<u>Supplemental Material</u>: CPIC guideline for *SLCO1B1* and simvastatin-induced myopathy

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

[1] Oates Institute for Experimental Therapeutics, Vanderbilt University Medical Center, Nashville, TN
[2] Department of Medicine, Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN
[3] Pharmaceutical Sciences Department, St. Jude Children's Research Hospital, Memphis, TN
[4] Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Denver, CO
[5] Clinical Pharmacy Services, Kaiser Permanente Colorado, Denver, CO
[6] Department of Clinical Pharmacy and Outcomes Sciences, South Carolina College of Pharmacy, Columbia, SC
[7] Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC
[8] Institute for Genome Sciences & Policy, Duke University, Durham, NC
[9] Director, Atherosclerosis Research, Children's Hospital Oakland Research Institute, Oakland, CA
[10] Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics and Division of Cardiovascular Medicine, University of Florida, Gainesville, FL
[11] Department of Genetics, Stanford University, Palo Alto, CA
[12] Director, PharmGKB (Pharmacogenetics and Pharmacogenomics Knowledge Base)
[13] Department of Medical Sciences, Clinical Pharmacology, Uppsala University, Uppsala, Sweden
[14] Department of Clinical Pharmacology, University of Helsinki and HUSLAB, Helsinki University Central Hospital, Helsinki, Finland

Rationale:

The field of pharmacogenomics is advancing rapidly. To date, CPIC has published guidelines for several drug-gene-outcome relationships relevant to cardiovascular disease and many more guidelines are being constructed. For drugs with narrow therapeutic indices (e.g., anticoagulants and antiarrhythmics), inherited (or acquired) variability in pharmacokinetic (PK) processes can have devastating clinical effects. HMG-CoA reductase inhibitors (statins), however, have a relatively wide therapeutic index, raising the question "why use *SLCO1B1* genotype to optimize prescribing in the context of simvastatin therapy?"

Statins are the most commonly prescribed class of drugs in the industrialized world. While the *relative* rate of serious ADRs is extremely low for statins, their frequent use leads to a high *absolute* number of ADRs. As a result, any reduction in statin-related ADRs has the potential to improve public health.

Our recommendations are based upon ten important principles: **(A)** clinical indication for the use of a statin is extremely common (i.e., coronary heart disease is the most common cause of death in the industrialized world), **(B)** the drug is highly efficacious in the primary and secondary prevention of coronary heart disease (1-4), **(C)** statins are among the most commonly prescribed drugs, **(D)** at present, simvastatin is the most commonly prescribed statin, **(E)** severe adverse drug reactions (myopathy and rhabdomyolysis) are potentially fatal (5-20), **(F)** mild adverse drug reactions (myalgias) occur rather frequently (i.e., more than 1% of subjects exposed) (21-23), **(G)** the association between rs4149056 in *SLCO1B1* and muscle toxicity has a large effect size for simvastatin (odds ratio from 2.0 to 20.0,

depending upon drug dose, gene dose, and the definition of intolerance) (24), **(H)** rs4149056 in *SLCO1B1* is quite common within the general population (25-27), **(I)** simvastatin intolerance often leads to nonadherence (28), and **(J)** the public health implications of nonadherence are disastrous (an increase in the overall burden of coronary heart disease). Our dosing guideline therefore leverages rs4149056 to optimize simvastatin therapy, in the context of recent FDA recommendations (Supplemental Table 1).

All CPIC guidelines are simultaneously published and updated on-line at www.pharmgkb.org.

Literature Review:

We searched the PubMed database (1966 to May 2010) and Ovid MEDLINE (1950 to May 2010) using several keyword strategies: SLCO1B1, SLCO1B1 x myopathy (26, 27, 29-48), SLCO1B1 x statin myopathy (26, 27, 29-48), SLCO1B1 x simvastatin (26, 27, 29, 32, 34, 35, 38, 49-52) (45, 48, 53-58), SLCO1B1 x LDL lowering (30, 31, 49, 55, 56, 59-64), SLCO1B1 x statin efficacy (30, 31, 36-38, 41, 46, 55-57, 59-68), SLCO1B1 x statin kinetics x human x polymorphism (26, 27, 33, 34, 36, 38, 50, 51, 57, 60, 65, 68-80), SLCO1B1 x cardiovascular (7, 27, 29, 32, 36, 38, 47, 49, 51, 55-57, 59, 81), and SLCO1B1 x statin uptake x hepatocyte (51, 54, 75, 82-88). The results of our search have been summarized within the body of the main guideline manuscript, and all references have been included in this Supplement.

SLCO1B1 nomenclature is summarized in Supplemental Table 2. For rs4149056, the racial distribution has been summarized in Supplemental Table 3 with details by geographic locale in Supplemental Table 4.

To construct tables showing *SLCO1B1* minor allele frequency based on ancestry, the PubMed database was further searched using the following criteria: *SLCO1B1*, OATP1B1, population, rs4149056, *SLCO1B1*5*, *SLCO1B1 *15*. Studies were included if: **(A)** the race of the population was clearly indicated, **(B)** allele frequencies or minor allele percentages for *SLCO1B1* haplotypes were reported, **(C)** the method by which *SLCO1B1* was genotyped was reliable, **(D)** the sample size was at least 20 subjects.

Because the pharmacokinetic effect of the C allele at rs4149056 appears to be larger for simvastatin than any other statin, we present a detailed list of published findings drug-by-drug in Supplemental Table 5.

Available Genetic Test Options

Commercially available genetic testing options change over time. Several current options are listed at http://www.pharmgkb.org . Many of our contributing institutions already conduct *SLCO1B1* genotyping.

At present, Vanderbilt University genotypes *SLCO1B1* on the Illumina ADME array in a CLIA approved environment, and actively moves the genotypes into their medical record at the point of prescribing. The Pharmaceutical Sciences Department at St. Jude Children's Research Hospital genotypes *SLCO1B1* through routine application of the DMET™ Plus Affymetrix array in a CLIA approved environment.

Several additional CLIA-approved labs offer genotyping via the Illumina VeraCode ADME array or the DMET™ Plus Affymetrix array, without direct links to medical records. Examples of readily available CLIA-approved ADME genotyping include Illumina Clinical Services Laboratory (San Diego, CA) and BioReliance (Rockville, MD). Examples of readily available CLIA-approved DMET™ genotyping include SeqWright DNA Technology Services (Houston, TX), Beckman Coulter Genomics (Morrisville, NC), Coriell Institute for Medical Research (Camden, NJ) and Expression Analysis (Durham, NC).

Single SNP genotyping is available through QPS, LLC (Quality Performance Service), a full-service CLIA-compliant contract research organization providing testing services to support preclinical and clinical research and development (in Newark, DE, Groningen, the Netherlands, and Taipei, Taiwan). QPS uses a Taqman assay to genotype rs4149056 (and rs2306283), and therefore provides results for the *1A, *1B, *5, *15 haplotypes. *SLCO1B1*5* genotyping (rs4149056 alone) is also available for clinical use at Uppsala University Hospital, in Sweden (www.genotypning.se) and at HUSLAB in Finland (www.huslab.fi). Uppsala University uses a method based upon Applied Biosystems real-time PCR (Life Technologies, Carlsbad, CA) and HUSLAB uses an accredited method based on cyclic minisequencing.

Levels of Evidence

The evidence summarized within the main guideline manuscript has been graded using the three-tiered system required by the Clinical Pharmacogenetics Implementation Consortium (Relling MV, Klein TE. Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clinical Pharmacology Therapeutics* 2011 89(3):464-7.), as modified slightly from Valdes *et al.* (2010).

HIGH: Evidence includes consistent results from well-designed, well-conducted studies.

