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The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for \textit{SLCO1B1} and Simvastatin-Induced Myopathy

RA Wilke\textsuperscript{1,2}, LB Ramsey\textsuperscript{3}, SG Johnson\textsuperscript{4,5}, WD Maxwell\textsuperscript{6}, HL McLeod\textsuperscript{7}, D Voora\textsuperscript{8}, RM Krauss\textsuperscript{9}, DM Roden\textsuperscript{1,2}, Q Feng\textsuperscript{1,2}, RM Cooper-DeHoff\textsuperscript{10}, L Gong\textsuperscript{11}, TE Klein\textsuperscript{11,12}, M Wadelius\textsuperscript{13} and M Niemi\textsuperscript{14}

Cholesterol reduction from statin therapy has been one of the greatest public health successes in modern medicine. Simvastatin is among the most commonly used prescription medications. A non-synonymous coding single-nucleotide polymorphism (SNP), rs4149056, in \textit{SLCO1B1} markedly increases systemic exposure to simvastatin and the risk of muscle toxicity. This guideline explores the relationship between rs4149056 (c.521T>C, p.V174A) and clinical outcome for all statins. The strength of the evidence is high for myopathy with simvastatin. We limit our recommendations accordingly.

FOCUSED LITERATURE REVIEW
A systematic literature review was conducted that focused on \textit{SLCO1B1} gene polymorphisms and statin-related end points in humans. Emphasis was placed on the \textit{SLCO1B1} variant rs4149056 and two primary end points: (i) statin pharmacokinetics (including parent drugs, lactones, acids, and derivatives related to phase I oxidation and/or phase II conjugation) and (ii) relevant studies of clinical outcome. Because rs4149056 acts via its damaging effect on OATP1B1 protein function, it is assumed that other damaging \textit{SLCO1B1} gene variants may have similar clinical impact. However, we limit our recommendations to rs4149056 because the vast majority of pharmacokinetic and clinical outcome data have been published for this variant only.

At present, our recommended approach does not include other pharmacokinetic genes. The quality of evidence linking other pharmacokinetic candidates to myopathy is low to moderate, and additional study is needed. The evidence linking pharmacodynamic candidates to statin-induced myopathy is sparse. The mechanism underlying this adverse drug reaction (ADR) is only partly understood. Although some data show promise in terms of identifying pharmacodynamic variants, the clinical utility of typing these variants remains unclear.

SCOPE OF THE PROBLEM
The first statin to be approved by the US Food and Drug Administration (FDA) was lovastatin in 1987, followed by simvastatin in 1988, pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998, rosuvastatin in 2003,

\textsuperscript{1}Oates Institute for Experimental Therapeutics, Vanderbilt University Medical Center, Nashville, Tennessee, USA; \textsuperscript{2}Department of Medicine, Division of Clinical Pharmacology, Vanderbilt University, Nashville, Tennessee, USA; \textsuperscript{3}Pharmaceutical Sciences Department, St. Jude Children’s Research Hospital, Memphis, Tennessee, USA; \textsuperscript{4}Department of Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver, Colorado, USA; \textsuperscript{5}Clinical Pharmacy Services, Kaiser Permanente Colorado, Denver, Colorado, USA; \textsuperscript{6}Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy, Columbia, South Carolina, USA; \textsuperscript{7}Department of Pharmacy, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, North Carolina, USA; \textsuperscript{8}Department of Medicine, Institute for Genome Sciences and Policy, Duke University, Durham, North Carolina, USA; \textsuperscript{9}Department of Medicine, Atherosclerosis Research, Children’s Hospital Oakland Research Institute, Oakland, California, USA; \textsuperscript{10}Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics and Division of Cardiovascular Medicine, University of Florida, Gainesville, Florida, USA; \textsuperscript{11}Department of Genetics, Stanford University, Palo Alto, California, USA; \textsuperscript{12}PharmGKB (Pharmacogenetics and Pharmacogenomics Knowledge Base), Stanford University, Palo Alto, California, USA; \textsuperscript{13}Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, Sweden; \textsuperscript{14}Department of Clinical Pharmacology, University of Helsinki and HUSLAB, Helsinki University Central Hospital, Helsinki, Finland. Correspondence: RA Wilke (ra.wilke@vanderbilt.edu)

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CLINICAL PHARMACOLOGY & THERAPEUTICS
and pitavastatin in 2009.\textsuperscript{1,2} Cerivastatin was withdrawn in 2001, because of its higher frequency of rhabdomyolysis. Seven of these agents remain in clinical use; and five are currently available as generic formulations (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). In 2010, simvastatin was the most commonly prescribed generic statin formulation and the third most commonly prescribed drug in the United States (http://www.pharmacytimes.com/publications/issue/2011/May2011/Top-200-Drugs-of-2010).

