shek, *et al.* (2017) (134)  
Bakar, *et al.* (2018) (135)  
Carr, *et al.* (2019) (137)  
| Clinical | **SLCO1B1***17 is associated with an increased risk of simvastatin-induced myopathy. | Chan, *et al.* (2019) (139) | Weak |
| Clinical | **SLCO1B1** rs4149056 C (c.521T>C) polymorphism markedly affects the pharmacokinetics of active simvastatin acid, but has no significant effect on parent simvastatin. | Pasanen, *et al.* (2006) (4)  
Tsamandouras, *et al.* (2014) (141) | High |
<p>| Clinical | Individuals with the \texttt{rs4149056} \texttt{C} (c.521T&gt;C) \texttt{allele may be more likely to have dose decrease or switch.} | De Keyser, \textit{et al.} (2014) (113) | Weak |
| Clinical | \textit{SLCO1B1} \texttt{rs2306283} (c.388A&gt;G) is not significantly associated with risk of myotoxicity in individuals that received \textit{atorvastatin}, \textit{simvastatin}. | Liu, \textit{et al.} (2017) (91) | Weak |
| Clinical | \textit{SLCO1B1} \texttt{rs2306283} (c.388A&gt;G) is not significantly associated with \textit{simvastatin} or \textit{simvastatin acid pharmacokinetics}. | Birmingham, \textit{et al.} (2015) (101) | Weak |</p>
<table>
<thead>
<tr>
<th>Statin</th>
<th>\textit{SLCO1B1} \texttt{rs2900478} is associated with a statistically significant though clinically negligible, lipid-lowering effect of \textit{statin}.</th>
<th>Postmus, \textit{et al.} (2014) (20)</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>Presence of the <strong>SLCO1B1</strong> rs4149056 (c.521T&gt;C) C allele is associated with increased risk of composite adverse events when treated with statins (atorvastatin, pravastatin or simvastatin) in patients with hypercholesterolemia.</td>
<td>Voora, et al. (2009) (156) Carr, et al. (2013) (159)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>SLCO1B1</strong> rs4149056 (c.521T&gt;C) C allele is associated with an increased LDL-C levels in statin-treated patients.</td>
<td>Li, et al. (2015) (151)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>SLCO1B1</strong> rs2306283 (c.388A&gt;G) is not associated with an increased LDL-C levels in statin-treated patients.</td>
<td>Li, et al. (2015) (151)</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
TABLE S2. EVIDENCE LINKING ABCG2 GENOTYPE WITH STATIN PHENOTYPE