MODERATE: Evidence is sufficient to determine the effects, but the strength of evidence is limited by the number, quality, or consistency of the individual studies, by the inability to generalize to routine practice, or by the indirect nature of the evidence.

LOW: Evidence is insufficient to assess the effects on health outcomes because of the limited number of studies, insufficient power of the studies, important flaws in their design or in the way they were conducted, gaps in the chain of evidence, or lack of information.

Strength of Recommendations

Multiple rating schemes were evaluated. Ultimately, we (CPIC) chose to use a slight modification of a transparent and simple system for just three categories for recommendations: strong, where "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"; moderate, in which "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects; and optional, for recommendations in-between strong and weak where there is room for differences in opinion as to the need for the recommended course of action.

CPIC's dosing recommendations weigh the evidence from a combination of preclinical and clinical data. Some of the factors that are taken into account include *in vivo* clinical outcome data for statins, *in vivo* pharmacodynamic data for statins, and *in vivo* pharmacokinetic data for statins, in individuals who vary by *SLCO1B1* genotype. We also consider *in vitro* pharmacodynamic and pharmacokinetic data for statins.

The dosing recommendations are simplified to allow rapid interpretation by clinicians, as adapted from the rating scale for evidence-based therapeutic recommendations on the use of retroviral agents (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. DHHS October 14, 2011; 1–167. Guideline available on-line at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf . Accessed [January 15, 2012]).

- Strong recommendation for the statement
- Moderate recommendation for the statement
- Optional recommendation for the statement

Current Models for Implementation

Model #1: Genotyping "just in time." Duke University's Center for Personalized Medicine genotypes individuals with prior statin intolerance for *5 (rs4149056 alone) and provides patient and providers with genotype specific education and guidance. Duke also offers *SLCO1B1*5* genetic testing to assist primary care physicians (via test results and interpretation via the EMR) in reinitiating statin therapy for patients who are nonadherent to statin therapy. Patients found to be carriers of the *5 allele are provided with their genotype, and steered toward an alternate drug with lower risk for kinetic changes; e.g., rosuvastatin (if high potency is desired), pravastatin (if low potency is acceptable), or fluvastatin (to minimize drug-drug interaction). Noncarriers are advised to consider restarting their prior statin and monitor CK level.

Model #2: Genotyping "just in case." This pre-emptive model, assumes that – at some point in the not too distant future – *SLCO1B1* genotype data will be available on a patient by patient basis, through electronic access to whole genome sequencing data within comprehensive electronic medical records. One such model was implemented at Vanderbilt University Medical Center in 2011, wherein an Illumina ADME assay is run in a CLIA approved environment, and stored behind each patient's EMR. The data are brought forward, gene-by-gene, at the point of prescribing, when any physician attempts to prescribe a drug from within a pre-selected group determined by the hospital Pharmacy and Therapeutics Committee. This committee meets quarterly to review the dynamic list of drugs on this list. At present, this list is based upon published CPIC guidelines: clopidogrel, warfarin, and simvastatin (with decision support algorithms for thiopurines and codeine under construction and scheduled for implementation soon). The initiative, called PREDICT (Pharmacogenomics Resource for Enhanced Decisions in Clinical Care and Treatment) was activated in 3000 subjects undergoing percutaneous coronary intervention in 2011, and recently expanded to 10,000 high risk individuals served by the Vanderbilt University primary care clinics. When a provider attempts to prescribe simvastatin, the patient's EMR is immediately populated with rs4149056 genotype in a chart section called drug-genome interactions (just below drug allergies). (Pulley, J.M. et al. Operational implementation of prospective genotyping for personalized medicine: The design of the Vanderbilt PREDICT project. *Clinical Pharmacology and Therapeutics* in press)

Incidental findings

Hepatic uptake of unconjugated bilirubin is mediated by *SLCO1B1* (67). Variation in *SLCO1B1* has been shown to alter total serum bilirubin levels (67, 89-92) and has been associated with hyperbilirubinemia in adult Asians (93). Variants in *SLCO1B1* are also associated with increased risk for gallstone disease (rs11045819) (94), as well as hypertension (rs4149014) (95) and coronary artery disease (rs4149013) (96).

The *SLCO1B1* gene product transports many drugs and biochemicals (reviewed in details by Niemi et al, 2011). The C allele at rs4149056 is related to impaired transport of many drugs *in vitro* and *in vivo,* including for example changes in irinotecan disposition (97, 98) and clearance of the antiretroviral drug lopinavir (99). Other variants have an impact as well. For example, *SLCO1B1* rs11045819 polymorphism (c.463C>A) is associated with lower rifampin exposure in adults with pulmonary tuberculosis (100).

The Role of Ancestry

Our guideline reflects recent recommendations from the U.S. FDA regarding the strong dose-dependence of muscle toxicity for simvastatin. For other statins, the FDA has further recommended limiting the dose based upon major continental race (FDA Public Health Advisory on rosuvastatin; Media release March 2, 2005). For rosuvastatin, specifically, the FDA recommends limiting patients of Asian ancestry to a 5 mg starting dose, based upon two clinical observations: first, that patients of Asian ancestry exhibit a 2-fold increase in AUC for rosuvastatin, compared to patients of European ancestry, following single dose exposure (72) and second, that patients of Asian ancestry have greater lipid lowering efficacy at lower doses of rosuvastatin, compared to patients of European ancestry (72). As a result, the FDA has concluded that Asian Americans are one of three important groups with an elevated risk/benefit ratio (the others were patients on CSA/immune suppression and patients with severe kidney failure) (81, 83, 101-105).

Geographic differences in allele frequency for rs4149056 in *SLCO1B1* do not appear to contribute to this race discrepancy (72). 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 (Feng et al. Genetic and non-genetic determinants of statin-induced muscle toxicity. *Pharmacogenomics* in press). For simvastatin, race-dependent differences in *SLCO1B1* variant frequency carry an undefined impact on outcome. Because there is great variability in the distribution of this variant by race (106), we present a summary in Supplemental Table 3 and details in Supplemental Table 4.

Other Limitations

The pharmacokinetic predictors of statin-induced myopathy are well understood (16, 29, 31-34, 51, 70, 76-78, 107-113). 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 (12, 36, 114, 115). 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.

Genotype at rs4149056 (PK variability) also alters statin efficacy (37, 56). Because rs4149056 influences hepatic uptake of statins, the minor allele has opposite effects on toxicity and efficacy; i.e., the presence of the minor allele attenuates the LDL-lowering effect (because the liver is the primary site for *de novo* cholesterol biosynthesis). Carriers of the rs4149056 C allele thus experience decreased efficacy with regard to LDL-lowering when taking simvastatin (31, 55, 116, 117) compared to other statins such as atorvastatin (61) or fluvastatin (59). As anticipated from the kinetic data, the effect of rs4149056 on efficacy is minimal for pravastatin (60, 69, 84), rosuvastatin (49, 118), and pitavastatin (62, 71, 82, 119, 120). Even for simvastatin, however, the change in LDL level due to rs4149056 is small (<10 mg/dl) (31), and there is no evidence that this variant impacts vascular events. As such, we do not make recommendations based upon the relationship between rs4149056 and efficacy.

We also do not make recommendations based upon gain of function alleles (30). Because rs4149056 can be inherited in combination with other *SLCO1B1* variants that carry a protective effect, the C allele at

rs4149056 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 inherent in our approach is that both rare and *de novo* variants are not determined within currently available genotyping tests. Yet, rare exonic variants in *SLCO1B1* have been shown to have clinical impact (e.g., methotrexate clearance) (121). Therefore, altered drug kinetics and increased risk for severe drug toxicity may still occur in the absence of a C allele at rs4149056, and a TT genotype at rs4149056 does not imply the absence of another potentially deleterious variant in *SLCO1B1*.

References

(1) Pedersen, T.R. et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. Jama 294, 2437-45 (2005).

