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# Simvastatin Therapy and *SLCO1B1* Genotype

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Introduction

Simvastatin (brand name Zocor) is a member of the statin class of drugs, used to regulate low-density lipoprotein (LDL) cholesterol levels in various conditions, including familial hypercholesterolemia (FH), primary hyperlipidemia, hypertriglyceridemia, and primary dysbetalipoproteinemia. Statins are also used to reduce total mortality risk associated with coronary heart disease, non-fatal myocardial infarction, and revascularization procedures in adults at high risk of coronary heart disease events, including those with established vascular disease or diabetes. Approved by the US FDA for use primarily in adults, simvastatin is also approved for children aged 10 and older to manage FH (1). Administered as a pro-drug, simvastatin must be metabolized to simvastatin acid, which then acts in the liver and other tissues to reduce cholesterol production by competitively inhibiting HMG-CoA reductase (3-hydroxy-methylglutaryl-coenzyme). Simvastatin acid also promotes an increase in the uptake of LDL from the bloodstream, resulting in a reduction in cardiovascular risk and improved health outcomes for most individuals. However, individuals can experience adverse reactions; the most common are statin-associated musculoskeletal symptoms (SAMS) or other serious reactions.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy indicate that individuals with decreased function in the organic anion transporting polypeptides 1B1 (OATP1B1) hepatic transport enzyme (encoded by the *SLCO1B1* gene) have an increased risk of SAMS (2, 3). The CPIC guidelines provide dosing recommendations based on an individual's predicted phenotype, stating that individuals with decreased or poor metabolizer phenotypes should be prescribed an alternative statin or a lower dose of simvastatin (Table 1) (2). Criteria for choosing the relative potency of an alternative statin or the dose of simvastatin are also outlined by CPIC (Figure 1) (2). The DPWG guidelines focus on the most common functional variant, a single nucleotide variation (SNV) at rs4149056, NM_006446.5:c.521T>C, recommending that individuals heterozygous or homozygous for the variant allele, resulting in decreased or poor function phenotype, choose an alternative statin (Table 2) (3, 4). The US FDA does not specifically address *SLCO1B1* genetic variation in the simvastatin drug label, but it does discuss various medications that are either contraindicated (strong cytochrome P450 enzyme 3A4 [CYP3A4] inhibitors, gemfibrozil, cyclosporin and danazol) with simvastatin or may increase the risk of myopathy (1). The drug label for simvastatin in Switzerland, however, describes the increased risk of SAMS for individuals who have at least one variant allele at rs4149056, and recommends considering genotyping results indicating a CC genotype at this SNV during risk-benefit assessment before prescribing 80 mg doses of simvastatin due to higher myopathy risks (5). The interplay of genetics, co-

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medications, comorbidities, and simvastatin dose highlights the complex factors that contribute to an individual's risk of developing SAMS.
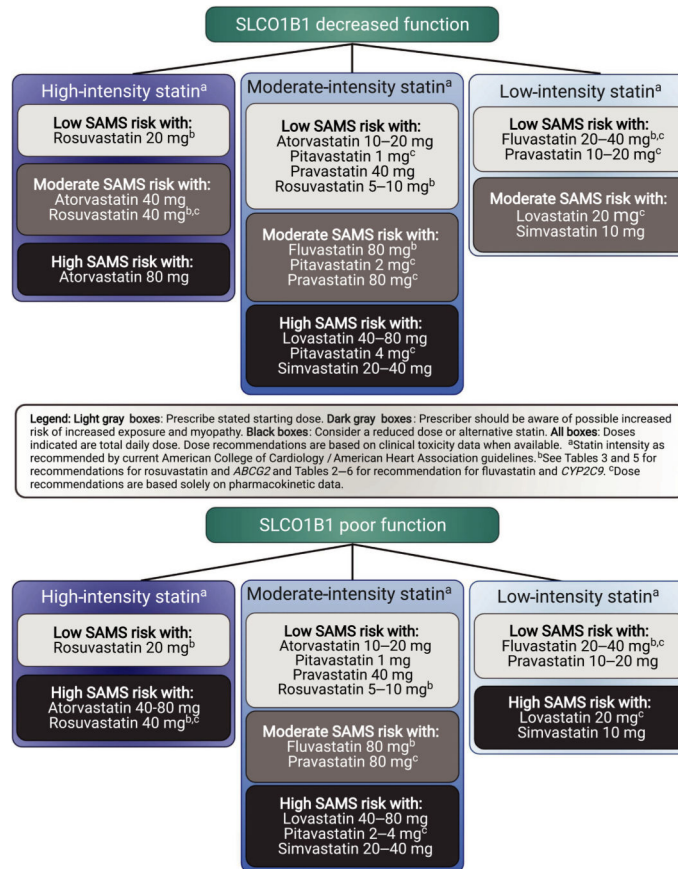
Figure 1: The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms.

SLCO1B1 recommendations with intensity and statin dose stratified by SLCO1B1 phenotype; all doses assume adult dosing. SAMS, statin-associated musculoskeletal symptoms.