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major Findings</th>
<th>References</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) CA genotype is found to be more frequent in statin-intolerant cases.</td>
<td>Shek, <em>et al.</em> (2017) (134)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) is associated with simvastatin-induced liver symptoms.</td>
<td>Shek, <em>et al.</em> (2018) (162)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) may be associated with statin-induced muscle symptoms.</td>
<td>Chan, <em>et al.</em> (2019) (139)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) is not significantly associated with the lipid-lowering effect of simvastatin.</td>
<td>Bailey, <em>et al.</em> (2010) (148)</td>
<td>High</td>
</tr>
<tr>
<td>In vitro</td>
<td>Rosuvastatin is a substrate of SLCO1B1, SLCO1B3, and SLCO2B1 in sinusoidal uptake and of MRP2, MDR1, and ABCG2 in biliary excretion. SLCO1B1 as well as NTCP plays an important role in rosuvastatin uptake into human hepatocytes.</td>
<td>Kitamura, <em>et al.</em> (2018) (164)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In vitro</td>
<td>Rosuvastatin is transported efficiently by ABCG2 and suggest that ABCG2 plays a significant role in the disposition of rosuvastatin.</td>
<td>Huang, <em>et al.</em> (2006) (165)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) is not significantly associated with high SIM risk.</td>
<td>Sreter, <em>et al.</em> (2017) (166) Bai, <em>et al.</em> (2019) (23)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>ABCG2</em> rs2231142 (c.421C&gt;A) is associated with greater LDL response to rosuvastatin.</td>
<td>Tomlinson, <em>et al.</em> (2010) (167)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>ABCG2</strong> SNP rs2199936 is significantly associated with absolute LDL-C reduction. (rs2231142 (421C&gt;A) is in LD with rs2199936 in the HapMap (CEU, r²=0.81)).</td>
<td>Lee, <em>et al.</em> (2013) (168) Kim, <em>et al.</em> (2017) (169) Kim, <em>et al.</em> (2019) (170)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>ABCG2</strong> rs2231142 (c.421C&gt;A) is significantly associated with rosvastatin exposure. Genotypes AC + AA are associated with increased exposure to rosvastatin compared to CC.</td>
<td>Chasman, <em>et al.</em> (2012) (171)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>ABCG2</strong> rs2231142 (c.421C&gt;A) A allele is not significantly associated with an increased risk of atorvastatin-induced liver tox.</td>
<td>Fukunaga, <em>et al.</em> (2016) (98)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><strong>ABCG2</strong> rs2231142 (c.421C&gt;A) A allele is significantly associated with an increased risk of atorvastatin-induced adverse events.</td>
<td>Mirosevic Skvrce, <em>et al.</em> (2015) (90)</td>
<td>Moderate</td>
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<tr>
<td>Clinical</td>
<td>In vitro study showed that $ABCG2$ affect atorvastatin transport.</td>
<td>Keskitalo, et al. (2009) (21)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical</td>
<td>$ABCG2$ rs2231142 (c.421C&gt;A) is not associated with atorvastatin response.</td>
<td>Prado, et al. (2018) (181)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In vitro</td>
<td>Pitavastatin acid is a substrate of $ABCG2$, whereas the lactone form is not. $ABCG2$ is involved in the biliary excretion of pitavastatin.</td>
<td>Fujino, et al. (2005) (184) Hirano, et al. (2005) (185)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td>$ABCG2$ rs2231142 (c.421C&gt;A) is not significantly associated with concentration of pitavastatin.</td>
<td>Ieiri, et al. (2007) (127) Oh, et al. (2013) (128)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td>$ABCG2$ rs2231142 (c.421C&gt;A) AA genotype is associated with higher fluvastatin AUC.</td>
<td>Keskitalo, et al. (2009) (163)</td>
<td>High</td>
</tr>
<tr>
<td>Clinical</td>
<td>$ABCG2$ rs2231142 (c.421C&gt;A) is associated with greater odds of developing fluvastatin-induced adverse effects (liver and muscle toxicity).</td>
<td>Mirosevic, et al. (2013) (186)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Clinical</td>
<td>$ABCG2$ rs2231142 (c.421C&gt;A) is not associated with concentration of lovastatin acid and lovastatin lactone.</td>
<td>Zhao, et al. (2017) (123)</td>
<td>Weak</td>
</tr>
</tbody>
</table>
### TABLE S3. EVIDENCE LINKING CYP2C9 GENOTYPE WITH STATIN PHENOTYPE

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major Findings</th>
<th>References</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>CYP2C9*2, *3 were associated with reduced clearance of fluvastatin enantiomers in vitro.</td>
<td>Hirvensalo, et al. (2019) (119)</td>
<td>Moderate</td>
</tr>
<tr>
<td>In vitro</td>
<td>Fluvastatin and lovastatin increased CYP2C9 protein level in endothelial cells.</td>
<td>Bertrand-Thiebault, et al. (2007) (191)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP2C9*2 influences the pharmacokinetics of the fluvastatin (affect the AUC of both fluvastatin enantiomers).</td>
<td>Fischer, et al. (1999) (187)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Unknown</td>
<td>Statins, CYP2C9 genotypes are not significantly associated with muscle tox or lipid response to statins (simvastatin, fluvastatin, rosvastatin).</td>
<td>Mirosevic, et al. (2013) (186)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>A case with liver cirrhosis who experienced fluvastatin-induced fatal rhabdomyolysis. This patient had been treated with simvastatin (20 mg/day) for coronary artery disease and was switched to fluvastatin (20 mg/day) 10 days before admission.</td>
<td>Zuccaro, et al. (2007) (193)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP2C9*3 allele is associated with an increased concentration of pitavastatin.</td>
<td>Zhou, et al. (2013) (129)</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE S4. EVIDENCE LINKING HMGCR GENOTYPE WITH STATIN PHENOTYPE