In general, statins are safe. The most common statin-related ADR is skeletal muscle toxicity.\textsuperscript{3} Statin-related muscle problems include myalgias (pain), myopathy (pain with evidence of muscle degradation), and rhabdomyolysis (severe muscle damage with acute kidney injury). Frequency varies by definition, but, overall, statin-related myalgias are common, occurring in 1–5% of subjects exposed. In patients without arthritis, National Health and Nutrition Examination Survey data suggest a “number needed to harm” of 17 (ref. 4).

Clinicians often measure serum creatine kinase (CK) levels, as a rough proxy for severity, but the correlation between symptoms and CK level is incomplete. Therefore, the clinical interpretation of CK level is complex. Elevations less than threefold the upper limit of normal (ULN) are typically of little consequence. Conversely, clinicians often intervene (change dose or change drug) when CK levels exceed threefold the ULN. At present, the literature support three diagnostic strata: (i) incipient myopathy (CK above 3-fold the ULN, less than 10-fold the ULN), (ii) myopathy (CK above 10-fold the ULN, less than 50-fold the ULN), and (iii) rhabdomyolysis (CK above 50-fold the ULN).\textsuperscript{5,6} In the context of statin monotherapy, the frequency of myopathy is \(\sim 1/1,000\), and the frequency of rhabdomyolysis is \(\sim 1/100,000\). As discussed further below, frequency increases with dose.

**CLINICAL DETERMINANTS OF RISK**

Clinical factors known to influence a patient’s risk for developing statin-induced muscle toxicity include increased statin dose, advanced age, low body mass index, female gender, metabolic comorbidities (e.g., hypothyroidism), intense physical exercise, and Asian or African ancestry.\textsuperscript{3,7–10} Because polypharmacy is common in the elderly, the association with age is partly attributable to drug–drug interactions as well as to increases in chronic renal or hepatic disease.\textsuperscript{11}

After studying the medical records of more than 250,000 patients, Scheck\textsuperscript{·}et al.\textsuperscript{ reported that statin users over age 65 years have four times the risk of hospitalization due to muscle toxicity than younger statin users (composite end point including myositis, myopathy, and/or rhabdomyolysis) (odds ratio (OR) 4.36; 95% confidence interval (CI) = 1.5–14.1).\textsuperscript{12} Although controversial, female gender may also increase risk because of smaller volumes of distribution.\textsuperscript{12,13} Although vigorous exercise often contributes to CK elevation in the context of statin exposure,\textsuperscript{14,15} the impact of physical activity can be difficult to interpret. Even in the absence of drug exposure or underlying muscle pathology, strenuous exercise can be associated with elevated serum CK levels exceeding 10-fold ULN.

Statin dose is the strongest independent predictor of risk. McClure and colleagues have reported an incidence rate for myotoxicity roughly sixfold higher in patients on high-dose statin therapy.\textsuperscript{16} Although the dose dependence of this relationship appears to be a class effect, a growing body of evidence suggests that the influence of dose may be greatest for simvastatin.\textsuperscript{17} Therefore, in 2011 the FDA announced an update to the simvastatin product label recommending against initiation of the 80-mg dose and cautioning against continuation of an 80-mg dose unless the patient has already tolerated it without muscle problems for more than 1 year.

**DRUG–DRUG INTERACTIONS**

In the context of statin monotherapy, myopathy rates are low.\textsuperscript{13} The frequency of this ADR increases with coadministration of medications altering the pharmacokinetic handling of statins. Between 1998 and 2001, more than 40 cases of muscle toxicity associated with the use of cerivastatin were found to be fatal. Many of these occurred within the context of use 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.\textsuperscript{18,19}

The biological disposition of this class of drugs differs on a drug-by-drug basis. Some statins (atorvastatin, fluvastatin, lovastatin, and simvastatin) undergo extensive phase I oxidation; others (pitavastatin, pravastatin, and rosuvastatin) do not. 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).\textsuperscript{20}

Many statins also undergo additional modification through phase II conjugation by enzymes in the UDP-glucuronosyltransferase-1 (UGT1) family. This process can be altered by concomitant administration of fibric acids.\textsuperscript{21} Gemfibrozil, a fibric acid derivative, alters pharmacokinetic handling of a variety of statins. By inhibiting the glucuronidation and membrane transport of simvastatin hydroxy acids, gemfibrozil increases systemic exposure to active simvastatin acid,\textsuperscript{22} placing patients at increased risk for developing myopathy. Because of interactions such as these, the FDA label update also recommends reducing the dose of simvastatin in patients using concomitant medications known to alter its pharmacokinetics (details in Supplementary Table S1 online).