(2) LaRosa, J.C. et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 352, 1425-35 (2005).

(3) Cannon, C.P. et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 350, 1495-504 (2004).

(4) de Lemos, J.A. et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. Jama 292, 1307-16 (2004).

(5) Abd, T.T. & Jacobson, T.A. Statin-induced myopathy: a review and update. Expert Opin Drug Saf 10, 373-87 (2011).

(6) Egan, A. & Colman, E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. N Engl J Med 365, 285-7 (2011).

(7) Marciante, K.D. et al. Cerivastatin, genetic variants, and the risk of rhabdomyolysis. Pharmacogenet Genomics 21, 280-8 (2011).

(8) Meador, B.M. & Huey, K.A. Statin-associated myopathy and its exacerbation with exercise. Muscle Nerve 42, 469-79 (2010).

(9) Rowan, C. et al. Rhabdomyolysis reports show interaction between simvastatin and CYP3A4 inhibitors. Pharmacoepidemiol Drug Saf 18, 301-9 (2009).

(10) Schech, S. et al. Risk factors for statin-associated rhabdomyolysis. Pharmacoepidemiol Drug Saf 16, 352-8 (2007).

(11) Ronaldson, K.J., O'Shea, J.M. & Boyd, I.W. Risk factors for rhabdomyolysis with simvastatin and atorvastatin. Drug Saf 29, 1061-7 (2006).

(12) Sacher, J., Weigl, L., Werner, M., Szegedi, C. & Hohenegger, M. Delineation of myotoxicity induced by 3-hydroxy-3-methylglutaryl CoA reductase inhibitors in human skeletal muscle cells. J Pharmacol Exp Ther 314, 1032-41 (2005).

(13) Graham, D.J. et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. Jama 292, 2585-90 (2004).

(14) Schneck, D.W. et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther 75, 455-63 (2004).

(15) Thompson, P.D., Clarkson, P. & Karas, R.H. Statin-associated myopathy. Jama 289, 1681-90 (2003).

(16) Backman, J.T., Kyrklund, C., Neuvonen, M. & Neuvonen, P.J. Gemfibrozil greatly increases plasma concentrations of cerivastatin. Clin Pharmacol Ther 72, 685-91 (2002).

(17) Davidson, M.H. Controversy surrounding the safety of cerivastatin. Expert Opin Drug Saf 1, 207-12 (2002).

(18) Phillips, P.S. et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 137, 581-5 (2002).

(19) Wooltorton, E. Bayer pulls cerivastatin (Baycol) from market. Cmaj 165, 632 (2001).

(20) Furberg, C.D. & Pitt, B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med 2, 205-7 (2001).

(21) Rallidis, L.S., Fountoulaki, K. & Anastasiou-Nana, M. Managing the underestimated risk of statin-associated myopathy. Int J Cardiol, (2011).

(22) Mareedu, R.K. et al. Use of an electronic medical record to characterize cases of intermediate statin-induced muscle toxicity. Prev Cardiol 12, 88-94 (2009).

(23) McClure, D.L., Valuck, R.J., Glanz, M., Murphy, J.R. & Hokanson, J.E. Statin and statin-fibrate use was significantly associated with increased myositis risk in a managed care population. J Clin Epidemiol 60, 812-8 (2007).

(24) Puccetti, L., Ciani, F. & Auteri, A. Genetic involvement in statins induced myopathy. Preliminary data from an observational case-control study. Atherosclerosis 211, 28-9 (2010).

(25) Niemi, M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther 87, 130-3 (2010).

(26) Niemi, M., Pasanen, M.K. & Neuvonen, P.J. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol Rev 63, 157-81 (2011).

(27) Link, E. et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med 359, 789-99 (2008).

(28) McKenney, J.M., Davidson, M.H., Jacobson, T.A. & Guyton, J.R. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol 97, 89C-94C (2006).

(29) Brunham, L.R. et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. The Pharmacogenomics Journal, (2011).

(30) Donnelly, L.A. et al. Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. Clin Pharmacol Ther 89, 210-6 (2011).

(31) Generaux, G.T., Bonomo, F.M., Johnson, M. & Doan, K.M. Impact of SLCO1B1 (OATP1B1) and ABCG2 (BCRP) genetic polymorphisms and inhibition on LDL-C lowering and myopathy of statins. Xenobiotica 41, 639-51 (2011).

(32) Giorgi, M.A., Caroli, C., Arazi, H.C. & Di Girolamo, G. Pharmacogenomics and adverse drug reactions: the case of statins. Expert Opin Pharmacother 12, 1499-509 (2011).

(33) Hermann, M. et al. Exposure of atorvastatin is unchanged but lactone and acid metabolites are increased several-fold in patients with atorvastatin-induced myopathy. Clin Pharmacol Ther 79, 532-9 (2006).

(34) Kalliokoski, A. & Niemi, M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol 158, 693-705 (2009).

(35) Kameyama, Y., Yamashita, K., Kobayashi, K., Hosokawa, M. & Chiba, K. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. Pharmacogenet Genomics 15, 513-22 (2005).

(36) Maggo, S.D., Kennedy, M.A. & Clark, D.W. Clinical implications of pharmacogenetic variation on the effects of statins. Drug Saf 34, 1-19 (2011).

(37) Santos, P.C. et al. SLCO1B1 rs4149056 polymorphism associated with statin-induced myopathy is differently distributed according to ethnicity in the Brazilian general population: Amerindians as a high risk ethnic group. BMC Med Genet 12, 136 (2011).

(38) Voora, D. et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 54, 1609-16 (2009).

(39) Furihata, T. et al. Functional analysis of a mutation in the SLCO1B1 gene (c.1628T>G) identified in a Japanese patient with pravastatin-induced myopathy. The Pharmacogenomics Journal 9, 185-93 (2009).

(40) Ghatak, A., Faheem, O. & Thompson, P.D. The genetics of statin-induced myopathy. Atherosclerosis 210, 337-43 (2010).

(41) Harper, C.R. & Jacobson, T.A. Evidence-based management of statin myopathy. Curr Atheroscler Rep 12, 322-30 (2010).

(42) Kuncl, R.W. Agents and mechanisms of toxic myopathy. Curr Opin Neurol 22, 506-15 (2009).

(43) Mastaglia, F.L. Iatrogenic myopathies. Curr Opin Neurol 23, 445-9 (2010).

(44) Morimoto, K., Oishi, T., Ueda, S., Ueda, M., Hosokawa, M. & Chiba, K. A novel variant allele of OATP-C (SLCO1B1) found in a Japanese patient with pravastatin-induced myopathy. Drug Metab Pharmacokinet 19, 453-5 (2004).

(45) Peters, B.J., Klungel, O.H., Visseren, F.L., de Boer, A. & Maitland-van der Zee, A.H. Pharmacogenomic insights into treatment and management of statin-induced myopathy. Genome Med 1, 120 (2009).

(46) Sirtori, C.R., Mombelli, G., Triolo, M. & Laaksonen, R. Clinical response to statins: Mechanism(s) of variable activity and adverse effects. Ann Med, (2011).

(47) Toms, T.E., Smith, J.P., Panoulas, V.F., Douglas, K.M., Saratzis, A.N. & Kitas, G.D. Prevalence of risk factors for statin-induced myopathy in rheumatoid arthritis patients. Musculoskeletal Care 8, 2-9 (2010).

(48) Vladutiu, G.D. & Isackson, P.J. SLCO1B1 variants and statin-induced myopathy. N Engl J Med 360, 304 (2009).

(49) Bailey, K.M. et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. Circ Cardiovasc Genet 3, 276-85 (2010).