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major Findings</th>
<th>References</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td><em>HMGCR</em> haplotypes H2 and H7 were associated with attenuated reduction of LDL cholesterol when treated with simvastatin. Tag SNP rs17238540 and rs17244841 were also associated with altered LDL-C response.</td>
<td>Krauss, <em>et al.</em> (2008) (199)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Carriers of both <em>HMGCR</em> H2/H7 haplotype and LDLR L5 haplotype had significantly attenuated statin-mediated changes in LDLC and LDLR in comparison to either noncarriers or carriers of individual haplotypes. This effect is more evident in African-Americans than in European-Americans.</td>
<td>Mangravite, <em>et al.</em> (2010) (200)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>In vitro</strong></td>
<td><em>HMGCR</em> ScrF I polymorphism is associated with vLDL-C lowering effect by simvastatin.</td>
<td>Ying, <em>et al.</em> (2007) (201)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td><em>HMGCR</em> variant rs3846662 influenced <em>HMGCR</em> alternative splicing. Greater upregulation of <em>HMGCRv_1</em> in vitro was significantly correlated with reduced statin response (smaller reductions of plasma total and low-density lipoprotein cholesterol, triglycerides, and apolipoprotein B).</td>
<td>Medina, <em>et al.</em> (2008) (202)</td>
<td>Weak</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td><em>HMGCR</em> variants rs17238540 and rs17244841 were significantly associated with a smaller reduction in total cholesterol and LDL cholesterol following pravastatin therapy.</td>
<td>Chasman, <em>et al.</em> (2004) (203)</td>
<td>Weak</td>
</tr>
<tr>
<td>Study Approach</td>
<td>Findings</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Clinical</td>
<td><em>HMGCR</em> variants rs17238540, rs17244841 were not associated with lipid response to fluvastatin.</td>
<td>Polisecki, <em>et al.</em> (2008) (204)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>Multiple cases of statin-related immune-mediated necrotizing myopathy (SINAM) were described. All are previously atorvastatin treated. All are positive for anti-<em>HMGCR</em> antibody.</td>
<td>Singer, <em>et al.</em> (2007) (205)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td><em>HMGCR</em> variants rs17238540 and rs17244841 were significantly associated with reduction in total cholesterol and LDL-c levels.</td>
<td>Nichols, <em>et al.</em> (2015) (206)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td><em>HMGCR</em> variant rs17671591 is associated with greater plasma LDL-C reductions after therapy with atorvastatin.</td>
<td>Poduri, <em>et al.</em> (2010) (211)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td><em>HMGCR</em> rs3846662 was associated with LDL lowering response to atorvastatin.</td>
<td>Kirac, <em>et al.</em> (2017) (214)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td><em>HMGCR</em> variants (rs10474433, rs17671591, rs6453131) were associated with statin response by with smaller effect than the ApoE variants.</td>
<td>Thompson, <em>et al.</em> (2009) (214)</td>
<td></td>
</tr>
<tr>
<td>In vitro</td>
<td>Atorvastatin had no significant effect on LRP or <em>HMGCR</em> mRNA levels in circulating mononuclear cells.</td>
<td>Pocathikorn, <em>et al.</em> (2010) (214)</td>
<td></td>
</tr>
<tr>
<td>In vitro</td>
<td>Atorvastatin insensitivity is associated with upregulation of HMGCR and SCD.</td>
<td>Lettiero, <em>et al.</em> (2018) (218)</td>
<td></td>
</tr>
</tbody>
</table>
TABLE S5. EVIDENCE LINKING CYP3A4/5 GENOTYPE WITH STATIN PHENOTYPE