**SLCO1B1**

OATP1B1 (encoded by SLCO1B1) facilitates the hepatic uptake of statins as well as numerous endogenous compounds (e.g., bilirubin and 17-beta-glucuronosyl estradiol).\textsuperscript{23,24} Changes in the activity of this transporter (as occur during drug–drug interaction) can markedly increase the severity of statin-related muscle damage. For example, cyclosporine, a strong inhibitor of CYP3A4 and OATP1B1, increases the area under the curve for simvastatin acid three- to eightfold.\textsuperscript{24}

Beyond acquired inhibition, genetic variability in SLCO1B1 also alters plasma concentration of statins. The overall pharmacokinetic profiles appear to be altered more for simvastatin than
for any other drug in the class. Other transporters potentially influencing the distribution and tissue uptake of statins include OATP1B3 (encoded by SLCO1B3), OATP2B1 (encoded by SLCO2B1), OATP1A2 (encoded by SLCO1A2), and sodium-dependent taurocholate cotransporting polypeptide, NTCP.

**NOMENCLATURE**

The SLCO1B1 gene locus occupies 109 kb on chromosome 12 (Chr 12p12.2). Although many single-nucleotide polymorphisms (SNPs) have been identified in SLCO1B1, only a few are known to have functional effects. The common c.521T>C variant rs4149056 produces a p.V174A substitution. The minor C allele at this locus has been associated with decreased transport function in vitro and decreased clearance for a number of drugs in vivo. Assignment of OAT1B1 phenotype has been summarized in Table 1, based on rs4149056. In general, this variant is present at a minor allele frequency between 5 and 20% in most populations (see Supplementary Tables S2–S4 online).

**SLCO1B1** alleles are often named using *nomenclature*, representing various SNPs alone or in combination (http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=3). SLCO1B1 haplotypes are listed in Supplementary Table S2 online, including additional variants that are associated with low OAT1B1 protein expression or function. The minor C allele at rs4149056 is contained within SLCO1B1*5 (rs4149056 alone) as well as the *15, *16, and *17 haplotypes. As explained in detail below, although rs4149056 clearly influences the pharmacokinetic handling of simvastatin acid, the magnitude of this effect is similar for the *5, *15,*16, and *17 haplotypes.

**rs4149056 and Statin Kinetics**

Simvastatin is administered as an inactive lactone, and hydrolyzed in vivo to the corresponding hydroxy acid by nonspecific carboxysterases. Simvastatin acid is a potent inhibitor of HMG-CoA reductase. Simvastatin and lovastatin are the only statins requiring bioactivation. All other statins are administered directly as bioactive acid salts. For example, atorvastatin is administered in an active form (atorvastatin acid), and extensive first-pass metabolism by CYP3A4/5 yields ortho- and para-hydroxylated derivatives with similar activity to the parent compound.

SLCO1B1 polymorphisms clearly impact the pharmacokinetics of simvastatin and, to a lesser degree, the pharmacokinetics of other statins (Supplementary Table S5, online). Pasanen et al. determined that homozygous carriers of the C allele at rs4149056 (CC genotype) had much greater exposure to the active simvastatin acid (AUC0–12) than subjects homozygous for the ancestral T allele. In single-dose studies (Supplementary Figure S1 online), the observed plasma areas under the curve of active simvastatin acid, pitavastatin, atorvastatin, pravastatin, and rosuvastatin have been, respectively, 221, 162–191, 144, 57–130, and 62–117% higher in rs4149056 CC homozygotes than in rs4149056 TT homozygotes.

**rs4149056 and Myopathy Risk**

In 2008, the SEARCH Collaborative Group (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) conducted a case–control study of simvastatin-induced myopathy using archived DNA from a randomized trial including more than 12,000 subjects who had received either low-dose simvastatin (20 mg daily) or high-dose simvastatin (80 mg daily) after myocardial infarction. During the course of the trial, 49 subjects in the high-dose arm developed myopathy (CK > 10-fold the ULN with pain). An additional 49 subjects in the same treatment arm developed “incipient” myopathy (CK > threefold the ULN and five times the patient’s baseline level).