(50) Keskitalo, J.E., Pasanen, M.K., Neuvonen, P.J. & Niemi, M. Different effects of the ABCG2 c.421C>A SNP on the pharmacokinetics of fluvastatin, pravastatin and simvastatin. Pharmacogenomics 10, 1617-24 (2009).

(51) Neuvonen, P.J., Backman, J.T. & Niemi, M. Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. Clin Pharmacokinet 47, 463-74 (2008).

(52) Pasanen, M.K., Backman, J.T., Neuvonen, P.J. & Niemi, M. Frequencies of single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide 1B1 SLCO1B1 gene in a Finnish population. Eur J Clin Pharmacol 62, 409-15 (2006).

(53) Bernsdorf, A. et al. Simvastatin does not influence the intestinal P-glycoprotein and MPR2, and the disposition of talinolol after chronic medication in healthy subjects genotyped for the ABCB1, ABCC2 and SLCO1B1 polymorphisms. Br J Clin Pharmacol 61, 440-50 (2006).

(54) Greupink, R., Dillen, L., Monshouwer, M., Huisman, M.T. & Russel, F.G. Interaction of fluvastatin with the liver-specific Na+ -dependent taurocholate cotransporting polypeptide (NTCP). Eur J Pharm Sci 44, 487-96 (2011).

(55) Kaddurah-Daouk, R. et al. Enteric microbiome metabolites correlate with response to simvastatin treatment. PLoS One 6, e25482 (2011).

(56) Martin, N.G., Li, K.W., Murray, H., Putt, W., Packard, C.J. & Humphries, S.E. The effects of a single nucleotide polymorphism in SLCO1B1 on the pharmacodynamics of pravastatin. Br J Clin Pharmacol 73, 303-6 (2012).

(57) Romaine, S.P., Bailey, K.M., Hall, A.S. & Balmforth, A.J. The influence of SLCO1B1 (OATP1B1) gene polymorphisms on response to statin therapy. The Pharmacogenomics Journal 10, 1-11 (2010).

(58) Rosskopf, D., Meyer zu Schwabedissen, H.E., Kroemer, H.K. & Siegmund, W. [Pharmacogenomics in routine medical care]. Dtsch Med Wochenschr 135, 133-44; quiz 45-6 (2010).

(59) Couvert, P. et al. Association between a frequent allele of the gene encoding OATP1B1 and enhanced LDL-lowering response to fluvastatin therapy. Pharmacogenomics 9, 1217-27 (2008).

(60) Igel, M. et al. Impact of the SLCO1B1 polymorphism on the pharmacokinetics and lipid-lowering efficacy of multiple-dose pravastatin. Clin Pharmacol Ther 79, 419-26 (2006).

(61) Rodrigues, A.C. et al. Pharmacogenetics of OATP Transporters Reveals That SLCO1B1 c.388A>G Variant Is Determinant of Increased Atorvastatin Response. Int J Mol Sci 12, 5815-27 (2011).

(62) Yang, G.P. et al. Lack of effect of genetic polymorphisms of SLCO1B1 on the lipid-lowering response to pitavastatin in Chinese patients. Acta Pharmacol Sin 31, 382-6 (2010).

(63) Couvert, P., Chapman, M.J. & Carrie, A. Impact of genetic variation in the SLCO1B1 gene on statin efficacy in low-density lipoprotein cholesterol-lowering therapy. Pharmacogenomics 12, 137-9 (2011).

(64) Takane, H. et al. Pharmacogenetic determinants of variability in lipid-lowering response to pravastatin therapy. J Hum Genet 51, 822-6 (2006).

(65) Kivisto, K.T. & Niemi, M. Influence of drug transporter polymorphisms on pravastatin pharmacokinetics in humans. Pharm Res 24, 239-47 (2007).

(66) Pasanen, M.K., Neuvonen, M., Neuvonen, P.J. & Niemi, M. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 16, 873-9 (2006).

(67) Zhang, W. et al. OATP1B1 polymorphism is a major determinant of serum bilirubin level but not associated with rifampicin-mediated bilirubin elevation. Clin Exp Pharmacol Physiol 34, 1240-4 (2007).

(68) Hedman, M. et al. Pharmacokinetics and response to pravastatin in paediatric patients with familial hypercholesterolaemia and in paediatric cardiac transplant recipients in relation to polymorphisms of the SLCO1B1 and ABCB1 genes. Br J Clin Pharmacol 61, 706-15 (2006).

(69) Ho, R.H. et al. Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. Pharmacogenet Genomics 17, 647-56 (2007).

(70) Ide, T., Sasaki, T., Maeda, K., Higuchi, S., Sugiyama, Y. & Ieiri, I. Quantitative population pharmacokinetic analysis of pravastatin using an enterohepatic circulation model combined with pharmacogenomic Information on SLCO1B1 and ABCC2 polymorphisms. J Clin Pharmacol 49, 1309-17 (2009).

(71) Ieiri, I. et al. SLCO1B1 (OATP1B1, an uptake transporter) and ABCG2 (BCRP, an efflux transporter) variant alleles and pharmacokinetics of pitavastatin in healthy volunteers. Clin Pharmacol Ther 82, 541-7 (2007).

(72) Lee, E. et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 78, 330-41 (2005).

(73) Lee, S.K., Kim, Y.C., Song, S.B. & Kim, Y.S. Stabilization and translocation of p53 to mitochondria is linked to Bax translocation to mitochondria in simvastatin-induced apoptosis. Biochem Biophys Res Commun 391, 1592-7 (2010).

(74) Niemi, M. et al. Association of genetic polymorphism in ABCC2 with hepatic multidrug resistance-associated protein 2 expression and pravastatin pharmacokinetics. Pharmacogenet Genomics 16, 801-8 (2006).

(75) Niemi, M., Pasanen, M.K. & Neuvonen, P.J. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. Clin Pharmacol Ther 80, 356-66 (2006).

(76) Niemi, M. et al. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenetics 14, 429-40 (2004).

(77) Pasanen, M.K., Fredrikson, H., Neuvonen, P.J. & Niemi, M. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 82, 726-33 (2007).

(78) Suwannakul, S. et al. Pharmacokinetic interaction between pravastatin and olmesartan in relation to SLCO1B1 polymorphism. J Hum Genet 53, 899-904 (2008).

(79) Xiang, X. et al. Pharmacogenetics of SLCO1B1 gene and the impact of *1b and *15 haplotypes on irinotecan disposition in Asian cancer patients. Pharmacogenet Genomics 16, 683-91 (2006).

(80) Kalliokoski, A., Backman, J.T., Kurkinen, K.J., Neuvonen, P.J. & Niemi, M. Effects of gemfibrozil and atorvastatin on the pharmacokinetics of repaglinide in relation to SLCO1B1 polymorphism. Clin Pharmacol Ther 84, 488-96 (2008).

(81) Lepre, F., Rigby, R., Hawley, C., Saltissi, D., Brown, A. & Walsh, Z. A double-blind placebo controlled trial of simvastatin for the treatment of dyslipidaemia in renal allograft recipients. Clin Transplant 13, 520-5 (1999).

(82) Chung, J.Y. et al. Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. Clin Pharmacol Ther 78, 342-50 (2005).

(83) Neuvonen, P.J., Niemi, M. & Backman, J.T. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 80, 565-81 (2006).

(84) Niemi, M. et al. Acute effects of pravastatin on cholesterol synthesis are associated with SLCO1B1 (encoding OATP1B1) haplotype *17. Pharmacogenet Genomics 15, 303-9 (2005).

(85) Hirano, M., Maeda, K., Shitara, Y. & Sugiyama, Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos 34, 1229-36 (2006).

(86) Kindla, J., Muller, F., Mieth, M., Fromm, M.F. & Konig, J. Influence of non-steroidal anti-inflammatory drugs on organic anion transporting polypeptide (OATP) 1B1- and OATP1B3-mediated drug transport. Drug Metab Dispos 39, 1047-53 (2011).