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Table 1: The Clinical Pharmacogenetics Implementation Consortium (CPIC) Recommendations for Simvastatin Based on *SLCO1B1* Phenotype in Adults (2022)

Phenotype	Implications	Dosing recommendation	Classification of recommendation	Considerations
SLCO1B1 increased function	Typical myopathy risk and statin exposure	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated before initiating a statin.
SLCO1B1 normal function	Typical myopathy risk and statin exposure	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated before initiating a statin.

Table 1 continued from previous page.

Phenotype	Implications	Dosing recommendation	Classification of recommendation	Considerations
SLCO1B1 decreased (or possible decreased) function	Increased simvastatin acid exposure as compared with normal function; increased risk of myopathy	Prescribe an alternative statin depending on the desired potency[a]. If simvastatin therapy is warranted, limit dose to <20 mg/day.	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated before initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy.
SLCO1B1 poor function	Increased simvastatin acid exposure as compared with normal function; highly increased myopathy risk	Prescribe an alternative statin depending on the desired potency[a].	Strong	The potential for drug–drug Interactions and dose limits based on renal and hepatic function should be evaluated before initiating a statin. The effects of drug–drug interactions may be more pronounced, resulting in a higher risk of myopathy.

[a] Statin potency and genotype recommendations are summarized in Figure 1.
Table adapted from (2).

Table 2: The Dutch Pharmacogenetics Working Group (DPWG) Recommendations for Simvastatin Based on *SLCO1B1* Genotype (2020)

SLCO1B1 genotype[a]	Risk	Recommendation
521CC	When using simvastatin 80 mg/day, the risk of myopathy is increased 30-fold to 18% and the risk of severe myopathy is increased 48-fold to 12%. When using 40 mg/day, this risk is increased 7-fold to 1% and 11-fold to 0.68%. The gene variation leads to reduced simvastatin transport to the liver, which increases the simvastatin plasma concentration and therefore the risk of side effects.	Choose an alternative. Consider any additional risk factors for statin-induced myopathy. Atorvastatin is affected less severely by the *SLCO1B1* gene variation but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil, and diltiazem. Use of atorvastatin is not recommended for individuals with additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by the *SLCO1B1* gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil, and diltiazem. Fluvastatin is not significantly influenced by the *SLCO1B1* gene variation or CYP3A4 inhibitors.

Table 2 continued from previous page.

SLCO1B1 genotype[a]	Risk	Recommendation
521TC	When using simvastatin 80 mg/day, the risk of myopathy is increased 5-fold to 3% for moderately severe to severe myopathy and 1.3% for severe myopathy. When using 40 mg/day, this risk is increased 2.6-fold to 0.39% and 0.17%. The gene variation leads to reduced simvastatin transport to the liver, which increases the simvastatin plasma concentration and therefore the risk of side effects.	Choose an alternative. Consider any additional risk factors for statin-induced myopathy. Atorvastatin is affected less severely by the *SLCO1B1* gene variation but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil, and diltiazem. Use of atorvastatin is not recommended for individuals with additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by the *SLCO1B1* gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil, and diltiazem. Fluvastatin is not significantly influenced by the *SLCO1B1* gene variation or CYP3A4 inhibitors. If an alternative is not an option: 1. Avoid simvastatin doses exceeding 40 mg/day (for example, by adding ezetimibe) 2. Advise the individual to report muscle symptoms.

[a] DPWG literature review found association with only the T>C variation at rs4149056 (NM_006446.5:c.521T>C) and simvastatin side effects, though other gene variations were assessed (4).
This table adapted from (3) and personal communication from M. Nijenhuis (see Acknowledgements).

Drug: Simvastatin

Simvastatin, an HMG-CoA reductase inhibitor, is used with diet to manage FH, hypertriglyceridemia, primary dysbetalipoproteinemia, and to lower the risk of fatal cardiovascular events in individuals with coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, or a combination of these conditions. Simvastatin is primarily indicated for adults but is also approved for pediatric use in individuals aged 10 and older with FH. The recommended pediatric dose ranges from 10 mg to 40 mg daily, while adults are recommended 40 mg daily, with a rare exception of 80 mg daily only for those who have been taking this higher dose for more than 12 months without evidence of muscle toxicity. (1)

Statins are recommended as a first-line treatment for elevated LDL cholesterol levels or for diabetic individuals by the American College of Cardiology and American Heart Association (6) as well as by the American Association of Clinical Endocrinologists and American College of Endocrinology (7). Statins are contraindicated in individuals with acute liver failure or decompensated cirrhosis (1). Simvastatin should not be used with medications that strongly inhibit CYP3A4 (which includes macrolide antibiotics, some azole anti-fungal medications, antiviral medications, and nefazodone), nor with cyclosporine, danazol, or gemfibrozil (1). Consuming grapefruit juice while taking simvastatin can also increase the plasma levels of simvastatin due to inhibition of CYP3A4 (1, 5)

Statins, including simvastatin, work by inhibiting the HMG-CoA reductase enzyme, leading to decrease cholesterol production (8). This inhibition also reduces levels of mevalonate, which leads to upregulation of other enzymes involved in cholesterol biosynthesis, including the LDL receptor, further decreasing plasma LDL cholesterol levels (9). For individuals with FH due to LDL receptor loss of function, statins reduce cholesterol levels by decreasing the production of apolipoprotein-B containing lipoproteins in the liver (9). Decreased circulating lipid levels are associated with decreased risk of cardiovascular disease (CVD) and atherosclerotic CVD (ASCVD) (10). Simvastatin is absorbed by cells expressing the OATP1B1 drug transporter; in the liver, it is metabolized by CYP3A enzymes to simvastatin acid, which inhibits HMG-CoA reductase (11, 12). Simvastatin can be excreted from the liver via ABCB1 and ABCC2 transporters (11).