**Table 1 Assignment of likely SLCO1B1 phenotype based on genotype**

<table>
<thead>
<tr>
<th>Genotype definitions</th>
<th>Diplootypes observed</th>
<th>Genotype at rs4149056</th>
<th>Observed phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>An individual carrying two functional alleles</td>
<td>*1/*1</td>
<td>TT</td>
<td>Homozygous wild-type or normal (55–88% of patients) high activity</td>
</tr>
<tr>
<td>An individual carrying one functional allele plus one reduced-function allele</td>
<td>*1/*5 (or *1/*15, *1/*16, or *1/*17)</td>
<td>TC</td>
<td>Heterozygous (11–36% of patients) intermediate activity</td>
</tr>
<tr>
<td>An individual carrying two reduced-function alleles</td>
<td>*5/*5 (or *5/*15, *5/*16, *5/*17, *15/*15, *15/*16, *15/*17, *16/*16, *16/*17, or *17/*17)</td>
<td>CC</td>
<td>Homozygous variant or mutant (0–6% of patients) low activity</td>
</tr>
</tbody>
</table>
controlled treatment trials, the effect size for rs4149056 was lower in the latter (i.e., at the 40-mg dose) than in SEARCH (i.e., at the 80-mg dose), underscoring the importance of dose.

Practice-based data suggest that the association between rs4149056 and muscle toxicity is stronger for simvastatin than for other drugs within the class. The C allele at rs4149056 has recently been shown to influence the rate of medication adherence for simvastatin. In the STRENGTH study, 509 hypercholesterolemic patients were randomized to simvastatin, atorvastatin, or pravastatin and followed for 16 weeks. The primary end point of the study was a composite of study drug discontinuation for any adverse effect, myalgia or muscle cramping, and/or elevated serum CK levels more than threefold the ULN. The overall effect size was striking for simvastatin (OR: 2.8, 95% CI: 1.3–6.0) but rather modest for atorvastatin (OR 1.6, 95% CI: 0.7–3.7). No significant association was observed for pravastatin (OR 1.0, 95% CI: 0.4–2.6). As in the STRENGTH study, other groups have reported a modest association between rs4149056 and atorvastatin intolerance based on adverse muscle symptoms, but the association between rs4149056 and laboratory-confirmed myopathy has been less compelling for atorvastatin.

From the medical records of nearly 9,000 patients followed in an academic lipid clinic, Brunham and colleagues identified 25 laboratory-confirmed myopathy cases (frequency 0.26%). All 25 cases were genotyped for rs4149056, along with drug-exposed controls (frequency-matched 2:1), revealing an OR for myopathy of 2.3 per copy of the minor C allele at rs4149056. The OR was highest, 3.2 (95% CI: 0.83–11.96), for subjects with the CC genotype exposed to simvastatin. No such relationship was observed using a similar number of atorvastatin cases (OR 1.06, 95% CI 0.22–4.80). These observations are consistent with reported differences in clearance (Supplementary Figure S1 online). To date, there is little evidence that rs4149056 genotype influences symptomatic intolerance or myopathy for pravastatin or rosuvastatin. Hence, the observed clinical association between rs4149056 and myopathy may not be a class effect.

AVAILABLE GENETIC-TEST OPTIONS

The commercially available clinical testing options listed in the Supplementary Material online and are freely available at http://www.PharmGKB.org. The rs4149056 SNP can be genotyped alone (e.g., PCR-based single SNP assay) or multiplexed on a variety of array-based platforms (e.g., with other pharmacokinetic variants). Array-based technologies are readily available within a Clinical Laboratory Improvement Amendments–approved environment for the Illumina VeraCode ADME array or the DMET Plus Affymetrix array. See Supplementary Material for details. This variant is also among the pharmacogenetic content available for participants in direct-to-consumer genomic offerings (e.g., 23andMe.com).

INCIDENTAL FINDINGS

Genetic variability in SLC01B1 influences the hepatic uptake of other drugs (e.g., methotrexate) as well as important endogenous compounds (e.g., bilirubin) (Supplementary Material online).