(87) Kitamura, A., Imai, S., Yabuki, M. & Komuro, S. The new acyl-CoA cholesterol acyltransferase inhibitor SMP-797 does not interact with statins via OATP1B1 in human cryopreserved hepatocytes and oocytes expressing systems. Biopharm Drug Dispos 28, 517-25 (2007).

(88) Nakagomi-Hagihara, R., Nakai, D., Tokui, T., Abe, T. & Ikeda, T. Gemfibrozil and its glucuronide inhibit the hepatic uptake of pravastatin mediated by OATP1B1. Xenobiotica 37, 474-86 (2007).

(89) Ieiri, I. et al. Influence of common variants in the pharmacokinetic genes (OATP-C, UGT1A1, and MRP2) on serum bilirubin levels in healthy subjects. Hepatol Res 30, 91-5 (2004).

(90) Ho, R.H. et al. Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. Gastroenterology 130, 1793-806 (2006).

(91) Bielinski, S.J. et al. Mayo Genome Consortia: a genotype-phenotype resource for genome-wide association studies with an application to the analysis of circulating bilirubin levels. Mayo Clin Proc 86, 606-14 (2011).

(92) Johnson, A.D. et al. Genome-wide association meta-analysis for total serum bilirubin levels. Hum Mol Genet 18, 2700-10 (2009).

(93) Huang, C.S., Huang, M.J., Lin, M.S., Yang, S.S., Teng, H.C. & Tang, K.S. Genetic factors related to unconjugated hyperbilirubinemia amongst adults. Pharmacogenet Genomics 15, 43-50 (2005).

(94) Srivastava, A., Srivastava, N., Choudhuri, G. & Mittal, B. Organic anion transporter 1B1 (SLCO1B1) polymorphism and gallstone formation: High incidence of Exon4 CA genotype in female patients in North India. Hepatol Res 41, 71-8 (2011).

(95) Lin, R. et al. Association of polymorphisms in the solute carrier organic anion transporter family member 1B1 gene with essential hypertension in the Uyghur population. Ann Hum Genet 75, 305-11 (2011).

(96) Lin, R. et al. Common variants of four bilirubin metabolism genes and their association with serum bilirubin and coronary artery disease in Chinese Han population. Pharmacogenet Genomics 19, 310-8 (2009).

(97) Han, J.Y. et al. Influence of the organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer. Lung Cancer 59, 69-75 (2008).

(98) Zhang, W. et al. Role of BCRP 421C>A polymorphism on rosuvastatin pharmacokinetics in healthy Chinese males. Clin Chim Acta 373, 99-103 (2006).

(99) Lubomirov, R. et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. J Infect Dis 203, 246-57 (2011).

(100) Weiner, M. et al. Effects of tuberculosis, race, and human gene SLCO1B1 polymorphisms on rifampin concentrations. Antimicrob Agents Chemother 54, 4192-200 (2010).

(101) Hermann, M., Asberg, A., Christensen, H., Holdaas, H., Hartmann, A. & Reubsaet, J.L. Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. Clin Pharmacol Ther 76, 388-91 (2004).

(102) Stein, C.M., Sadeque, A.J., Murray, J.J., Wandel, C., Kim, R.B. & Wood, A.J. Cyclosporine pharmacokinetics and pharmacodynamics in African American and white subjects. Clin Pharmacol Ther 69, 317-23 (2001).

(103) Capone, D., Stanziale, P., Gentile, A., Imperatore, P., Pellegrino, T. & Basile, V. Effects of simvastatin and pravastatin on hyperlipidemia and cyclosporin blood levels in renal transplant recipients. Am J Nephrol 19, 411-5 (1999).

(104) Pflugfelder, P.W., Huff, M., Oskalns, R., Rudas, L. & Kostuk, W.J. Cholesterol-lowering therapy after heart transplantation: a 12-month randomized trial. J Heart Lung Transplant 14, 613-22 (1995).

(105) Vanhaecke, J., Van Cleemput, J., Van Lierde, J., Daenen, W. & De Geest, H. Safety and efficacy of low dose simvastatin in cardiac transplant recipients treated with cyclosporine. Transplantation 58, 42-5 (1994).

(106) Pasanen, M.K., Neuvonen, P.J. & Niemi, M. Global analysis of genetic variation in SLCO1B1. Pharmacogenomics 9, 19-33 (2008).

(107) He, Y.J. et al. Rifampicin alters atorvastatin plasma concentration on the basis of SLCO1B1 521T>C polymorphism. Clin Chim Acta 405, 49-52 (2009).

(108) Mwinyi, J., Johne, A., Bauer, S., Roots, I. & Gerloff, T. Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics. Clin Pharmacol Ther 75, 415-21 (2004).

(109) Backman, J.T., Kyrklund, C., Kivisto, K.T., Wang, J.S. & Neuvonen, P.J. Plasma concentrations of active simvastatin acid are increased by gemfibrozil. Clin Pharmacol Ther 68, 122-9 (2000).

(110) Hamelin, B.A. & Turgeon, J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. Trends Pharmacol Sci 19, 26-37 (1998).

(111) Rehman, M.A. et al. Effects of simvastatin in hyperlipidemic renal transplant patients receiving cyclosporine. Transplantation 60, 397-9 (1995).

(112) Arnadottir, M., Eriksson, L.O., Germershausen, J.I. & Thysell, H. Low-dose simvastatin is a well-tolerated and efficacious cholesterol-lowering agent in ciclosporin-treated kidney transplant recipients: double-blind, randomized, placebo-controlled study in 40 patients. Nephron 68, 57-62 (1994).

(113) Arnadottir, M., Eriksson, L.O., Thysell, H. & Karkas, J.D. Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. Nephron 65, 410-3 (1993).

(114) Werner, M., Sacher, J. & Hohenegger, M. Mutual amplification of apoptosis by statin-induced mitochondrial stress and doxorubicin toxicity in human rhabdomyosarcoma cells. Br J Pharmacol 143, 715-24 (2004).

(115) Dirks, A.J. & Jones, K.M. Statin-induced apoptosis and skeletal myopathy. Am J Physiol Cell Physiol 291, C1208-12 (2006).

(116) Ho, R.H. & Kim, R.B. Transporters and drug therapy: implications for drug disposition and disease. Clin Pharmacol Ther 78, 260-77 (2005).

(117) Campana, C. et al. Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. Ann Pharmacother 29, 235-9 (1995).

(118) Choi, J.H., Lee, M.G., Cho, J.Y., Lee, J.E., Kim, K.H. & Park, K. Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. Clin Pharmacol Ther 83, 251-7 (2008).

(119) Wen, J. & Xiong, Y. OATP1B1 388A>G polymorphism and pharmacokinetics of pitavastatin in Chinese healthy volunteers. J Clin Pharm Ther 35, 99-104 (2010).

(120) Deng, J.W. et al. The effect of SLCO1B1*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1*15. Pharmacogenet Genomics 18, 424-33 (2008).

(121) Ramsey, L.B. et al. Rare versus common variants in pharmacogenetics: SLCO1B1 variation and methotrexate disposition. Genome Res, (2011).

(122) Ho, R.H. et al. Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. Pharmacogenet Genomics 17, 647-56 (2007).

(123) Mwinyi, J., Kopke, K., Schaefer, M., Roots, I. & Gerloff, T. Comparison of SLCO1B1 sequence variability among German, Turkish, and African populations. Eur J Clin Pharmacol 64, 257-66 (2008).

(124) Aklillu, E. et al. Frequency of the SLCO1B1 388A>G and the 521T>C polymorphism in Tanzania genotyped by a new LightCycler(R)-based method. Eur J Clin Pharmacol, (2011).