Higher doses of simvastatin and higher plasma levels of simvastatin are associated with higher rates of adverse effects, (12). including SAMS, a leading cause of drug discontinuation. The frequency of SAMS was found to directly correlate with simvastatin dose in clinical studies, ranging between 0.61–0.9% of individuals taking an 80 mg dose to 0.02–0.03% frequency with a 20 mg dose (1). Risk factors for SAMS include age of 65 or older, uncontrolled hypothyroidism, renal impairment, certain drug–drug interactions (discussed below), and Chinese ancestry (1). Individuals with reduced function in the drug-transporting enzyme OATP1B1 may be more likely to experience this toxicity (2, 3, 13) due to increased plasma concentration of simvastatin and its metabolites (14, 15). The CPIC guidelines stratify the relative risk of SAMS for statin use by decreased or poor OATP1B1 function (Figure 1) and are intended to be used with cardiovascular expert guidelines when selecting which statin and dose to use (see Therapeutic Recommendations Based on Genotype below for more information). The clinical presentation of SAMS can range from no muscle symptoms with serum creatine kinase (CK) elevations less than 4 times the upper normal limit (severity rating scale [SRM] 0) through the most severe presentation of immune-mediated necrotizing myositis (IMNM) (SRM 6). This standardized scale aids clinicians and researchers in understanding and managing SAMS (16).

Reports of muscle pain while taking statins may be a result of the nocebo effect, as suggested by a study of individuals with a history of SAMS. Out of 200 participants, 151 individuals reported similar frequencies of muscle pain during alternating periods of statin and placebo use, with two-thirds of the cohort resuming long-term statin use at the conclusion of the study (17). Balancing the concerns of SAMS with the therapeutic aim of statin therapy is important, as suboptimal statin use can increase cardiovascular event risk. Suboptimal use included discontinuation, nonadherence, dose reduction, and statin switching leading to reduced efficacy. One study in the UK reported that out of 1005 study participants, 156 individuals had suboptimal statin use and these individuals were at an increased risk of major adverse cardiovascular events (hazard ratio of 2.1) and all-cause mortality (hazard ratio 2.46) (18). Subgroup analysis determined that statin discontinuation or nonadherence were the major contributors to this risk (18).

Serious complications with simvastatin therapy include IMNM and hepatic dysfunction, and therapy should be discontinued if IMNM is suspected or serious hepatic injury (with clinical symptoms, jaundice, or both) occurs (1). Signs of IMNM include proximal muscle weakness, elevated serum CK persisting after statin discontinuation, and necrotizing myopathy on muscle biopsy (1). Two myositis-specific autoantibodies can also be detected during IMNM: anti-signal recognition particle and anti-HMG-CoA Reductase antibodies (19, 20). Individuals with IMNM may require treatment with immunosuppressive agents (1). More common but less severe side effects include upper respiratory infection, headache, abdominal pain, constipation, and nausea (1). There have also been reports of elevated hemoglobin A1c (HbA1C) and fasting glucose levels with statin therapy (1). Simvastatin is not recommended during pregnancy due to decreased synthesis of cholesterol and other biologically active substances derived from cholesterol (1). The specific therapeutic needs of the individual should be considered, though the FDA-approved label states that hyperlipidemia treatment during pregnancy is generally not necessary, given the chronic nature of the atherosclerotic process (1). Clinical information does not indicate a drug-associated risk of major congenital malformations if used during pregnancy, but there is insufficient evidence to evaluate the risk of miscarriage associated with simvastatin therapy (1). There is also a lack of data on the safety of simvastatin use during breastfeeding, and the consensus for clinical practice is to avoid its use by breastfeeding mothers (21). Some advocate for the continued use of statins by expectant mothers and women attempting to conceive with FH due to the increase in lipid levels during pre-conception and pregnancy (12–15 months per pregnancy) (22). Additionally, adverse pregnancy outcomes (including gestational hypertension or diabetes, preeclampsia, or pre-term birth) can increase ASCVD risk, and the natural lipid fluctuations during pregnancy may put individuals with elevated baseline cholesterol levels at greater risk (23). More clinical research is needed to assess the risk of various statins with adverse maternal and fetal or neonatal outcomes (23).

The use of statins in pediatric individuals has been shown to be safe and effective for individuals with heterozygous FH aged 10 and older. A controlled clinical study showed no significant effect on growth or sexual maturation in male (n=99) or female (n=76, all one-year post-menarche) participants (1). Additional studies have examined the efficacy and side effects of varying dosing of simvastatin in pediatric individuals with FH, and reported no clinically relevant side effects (24). Statin therapy in a pediatric population appears safe, though continuity of care remains important as these individuals transition from pediatric to adult clinical care (25).