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major Findings</th>
<th>References</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td><em>CYP3A5</em>&lt;sup&gt;3&lt;/sup&gt;/*3 genotype (6986A&gt;G) is more frequent in statin-intolerant cases.</td>
<td>Shek, et al. (2018) (162)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>CYP3A5</em>&lt;sup&gt;3&lt;/sup&gt;/*3 genotype (6986A&gt;G) is associated with simvastatin-induced liver symptoms.</td>
<td>Shek, et al. (2017) (134)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>When simvastatin-intolerant patients were switched to rosuvastatin, serious side effect were not observed and many of them carry <em>CYP3A5</em>&lt;sup&gt;3&lt;/sup&gt;/*3.</td>
<td>Shek, et al. (2018) (162)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>CYP3A4</em> rs2740574 (G&gt;A) G allele is associated with smaller risk of a dose decrease or switch to another drug during simvastatin and atorvastatin therapy.</td>
<td>Becker, et al. (2010) (218)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td><em>CYP3A4</em>&lt;sup&gt;22&lt;/sup&gt; is associated with lower statin dose (atorvastatin, simvastatin, or lovastatin).</td>
<td>Wang, et al. (2011) (219)</td>
<td>Weak</td>
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<tr>
<td>Clinical</td>
<td>CYP3A4*4 is not associated with LDL lowering response to simvastatin but may affect percentage reductions in total cholesterol and triglycerides.</td>
<td>Fiegenbaum, et al. (2005) (221)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 may be associated with higher simvastatin concentration.</td>
<td>Kim, et al. (2007) (228)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A4<em>22 is associated with higher plasma simvastatin concentration compared to CYP3A4</em>1/*1.</td>
<td>Kitzmiller, et al. (2014) (229)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is not significantly associated with risk of myotoxicity in individuals that received rosuvastatin.</td>
<td>Liu, et al. (2017) (91)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>Patients with CYP3A5<em>1 allele achieved LDL cholesterol target more frequently as compared to patients with CYP3A5</em>3/*3 when treated with rosuvastatin.</td>
<td>Bailey, et al. (2010) (148)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is not significantly associated with risk of myotoxicity in individuals that received atorvastatin, however it may affect the severity of myotoxicity (magnitude of serum CK elevation).</td>
<td>Wilke, et al. (2005) (27)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A4*22 is not significantly associated with adverse events in individuals that received atorvastatin.</td>
<td>Mirosevic, et al. (2015) (90)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is significantly associated with atorvastatin efficacy.</td>
<td>Kivisto, et al. (2004) (220)</td>
<td>Weak</td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A4 rs2242480 is associated with lower AUC and greater clearance when treated with atorvastatin.</td>
<td>He, et al. (2014) (236)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5 genotype has minimal effects on the pharmacokinetic parameters of atorvastatin.</td>
<td>Shin, et al. (2011) (237)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is associated with enhanced lovastatin lipid lowering efficacy.</td>
<td>Kivisto, et al. (2004) (220)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is not significantly associated with lipid lowering efficacy to fluvastatin.</td>
<td>Kivisto, et al. (2004) (220)</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>CYP3A5*3 is not significantly associated with lipid lowering efficacy to pravastatin.</td>
<td>Kivisto, et al. (2004) (220)</td>
<td></td>
</tr>
</tbody>
</table>

CPIC guidelines for SLCO1B1 and statin-induced myopathy- Supplement v3.0
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(68) PharmGKB. PGx Gene-specific Information Tables.


Brunham, L.R. et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacogenomics J 12, 233-7 (2012).


CPIC guidelines for SLCO1B1 and simvastatin-induced myopathy- Supplement v2.0