(125) Nozawa, T. et al. Genetic polymorphisms of human organic anion transporters OATP-C (SLC21A6) and OATP-B (SLC21A9): allele frequencies in the Japanese population and functional analysis. J Pharmacol Exp Ther 302, 804-13 (2002).

(126) Nishizato, Y. et al. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics. Clin Pharmacol Ther 73, 554-65 (2003).

(127) Lee, E. et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 78, 330-41 (2005).

(128) Chung, J.Y. et al. Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. Clin Pharmacol Ther 78, 342-50 (2005).

(129) Xiang, X. et al. Pharmacogenetics of SLCO1B1 gene and the impact of *1b and *15 haplotypes on irinotecan disposition in Asian cancer patients. Pharmacogenet Genomics 16, 683-91 (2006).

(130) Choi, J.H., Lee, M.G., Cho, J.Y., Lee, J.E., Kim, K.H. & Park, K. Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. Clin Pharmacol Ther 83, 251-7 (2008).

(131) Xu, L.Y. et al. Organic anion transporting polypeptide-1B1 haplotypes in Chinese patients. Acta Pharmacol Sin 28, 1693-7 (2007).

(132) Kim, E.Y. et al. Duplex pyrosequencing assay of the 388A>G and 521T>C SLCO1B1 polymorphisms in three Asian populations. Clin Chim Acta 388, 68-72 (2008).

(133) Kim, S.R. et al. Genetic variations and frequencies of major haplotypes in SLCO1B1 encoding the transporter OATP1B1 in Japanese subjects: SLCO1B1*17 is more prevalent than *15. Drug Metab Pharmacokinet 22, 456-61 (2007).

(134) Miura, M. et al. Influence of drug transporters and UGT polymorphisms on pharmacokinetics of phenolic glucuronide metabolite of mycophenolic acid in Japanese renal transplant recipients. Ther Drug Monit 30, 559-64 (2008).

(135) Ho, W.F., Koo, S.H., Yee, J.Y. & Lee, E.J. Genetic variations of the SLCO1B1 gene in the Chinese, Malay and Indian populations of Singapore. Drug Metab Pharmacokinet 23, 476-82 (2008).

(136) Tian, L. et al. Effect of organic anion-transporting polypeptide 1B1 (OATP1B1) polymorphism on the single- and multiple-dose pharmacokinetics of enalapril in healthy Chinese adult men. Clin Ther 33, 655-63.

(137) Rohrbacher, M., Kirchhof, A., Skarke, C., Geisslinger, G. & Lotsch, J. Rapid identification of three functionally relevant polymorphisms in the OATP1B1 transporter gene using Pyrosequencing. Pharmacogenomics 7, 167-76 (2006).

(138) Pasanen, M.K., Backman, J.T., Neuvonen, P.J. & Niemi, M. Frequencies of single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide 1B1 SLCO1B1 gene in a Finnish population. Eur J Clin Pharmacol 62, 409-15 (2006).

(139) Vormfelde, S.V., Toliat, M.R., Schirmer, M., Meineke, I., Nurnberg, P. & Brockmoller, J. The polymorphisms Asn130Asp and Val174Ala in OATP1B1 and the CYP2C9 allele *3 independently affect torsemide pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 83, 815-7 (2008).

(140) Picard, N. et al. The role of organic anion-transporting polypeptides and their common genetic variants in mycophenolic acid pharmacokinetics. Clin Pharmacol Ther 87, 100-8.

(141) Peters, B.J. et al. Pharmacogenetic interactions between ABCB1 and SLCO1B1 tagging SNPs and the effectiveness of statins in the prevention of myocardial infarction. Pharmacogenomics 11, 1065-76.

(142) Boivin, A.A., Cardinal, H., Barama, A., Pichette, V., Hebert, M.J. & Roger, M. Organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3: genetic variability and haplotype analysis in white Canadians. Drug Metab Pharmacokinet 25, 508-15.

(143) Nishizato, Y. et al. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics. Clin Pharmacol Ther 73, 554-65 (2003).

(144) Lee, Y.J., Lee, M.G., Lim, L.A., Jang, S.B. & Chung, J.Y. Effects of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Korean subjects. Int J Clin Pharmacol Ther 48, 36-45 (2010).

Supplemental Figure 1.

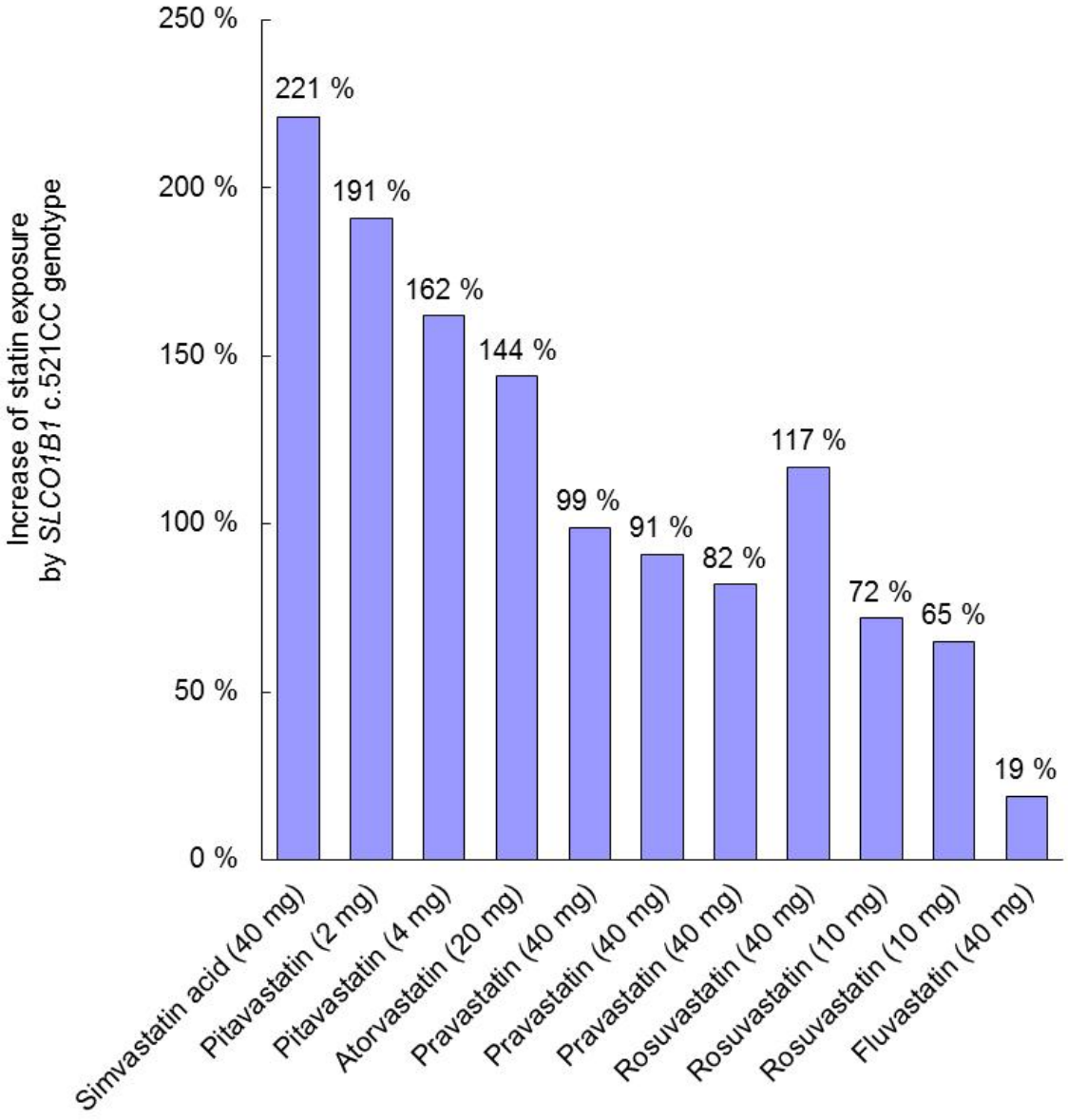

FIGURE LEGEND

Supplemental Figure 1. 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: 66 (Pasanen et al), 71 (Ieiri et al), 72 (Lee et al), 75 (Niemi et al), 77 (Pasanen et al), 118 (Choi et al), 120 (Deng et al), 122 (Ho et al).