Individuals aged 65 and over are at increased risk of adverse effects of simvastatin (1). Pharmacokinetic studies suggest that individuals aged 70–78 have a 45% higher plasma level of simvastatin compared with those aged 18–30. Individuals aged 65 and older taking 80 mg simvastatin are at increased risk of myopathy compared with those under 65 years of age taking the same high dose (1). A separate retrospective study reported that high-dose statin use (including simvastatin) in individuals aged 65 and older was associated with an increased burden of myalgia and elevated liver enzymes compared with a control cohort taking low-dose statins (26). Hepatic and renal impairment, often observed in geriatric individuals, are also risk factors for SAMS regardless of age (1).

Gene: *SLCO1B1*

The *SLCO1B1* gene, located on the short arm of chromosome 12, encodes OATP1B1, one of the major hepatic influx transport proteins. Primarily expressed on the basolateral surface of hepatocytes, OATP1B1 facilitates the uptake of various endogenous and exogenous compounds including bile acids, thyroid hormones, bilirubin, methotrexate, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins. Decreased expression or function of OATP1B1 can lead to increased plasma concentrations of these substrates, potentially resulting in systemic drug toxicity or adverse effects. Genetic variations at the *SLCO1B1* locus, as well as drug–drug interactions, can change OATP1B1 function and increase an individual's risk for adverse effects from these substrate medications. (27, 28)

The Pharmacogene Variation Consortium (PharmVar) maintains a standardized nomenclature of *SLCO1B1* variants, commonly called star (*) alleles (27). Each star allele is defined by a core variant or variants inherited together on a single allele, or haplotype, with the pair of alleles present in any individual called their diplotype or genotype. Star alleles are assigned a clinical function level by CPIC. Of the 44 star alleles defined by PharmVar, only 13 *SLCO1B1* star alleles have been assigned a clinical functional status by CPIC (Table 3) (29, 30). The *SLCO1B1*1* and *37* alleles are classified as normal function, while multiple alleles such as *SLCO1B1*5, *9*, and *15*, are classified as having no function. The *SLCO1B1*14* and *20* alleles are classified as increased-function alleles (29). It is common in pharmacogene nomenclature to assign the *1 allele as the reference allele and the baseline for "normal" allele function. Also, *1 is the presumed allele when no variants are identified by testing.

Table 3: Functional Classification of *SLCO1B1* Allele (CPIC, 2021)

Allele clinical functional status	*SLCO1B1* star alleles
Increased function	*14, *20
Normal function	*1, *37
No function	*5, *9, *15, *23, *31, *46, *47, *48, *49
Unknown function	*43, *44, *45

Table adapted from (29). CPIC - Clinical Pharmacogenetics Implementation Consortium

The normal-function *SLCO1B1*37* allele is defined by a SNV that substitutes an aspartic acid (D) for asparagine (N) at position 130 of the protein (rs2306283, NM_006446.5:c.388A>G) with no other functionally significant variants (29, 31). This variant is present in 18 other star alleles with varying clinical functions, underscoring the importance of testing the breadth of known star alleles for accurate genotyping (27). Another commonly studied

SNV is rs4149056 (NM_006446.5:c.521T>C), found in the *SLCO1B1*5*, *SLCO1B1*15, SLCO1B1*40*, *SLCO1B1*46*, and *SLCO1B1*47* alleles. All but one of these alleles are classified as no function by CPIC—the one outlier allele, *SLCO1B1*40*, has uncertain function due to the presence of other variants with unknown functional impact (27, 30). The rs4149056 variant is found in 4 out of the 9 no-function alleles. The remaining 5 no-function alleles are defined by other SNVs or structural variants resulting in either a full or partial gene deletion (31).

Historic star allele designations have been reviewed and standardized by PharmVar, leading to some alleles being reclassified as sub-alleles based on shared core variants and biochemical functional status (27). The biochemical activity of a protein does not automatically translate to the same level of clinical activity; thus, in vitro pharmacokinetic/pharmacodynamic studies identifying hypo-active forms of OATP1B1 may ultimately result in a clinical phenotype no different than a complete loss-of-function allele (27).

An individual's *SLCO1B1* genotype (pair of inherited alleles) can predict their phenotype (Table 4) (32). Individuals with normal or increased function OATP1B1 transporter phenotype are at a lower risk of adverse drug reactions, while those with poor function or decreased function phenotypes are at higher risk of adverse reactions due to higher plasma concentrations of the substrate medication and its metabolites. An individual is assigned a phenotype of "possible decreased function" when one known no-function allele is present, and the second allele has unknown or uncertain function (2).