GENE-BASED DOSING RECOMMENDATIONS

For simvastatin, the evidence linking myopathy to rs4149056 in SLC01B1 is of high quality, and this association has been reproduced in randomized trials and clinical practice–based cohorts. Conversely, the association of rs4149056 with myopathy has been less compelling for other statins. We therefore focus this guideline on simvastatin. Our recommended approach (Table 2 and Figure 1) begins with product-label changes recently implemented by the FDA. (The agency’s recommendations are further summarized in Supplementary Table S1 online.) Decision-support tools are already being used to direct providers away from initiating the 80-mg simvastatin dose. At many of our institutions, SLC01B1 genotype is further used to underscore this warning (i.e., myopathy risk for 80 mg of simvastatin) for subjects with a C allele at rs4149056 (see details in Supplementary Material).

At lower simvastatin doses (e.g., 40 mg daily), it is our position that this information should be used to warn providers about modest increases in myopathy risk for subjects with a C allele at rs4149056 (Figure 1). Under these circumstances, we also highlight the potential utility of routine CK surveillance (Table 2). If subjects with a C allele at rs4149056 do not achieve optimal low-density lipoprotein cholesterol–lowering efficacy with a

<table>
<thead>
<tr>
<th>Genotype at rs4149056</th>
<th>Anticipated phenotype</th>
<th>Implications for simvastatin</th>
<th>Dosing recommendations for simvastatina</th>
<th>Classification of the recommendationb</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>Normal activity</td>
<td>Normal myopathy risk</td>
<td>FDA recommends against 80 mg (unless already tolerated 12 months). Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.</td>
<td>Strong</td>
</tr>
<tr>
<td>TC</td>
<td>Intermediate activity</td>
<td>Intermediate myopathy risk</td>
<td>FDA recommends against 80 mg. Consider a lower dose; if suboptimal efficacy, consider an alternative statin.</td>
<td>Strong</td>
</tr>
<tr>
<td>CC</td>
<td>Low activity</td>
<td>High myopathy risk</td>
<td>FDA recommends against 80 mg. Prescribe a lower dose or consider an alternative statin; consider routine CK surveillance.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CK, creatine kinase.

*aIn all cases, the potential for drug–drug interaction should be evaluated prior to initiating a prescription. See Supplementary Materials (text section entitled “Levels of Evidence”) online for additional details regarding the three-tiered system used to grade the quality of evidence. Further information is available within ref. 41.

**Table 2 Dosing recommendations for simvastatin, when rs4149056 genotype (or phenotype) is available**
lower dose of simvastatin, we recommend that the prescribing physician consider an alternative statin based on (i) potency differences, (ii) kinetic differences, (iii) comediations, (iv) hepatic function, (v) renal function, and (vi) relevant comorbidities.

**POTENTIAL BENEFITS AND RISKS FOR THE PATIENT**

Statins have a wide therapeutic index, and severe ADRs are therefore relatively uncommon. Nonetheless, even though the myopathy rate is low, the high prevalence of the clinical indication (hypercholesterolemia and cardiovascular disease) creates a situation in which the absolute number of ADRs is substantial. Furthermore, in the absence of severe myopathy, many patients still opt to discontinue statin therapy because of intermediate toxicity, and statin nonadherence thus has the potential to increase the burden of cardiovascular disease on our health-care infrastructure. It is with this perspective, a goal toward optimizing adherence, that we present the current guideline.

**CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS**

For the 40-mg simvastatin dose, the relative risk of myopathy is 2.6 per copy of the C allele at rs4149056. The risk is even higher for the 80-mg simvastatin dose (myopathy OR 4.5 for TC genotype, ~20.0 for CC genotype). Nonetheless, simvastatin-related muscle toxicity can still occur in the absence of rs4149056. Thus, a TT genotype does not imply the absence of another potentially deleterious variant in SLCO1B1 or elsewhere. Furthermore, because rs4149056 can also be inherited in combination with other SLCO1B1 gene variants known to have protective effects, it should not be presumed that the C allele at rs4149056 confers risk with 100% certainty.

**CURRENT STATE OF IMPLEMENTATION**

Many academic medical centers have on-site array-based SNP genotyping available within a Clinical Laboratory Improvement Amendments–approved environment, and some have the capability to link this information directly to an electronic medical record. Few, however, integrate this information into the medical record preemptively; that is, before onset of the clinical indication requiring the drug. At present, there is no uniform approach to implementation of this information, but several institutions have begun providing automated decision support (examples provided in the Supplementary Material online).

**SUPPLEMENTARY MATERIAL** is linked to the online version of the paper at http://www.nature.com/cpt

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**CONFLICT OF INTEREST**

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