Portions of this figure have been reproduced from reference 26 (Niemi et al) with permission from the author (MN), the publisher, the American Society for Pharmacology and Experimental Therapeutics (ASPET), and *Pharmacological Reviews*.

Supplemental Table 1. FDA Dosing Recommendations for Simvastatin, posted in 2011.

Warning(s) Regarding 80 mg Simvastatin	Simvastatin Contraindicated	Maximum Simvastatin Dose	
		Max 10 mg daily (i.e., 20 mg dose contraindicated)	**Max 20 mg daily** (i.e., 40 mg dose contraindicated)
• imvastatin 80 mg should not be started in new patients • t is acceptable to continue simvastatin 80 mg daily in patients who have been taking it for 12 months or more without side effects • witch patients requiring on a drug that interacts with simvastatin to an alternative statin with less potential for drug-drug interaction	• traconazole, Ketoconazole, Posaconazole • rythromycin, Clarithromycin, Telithromycin • IV Protease inhibitors • efazedone • emfibrozil • yclosporine • anazol	• erapamil • iltiazem	• miodarone • mlodipine • anolazine

Supplemental Table 2. Genotypes that constitute the * alleles for *SLCO1B1*	
Allele	**Constituted by genotypes at:**
*1A	Wild-type at all loci
*1B	rs2306283 G allele (A ancestral) (c.388A>G, p.N130D)
*2	rs56101265 C allele (T ancestral) (c.217T>C, p.F73L)
*3	rs56061388 C allele (T ancestral) (c.245T>C, p.V82A)
*4	rs11045819 A allele (C ancestral) (c.463C>A, p.P155T)
*5	rs4149056 C allele (T ancestral) (c.521T>C, p.V174A)
*6	rs55901008 C allele (T ancestral) (c.1058T>C, p.I353T)
*7	rs56387224 G allele (A ancestral) (c.1294A>G, p.N432D)
*8	rs72559748 G allele (A ancestral) (c.1385A>G, p.D462G)
*9	rs59502379 C allele (G ancestral) (c.1463G>C, p.G488A)
*10	rs56199088 G allele (A ancestral) (c.1964A>G, p.D655G)
*11	rs55737008 G allele (A ancestral) (c.2000A>G, p.E667G)
*12	rs56101265 C allele (T ancestral); rs56199088 G allele (A ancestral)
*13	rs56061388 C allele (T ancestral); rs55737008 G allele (A ancestral); rs72559745 G allele (A ancestral)
*14	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral)
*15	rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*16	rs59710386 C allele (A ancestral; g.-10499A>C); rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*17	rs4149015 A allele (G ancestral; g.-11187G>A); rs2306283 G allele (A ancestral); rs4149056 C allele (T ancestral)
*22	rs34671512 C allele (A ancestral; c.1929A>C, p.L643F)
*23	hg19 chr12:21325710 A allele (G ancestral; c.211G>A, p.G71R)
*24	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral; c.733 A>G, p.I245V)
*25	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral; c.758 G>A, p.R253Q)
*26	rs142965323 A allele (G ancestral; c.1309G>A, p.G437R)
*27	rs2306283 G allele (A ancestral); rs59113707 G allele (C ancestral; c.1200C>G, p.F400L)
*28	rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral)
*29	rs2306283 G allele (A ancestral); rs140790673 T allele (C ancestral, c.2045C>T, p.S682F)
*30	rs2306283 G allele (A ancestral); rs79135870 G allele (A ancestral, c.664 A>G, p.I222V)
*31	rs2306283 G allele (A ancestral); rs59502379 C allele (G ancestral)
*32	rs2306283 G allele (A ancestral); rs11045819 A allele (C ancestral); rs11045852 G allele (A ancestral)
*33	rs139257324 G allele (C ancestral; c.169 C>G, p.R57W); rs2306283 G allele (A ancestral); rs11045852 G allele (A ancestral); rs11045853 A allele (G ancestral)
*34	hg19 chr12:21392079 T allele (C ancestral; c.2032 C>T, p.H678Y)
*35	rs2306283 G allele (A ancestral); rs34671512 C allele (A ancestral)
*36	hg19 chr12:21355487 G allele (T ancestral; c.1198 T>G, p.F400V)

All coordinates refer to GenBank SLCO1B1 mRNA sequence NM_006446.4 at http://www.ncbi.nlm.nih.gov/nuccore/NM_006446.4.
For detailed haplotype mapping information please see SLCO1B1 haplotype table at http://www.pharmgkb.org/gene/PA134865839?tabType=tabHaplotypes#tabview=tab4&subtab= .
All variants are annotated to the positive chromosomal strand.
PharmGKB will continue to update the list of * alleles on their website: http://www.pharmgkb.org/gene/PA134865839#tabview=tab4&subtab=33.

Supplemental Table 3. Observed frequencies for select *SLCO1B1* alleles[1] within major race/ethnic groups.

Allele	Functional Status	Caucasian	South/Central American	African	Middle Eastern	Asian	SW Asian	Oceania
*1A	normal/ wild type[2]	50%	37%	17%	49%	27%	47%	34%
*1B	normal/ wild type[2]	22%	39%	78%	31%	60%	46%	66%
*5	variant/ reduced function	1%	0%	0%	5%	0%	0%	0%
*15	variant/ reduced function	14%	24%	3%	15%	13%	6%	0%

[1] Average allele frequencies are presented based upon the actual numbers of subjects with each allele reported in multiple studies, and grouped according to major race/ethnic groups (see Supplemental Table 4 for references).
[2] An important caveat for all genotyping tests is that the decision to assign "wild-type" status is based upon a genotyping test that interrogates only the most common and already-proven sites of functional variation. In human DNA, it is always possible that new, previously undiscovered (and therefore un-interrogated) site of variation may confer loss-of-function in an individual, and thus lead to the rare possibility of a non-functional allele being erroneously called as "wild-type."

Supplemental Table 4. Detailed distribution of *SLCO1B1* allele frequency by race.