Table 4: Selected *SLCO1B1* Phenotype-Genotype Predictions (CPIC, 2022)

Clinical phenotype	Example *SLCO1B1* genotype	Clinical alert category[a]
Normal function	*1/*1 *1/*14 *1/*37	Low risk
Increased function	*14/*14 *14/*20 *20/*20	Low risk
Decreased function	*1/*5 *1/*9 *15/*37	High risk
Possible decreased function	*2/*5 *2/*15 *3/*9	High risk
Poor function	*5/*5 *5/*9 *9/*23 *15/*15	High risk

[a] These genotypes and phenotypes are recommended by CPIC to be flagged as low or high risk when implemented in electronic health records notifications. CPIC - Clinical Pharmacogenetics Implementation Consortium
This table is adapted from (32).

The frequency of *SLCO1B1* alleles can vary significantly based on population-specific genetic ancestry. However, allele frequencies cited reported in the literature may not fully represent allelic variation within a population. Owing to the recent reclassification of some historic star alleles and the underrepresentation of many populations in genetic and genomic research, these frequencies should be considered cautiously (27). For example, studies of populations living in the United Arab Emirates or Qatar examined only one or 2 SNVs and assigned the most common genotype based on those variants, excluding other star alleles (33, 34). Additional studies using current PharmVar allele definitions are needed across multiple populations to understand allele

and phenotype frequencies for *SLCO1B1*. The following information should be interpreted as approximate frequencies based on existing publications.

The *SLCO1B1*1* allele is clinically determined to be a normal-function allele, with a frequency of 50% or less for all CPIC biogeographical groups (35). However, the *SLCO1B1*37* allele—previously called *1B and also a normal-function allele—is the most frequently reported haplotype in African-American and Sub-Saharan-African populations, with a frequency of 76–80%, and 60% in East Asian populations (35).

Reduced- and increased-function alleles are less common globally. The no-function allele *SLCO1B1*15* is more common in many biogeographical groups compared with *SLCO1B1*5*. The combined frequency of both can range from 24% in American, 20% in Near Eastern, 17% in European, 12% in East Asian, 7% in Central/South Asian, 1–2% in African-American/Afro-Caribbean and Sub-Saharan populations, to not observed in Oceanian populations (35). The SNV that is shared between *SLCO1B1*5* and *SLCO1B1*15* was observed at a frequency of 24% in a Qatari population of mixed genetic ancestry, while the SNV associated with *SLCO1B1*37* was found in approximately 50% of study participants (33). Other no-function alleles are observed far less frequently, such as *SLCO1B1*9* due to variation at rs59502379, which has an allele frequency of 0–4.6% of the global populations in the Allele Frequency Aggregate (ALFA) data (36). The increased-function *SLCO1B1*14* allele has been reported almost exclusively in European genetic backgrounds at a frequency of 12% (35).

Variations in *SLCO1B1* causes altered transportation of endogenous substances such as bilirubin. The rare, inherited disorder Rotor syndrome is caused by bi-allelic loss of function variants in both *SLCO1B1* and *SLCO1B3*, which encodes another organic anion transporting polypeptide (37). Rotor syndrome presents with a benign form of hyperbilirubinemia and jaundice, clinically indistinguishable from Dubin-Johnson syndrome, though the elevated bilirubin seen in Rotor syndrome is a mix of both conjugated and unconjugated forms (38). Inherited in an autosomal recessive pattern, Rotor syndrome does not require therapy, but diagnosis is important to ensure other, more serious hepatobiliary disorders are not the cause of the jaundice (38).

Phenoconversion

Phenoconversion occurs when certain medications inhibit OATP1B1 activity, reducing transport of various substrates into hepatocytes and leading to a lower activity phenotype than predicted by genotype alone. Several drugs have been identified by in vitro assays to inhibit OATP1B1 including atorvastatin, cyclosporin, digoxin, gemfibrozil, ketoconazole, and rifampin among others (28). In vivo administration of cyclosporine with rosuvastatin or fluvastatin resulted in increased statin exposure, presumably due to decreased function of OATP and CYP3A4 (39, 40, 41). The US FDA's approved label for simvastatin states that concomitant use of simvastatin with cyclosporine, danazol, or gemfibrozil is contraindicated due to increased risk of myopathy (1).

Wojtyniak and colleagues have made available their drug–drug gene interaction data in the form of a clinical decision support tool at https://nemos.shinyapps.io/simvastatin_simulator/. However, the website states that "decisions on therapeutics and dosing recommendations should not exclusively be build[sic] based on the results of the simvastatin exposure simulator and do not replace clinical judgement" (42).

Linking *SLCO1B1* Genetic Variation with Treatment Response

The risk of SAMS for simvastatin correlates with *SLCO1B1* variants that reduce OATP1B1 function, thereby increasing an individual's exposure to simvastatin and its metabolites. Increased and normal function *SLCO1B1* haplotypes do not have a clinically significant impact on simvastatin metabolism or increase the risk of adverse effects above an individual's baseline risk (2). The variant at rs4149056 (c.521T>C; the defining SNV for *SLCO1B1*5* and also a part of *SLCO1B1*15*) was found to increase simvastatin acid exposure (as measured by total plasma concentration over time, or area under the curve) by approximately 40% in healthy volunteers, increasing the risk of SAMS (14). This variant also increased exposure to simvastatin acid in a pediatric population (43), though the CPIC found insufficient data to make pediatric-specific recommendations (2). A

pooled analysis of 11 studies on the association of rs4149056 variation and SAMS risk in Caucasians with the CC or TC genotype indicated a higher risk of myopathy, with the CC genotype carriers having a 2.81 odds ratio (OR) for myopathy compared with the wildtype (TT) genotype, and heterozygotes (CT genotype) having an OR of 1.78 (13). The pooled analysis of studies in Asian populations, though including only 2 publications, reported a 1.8 times higher risk of SAMS when the C allele was present (13). Increased plasma levels of simvastatin acid were also reported to be associated with *SLCO1B1* variants at rs11045819, (c.463C>A, which is the defining SNV for *SLCO1B1*4*) and rs34671512 (c.1929A>C, one of 2 SNVs in *SLCO1B1*20*) (12).

O'Brien and colleagues, in a retrospective analysis of more than 11,000 medical records over 5 years, found that, after correcting for covariates, individuals who self-reported as "Black/African-American" or "other/multiple race" were less likely to experience adverse reactions to simvastatin (44). This study also found that lower age and comorbid hypertension were significant covariates for increased probability of adverse reaction to simvastatin. However, the authors noted a relatively small number of adverse events and acknowledged the limitations off often incomplete electronic health record data (44). A study of nearly 300 individuals with FH found that variation at rs4149056 (c.521T>C) was not associated with SAMS; instead, increased age was the most significant risk factor (45). The US FDA's approved label also advises that advanced age (65 years and older) is a risk factor for SAMS (1).

Increased risk of developing type-2 diabetes is another side effect of statin use (46, 47, 48), and variation at rs4149056 has been associated with an increased risk, as indicated by elevated hemoglobin A1C levels (34). However, a large study of over 7,500 individuals (1,373 individuals treated with statins and 6,415 not treated with statins) found no association between rs4149056 T>C variation and incidence of diabetes or changes in blood glucose levels (15).

Studies examining the link between *SLCO1B1* genetic variation and the efficacy of statins reported that decreased OATP1B1 transport (most often studied in the context of rs4149056, c.521T>C genotype) correlates with an attenuated effect on the lipid-lowering capability of statins, including simvastatin. However, the effect is small (<10 mg/dl) and unlikely to impact the frequency of vascular events, leading CPIC to base their recommendations primarily on the risk of SAMS and pharmacokinetic data (see Supplement of (2)) rather than on efficacy concerns. Many studies reported a milder reduction in cholesterol in individuals with one or 2 copies of the variant rs4149056 c.521T>C allele, though it is unclear if this is due to medication nonadherence (specifically due to myopathy or other adverse effects), differences in genetic background, reduced OATP1B1 function, or a combination of these factors (49, 50, 51, 52, 53, 54, 55).

In contrast, no association was found between *SLCO1B1* variants at rs4149056 (c.521T>C), rs2306283 (c.388A>G), or rs4363657 (g.89595T>C) and lipid levels following simvastatin therapy in a cohort of nearly 400 Thai individuals with hypercholesterolemia (56). Similarly, a review of several studies in Brazil found no association between *SLCO1B1* variants (namely, the *SLCO1B1*5*, **15*, **4*, and **14* alleles) and efficacy of atorvastatin or simvastatin (57).

Additional Genes of Interest

Given the role of CYP3A enzymes in metabolizing simvastatin to simvastatin acid, it is not surprising that some studies have examined the association between *CYP3A4* variation and simvastatin pharmacokinetics. Like other cytochrome P450 family members, genetic variation at the *CYP3A* loci can result in decreased or no function of the encoded enzyme. While CPIC has not assigned a clinical function to *CYP3A4* haplotypes (58), the biochemical function has been used to predict metabolism phenotypes of intermediate or poor CYP3A4 metabolizers (12). One study reported a genome wide association with *CYP3A4*2* (rs55785340, c.664T>C) genotype, assigned as an intermediate metabolizer phenotype, and increased simvastatin acid exposure (12). Individuals heterozygous for the *CYP3A4*22* or *CYP3A5*3* alleles (classified as intermediate metabolizers) had significantly higher plasma simvastatin concentrations and lower total and plasma LDL cholesterol levels (59).

However, Kitzmiller and colleagues reported no association between *CYP3A4*22* (a decreased-function allele) or *CYP3A5*3* (clinically categorized by CPIC as a no-function allele (60)) and the cholesterol-lowering response to simvastatin (50).

Further research found a connection between statin response and variations in the hepatic efflux transporter *ABCB1* and a leukocyte immunoglobin receptor locus, *LILRB5* (61). The SNV at rs1045642 in the *ABCB1* gene, resulting in a synonymous protein change, was linked to a significant reduction in non-high-density lipoprotein (HDL) levels in a recessive inheritance model. The *LILRB5* variant rs12975366 showed effects in a dominant fashion, leading to a more pronounced decrease in non-HDL levels. These 2 loci appear to have a synergistic effect, although further studies are needed for confirmation.

An analysis of the UK Biobank data indicated a potential association between *NAT2* genetic variation and statin use. The *NAT2* locus encodes N-acetyltransferase 2 and has been liked to abnormal sensitivity to amifampridine. Wendt and colleagues reported an association between the *NAT2*5* allele and LDL cholesterol levels, with diplotypes including this allele being more common among statin users than non-users. They proposed a model where the NAT2 enzyme might acetylate LDL cholesterol, affecting its binding to LDL receptors and indirectly impacting statin efficacy (62).

An association has been observed between variants in HLA loci and IMNM in a Japanese cohort. Several variant alleles were found to be present at a higher rate in individuals with IMNM, although the study did not specifically assess statins as a trigger for IMNM. Candidate *HLA*-risk alleles for IMNM include *A*02:07, B*46, C*01:02, DRB1*08:03, DRB1*11:01, DQB1*06:01, DPB1*02:02, DPB1*05:01*. (20)

Genetic Testing

The NIH Genetic Testing Registry (GTR) offers tests for simvastatin response and *SLCO1B1* genetic variation. Considering the recent reclassification of *SLCO1B1* alleles by PharmVar, it is important to consider the specific testing methodology and review the genotype-phenotype assignments. Targeted SNV genotyping may only examine the most common functional variants without distinguishing between known haplotypes of differing functional status, such as *SLCO1B1*5* versus *SLCO1B1*40*. Gene sequencing may not detect structural variations or changes in copy number. Resources such as the Genotype Selection Interface (GSI) from PharmGKB, the Pharmacogenomics Clinical Annotation Tool (PharmCAT), and the PharmVar *SLCO1B1* allele definitions assist in report interpretation. The decision to test for *SLCO1B1* variation before or during standard -dose simvastatin therapy depends on the managing clinician. The FDA has no requirement to assay SLCO1B1 before therapy nor does CPIC issue guidance regarding testing. However, the DPWG recommends genotyping before starting an 80 mg/day dose of simvastatin for drug tolerance, and considers testing beneficial at a 40 mg/day dose, advising testing before or directly after initiating treatment (4). The data from PharmGKB for the Swissmedic drug labeling recommends *SLCO1B1* genotype testing with simvastatin therapy, both alone and with ezetimibe (11).

The clinical validity of *SLCO1B1* genotyping in predicting SAMS has been assessed. The SEARCH study, which focused on individuals with a history of myocardial infarction taking 80 mg simvastatin, found that individuals with at least one C allele at rs4149056, had a significantly increased risk of myopathy over 5 years, with an OR of 4.5 per C allele (63). An analysis of this study showed that at least one C allele found by genotyping has a positive predictive value (PPV) for myopathy risk of 4.1%, a negative predictive value (NPV) of 99.4%, a specificity of 73.7% and sensitivity of 70.4%; biallelic C genotype at this SNV has a PPV of 18.6%, NPV of 99.8%, specificity of 98.3%, and sensitivity of 25.1% (64). No additional risk loci for SAMS have been identified (65).

One study reported that utilization of *SLCO1B1* pharmacogenetic testing within a clinical decision support tool led to fewer prescriptions of medications that increase the risks of SAMS for individuals with *SLCO1B1* at-risk genotypes. This information is more likely to result in the cancellation of a simvastatin prescription if the genotype is known before prescribing rather than afterward (66). A similar study found that clinical testing and

reporting of the *SLCO1B1* genotype to guide simvastatin therapy resulted in noninferior outcomes for the genotype-guided group, with no instances of simvastatin prescribing for known OATP1B1 decreased or poor function phenotypes, suggesting that, given the information in advance, physicians avoid prescribing simvastatin to individuals with an at-risk genotype (67).

The *SLCO1B1* Gene Interactions with Medications Used for Additional Indications

The FDA has included the *SLCO1B1* gene on very few drug labels to date; including rosuvastatin (another statin), elagolix, and viloxazine (68). Elagolix is a gonadotropin-releasing hormone antagonist medication used to manage pain associated with endometriosis (69). Viloxazine is a selective norepinephrine reuptake inhibitor used for attention deficit hyperactivity disorder (70). Guidelines are available from CPIC on *SLCO1B1* and multiple statins,(2) and PharmGKB, CPIC, and the FDA also provide additional information on gene-drug interactions involving *SLCO1B1* (search for "SLCO1B1").

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2023 Statement from the US Food and Drug Administration (FDA):

Warnings and Precautions- Myopathy and Rhabdomyolysis

Simvastatin may cause myopathy and rhabdomyolysis… Risk factors for myopathy include age 65 years or greater, uncontrolled hypothyroidism, renal impairment, concomitant use with certain other drugs (including other lipid lowering therapies), and higher simvastatin dosage; Chinese patients on simvastatin may be at higher risk for myopathy…The risk of myopathy is increased by elevated plasma levels of simvastatin and simvastatin acid. The risk is also greater in patients taking an 80 mg daily dosage of simvastatin compared with patients taking lower simvastatin tablets dosages and compared with patients using other statins with similar or greater LDL-C lowering efficacy.

Steps to Prevent or Reduce the Risk of Myopathy and Rhabdomyolysis

The concomitant use of strong CYP3A4 inhibitors with simvastatin is contraindicated. If short-term treatment with strong CYP3A4 inhibitors is required, temporarily suspend simvastatin during the duration of strong CYP3A4 inhibitor treatment. The concomitant use of simvastatin with gemfibrozil, cyclosporine, or danazol is also contraindicated … Simvastatin dosage modifications are recommended for patients taking lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine or ranolazine.

Please review the complete therapeutic recommendations that are located here: (1)

2022 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC):

Phenotype: SLCO1B1 decreased function or SLCO1B1 possible decreased function

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[1] The FDA has distinct labels for specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance with nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.

Implications: Increased simvastatin acid exposure as compared with normal function; increased risk of myopathy.

Dosing recommendation: Prescribe an alternative statin depending on the desired potency (see Figure 1 for recommendations for alternative statins). If simvastatin therapy is warranted, limit dose to <20 mg/day.

Phenotype: SLCO1B1 poor function

Implications: Increased simvastatin acid exposure compared with normal and decreased function; highly increased myopathy risk.

Dosing recommendation: Prescribe an alternative statin depending on the desired potency (see Figure 1 for recommendations for alternative statins)

Please review the complete therapeutic recommendations that are located here: (2)

2020 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

SLCO1B1 521CC: [simvastatin]

When using simvastatin 80 mg/day, the risk of myopathy is increased 30-fold to 18% and the risk of severe myopathy is increased 48-fold to 12%. When using 40 mg/day, this risk is increased 7-fold to 1% and 11-fold to 0.68% respectively. The gene variation leads to reduced simvastatin transport to the liver, which increases the simvastatin plasma concentration and therefore the risk of side effects.

1. Choose an alternative

Consider any additional risk factors for statin-induced myopathy.

Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of atorvastatin is not recommended for patients with additional risk factors for statin-induced myopathy.

Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.

Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors.

SLCO1B1 521TC: [simvastatin]

When using simvastatin 80 mg/day, the risk of myopathy is increased 5-fold to 3% for moderately severe to severe myopathy and 1.3% for severe myopathy. When using 40 mg/day, this risk is increased 2.6-fold to 0.39% and 0.17% respectively. The gene variation may lead to reduced simvastatin transport to the liver, which may increase simvastatin plasma concentrations and therefore the risk of side effects.

1. Choose an alternative

Consider any additional risk factors for statin-induced myopathy.

Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of atorvastatin is not recommended for patients with additional risk factors for statin-induced myopathy.

Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.

Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors.

2. If an alternative is not an option:

1. Avoid simvastatin doses exceeding 40 mg/day (for example, by adding ezetimibe)[a]

2. Advise the patient to report muscle symptoms. [a]

Please review the complete therapeutic recommendations that are located here: (3) [a] Note that minor variations in wording versus the cited guidelines are included here based on personal communication from DPWG.

Nomenclature for Selected *SLCO1B1* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
SLCO1B1*1	SLCO1B1*1A	NM_006446.5	NP_006437.3	
SLCO1B1*4	35305C>A (P155T)	NM_006446.5:c.463C>A	NP_006437.3:p.Pro155Thr	rs11045819
SLCO1B1*5	37041T>C (V174A)	NM_006446.5:c.521T>C	NP_006437.3:p.Val174Ala	rs4149056
SLCO1B1*9	64425G>C (G488A)	NM_006446.5:c.1463G>C	NP_006437.3:p.Gly488Ala	rs59502379
SLCO1B1*14[a]	35230A>G (N130D)	NM_006446.5:c.388A>G	NP_006437.3:p.Asn130Asp	rs2306283
	35305C>A (P155T)	NM_006446.5:c.463C>A	NP_006437.3:p.Pro155Thr	rs11045819
SLCO1B1*15[b]	35230A>G (N130D)	NM_006446.5:c.388A>G	NP_006437.3:p.Asn130Asp	rs2306283
	37041T>C (V174A)	NM_006446.5:c.521T>C	NP_006437.3:p.Val174Ala	rs4149056
SLCO1B1*20[c]	35230A>G (N130D)	NM_006446.5:c.388A>G	NP_006437.3:p.Asn130Asp	rs2306283
	97468A>C (L643F)	NM_006446.5:c.1929A>C	NP_006437.3:p.Leu643Phe	rs34671512
SLCO1B1*37	SLCO1B1-*1B, *1F, *1G, *1H 35230A>G (N130D)	NM_006446.5:c.388A>G	NP_006437.3:p.Asn130Asp	rs2306283

[a] *SLCO1B1*14* represents a consolidated core haplotype encompassing the previously named *SLCO1B1*14* and *SLCO1B1*18* alleles.
[b] *SLCO1B1*15* represents a consolidated core haplotype encompassing the previously named *SLCO1B1*15A, SLCO1B1*15B,* and *SLCO1B1*17* alleles.
[c] *SLCO1B1*20* represents a consolidated core haplotype encompassing the previously named *SLCO1B1*20, SLCO1B1*21,* and *SLCO1B1*35* alleles.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (71).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature is from the Pharmacogene Variation (PharmVar) Consortium (27).

Acknowledgments

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