Race group	Ethnicity	Haplotype frequency (%)				Total patients	alleles observed					Total alleles	Source
		*1A	*1B	*5	*15/*16/*17		*1A	*1B	*5	*15/*16/*17	other		
African	American	22%	76%	0%	1%	38	17	58	0	1	0	76	(69, 122)
African	North African	34%	48%	2%	16%	29	20	28	1	9	0	58	(106)
African	Sub-Saharan Africa	21%	77%	0%	2%	105	44	162	0	4	0	210	(106)
African	Ugandan	22%	70%	0%	3%	109	48	153	0	7	10	218	(123)
African	Tanzanian	13%	84%	0%	3%	366	97	614	0	21	0	732	(124)
Asian	Japanese	35%	54%	1%	10%	267	188	287	4	55	0	534	(125)
Asian	Japanese	33%	46%	0%	18%	120	78	110	0	44	8	240	(126)
Asian	Malays	17%	70%	0%	13%	35	12	49	0	9	0	70	(127)
Asian	Korean	31%	46%	0%	23%	24	15	22	0	11	0	48	(128)
Asian	Chinese	19%	71%	0%	11%	94	35	133	0	20	0	188	(129)
Asian	Malays	12%	79%	0%	9%	97	23	153	0	18	0	194	(129)
Asian	Korean	29%	60%	0%	12%	200	115	238	0	47	0	400	(130)
Asian	Korean	18%	62%	0%	18%	81	29	101	0	29	3	162	(97)
Asian	Chinese	26%	60%	0%	14%	111	58	133	0	31	0	222	(131)
Asian	Chinese	22%	69%	1%	8%	106	46	146	3	17	0	212	(132)
Asian	Korean	26%	60%	0%	14%	469	247	560	0	131	0	938	(132)
Asian	Vietnamese	21%	63%	0%	16%	104	44	130	0	34	0	208	(132)
Asian	East Asian	25%	63%	0%	12%	239	120	301	0	57	0	478	(106)
Asian	Japanese	36%	47%	0%	17%	177	128	166	0	60	0	354	(133)
Asian	Japanese	33%	49%	0%	18%	80	52	79	0	29	0	160	(134)
Asian	Chinese	25%	64%	0%	12%	96	47	122	0	23	0	192	(135)
Asian	Malays	19%	71%	0%	9%	96	37	137	0	18	0	192	(135)
Asian	Chinese	30%	59%	0%	11%	32	19	38	0	7	0	64	(136)
Asian	Chinese	33%	59%	0%	9%	35	23	41	0	6	0	70	(127)
Caucasian		47%	31%	1%	21%	36	34	22	1	15	0	72	(127)
Caucasian	German	49%	33%	1%	11%	250	245	165	5	55	30	500	(137)
Caucasian	Finnish	11%	2%	3%	17%	468	100	21	25	161	629	936	(138)
Caucasian	American	61%	25%	1%	14%	69	84	34	1	19	0	138	(122)
Caucasian	German	58%	25%	3%	15%	99	114	49	5	30	0	198	(139)
Caucasian	European	56%	26%	2%	16%	151	169	79	6	48	0	302	(106)
Caucasian	German	60%	9%	3%	12%	276	333	48	17	66	88	552	(123)
Caucasian	Turkish	52%	22%	1%	9%	78	82	34	2	15	24	156	(123)
Caucasian	French	53%	14%	2%	15%	185	196	52	8	56	58	370	(140)
Caucasian	Dutch	57%	27%	1%	15%	1885	2148	1022	27	572	0	3770	(141)
Caucasian	Canadian	50%	5%	0%	18%	41	41	4	0	15	22	82	(142)
Caucasian	German	56%	35%	3%	7%	236	263	163	12	34	0	472	(124)
Middle East		49%	31%	5%	15%	133	130	83	13	40	0	266	(106)
Oceanic		34%	66%	0%	0%	28	19	37	0	0	0	56	(106)
South/Central American		37%	39%	0%	24%	64	47	50	0	31	0	128	(106)
SW Asian	Indian	46%	47%	0%	7%	35	32	33	0	5	0	70	(127)
SW Asian	Indian	41%	56%	2%	2%	93	76	104	3	3	0	186	(129)
SW Asian	South/Central Asian	52%	39%	0%	9%	192	200	150	0	34	0	384	(106)
SW Asian	Indian	44%	50%	0%	6%	96	85	96	0	11	0	192	(135)

Supplemental Table 5. Impact of rs4149056 (V174A) on the pharmacokinetics of various statins

Study	Patients	Treatment	Primary Endpoint(s)	Additional Finding(s)
(143)	N=23 healthy Japanese volunteers	Pravastatin 10 mg	Patients with the compound N130D + V174A variant had reduced total and non-renal pravastatin clearance, as compared with patients with the N130D variant.	*SLCO1B1*, including V174A, are likely associated with altered pravastatin pharmacokinetics (PK).
(108)	N=30 healthy white males	Pravastatin 40 mg	Pravastatin AUC and C_{max} increased for V174A carriers compared to WT or N130D carriers.	*SLCO1B1* variant haplotypes alter pravastatin disposition. Whereas V174A expression delayed hepatocellular uptake of pravastatin, N130D expression seemed to accelerate *SLCO1B1*-dependent uptake of the drug.
(76)	N=41 healthy Finnish volunteers	Pravastatin 40 mg	Pravastatin AUC increased with V174A and -11187G>A variant alleles compared to WT.	Carriers of the compound N130D + V174A variants, as well as carriers of the compound N130D + V174A + -1187G>A, also had higher pravastatin AUC compared with WT.
(82)	N=24 healthy Korean volunteers	Pitavastatin 1-8 mg	Pitavastatin AUC and C_{max} increased for carriers of the compound N130D + V174A variant versus patients with WT or N130D alleles alone.	No significant differences were found according to genotype in terms of dose-normalized AUC or C_{max} values of pitavastatin lactone
(72)	N=36 white, 36 Chinese, 35 Malay, and 35 Asian-Indian subjects living in Singapore, Singapore	Rosuvastatin 40 mg	Rosuvastatin AUC's were 2.36, 2.00, and 1.68 times higher in Chinese, Malay, and Asian-Indian subjects; respectively, compared with White subjects.	*SLCO1B1* genotypes did not account for the observed PK differences between Asians and White subjects.
(60)	N=16 healthy volunteers, including 8 carriers of an *SLCO1B1* variant haplotype and 8 control subjects	Pravastatin 40 mg orally daily for three weeks	Pravastatin AUC and C_{max} were significantly higher in patients with V174A alleles compared to controls. Patients with the compound N130D + V174A variant, and patients with the triplotype -11187G>A + N130D + V174A, also had higher pravastatin AUC and C_{max}	Despite considerably higher plasma pravastatin concentrations in carriers of an *SLCO1B1* variant haplotype, there was no significant difference in the lipid-lowering efficacy of pravastatin between the variant haplotype and control groups.
(75)	N=32 healthy Finnish volunteers	Pravastatin 40 mg and fluvastatin 40 mg	Pravastatin AUC, C_{max} increased for men homozygous for V174A compared to men who were carriers for V174A or WT. Women who were WT had significantly higher Pravastatin AUC, C_{max} than men who were WT. Fluvastatin PK did not differ between subjects with different *SLCO1B1* genotypes or between the sexes.	*SLCO1B1* polymorphism alters PK of pravastatin but not fluvastatin, which suggests that fluvastatin does not rely on *SLCO1B1* for hepatic uptake. Patient gender may affect pravastatin PK.
(66)	N=4 healthy Caucasian volunteers	Simvastatin 40 mg	Simvastatin acid AUC and C_{max} increased for V174A carriers vs. WT	The V174A variant may increase risk for myopathy as well as reduce lipid-lowering effects due to decreased hepatic uptake.
(69)	N=107 healthy volunteers (69 European-American and 38 African-Americans)	Pravastatin 40 mg	Pravastatin AUC, C_{max} increased in heterozygous carriers of the compound N130D + V174A variant and in N130D + V174A homozygotes	European-Americans had significantly higher pravastatin AUC and C_{max} than African-Americans.

(71)	N=38 healthy Japanese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, Cmax increased for N130D or compound N130D+ V174A heterozygotes, and for compound N130D+ V174A homozygotes	Pitavastatin lactone PK parameters were not altered by *SLCO1B1* genotype.
(77)	N=32 healthy volunteers	Atorvastatin 20 mg and rosuvastatin 10 mg	AUC and C_{max} for atorvastatin, 2-hydroxyatorvastatin, and rosuvastatin were increased in patients with the V174A variant.	Unexpectedly, *SLCO1B1* polymorphism has a larger effect on the PK of atorvastatin than rosuvastatin.
(118)	N=30 Korean volunteers	Rosuvastatin 10 mg	Rosuvastatin AUC increased for compound N130D + V174A homozygotes, compound N130D + V174A carriers, and N130D carriers compared with WT. C_{max} increased for compound N130D + V174A homozygotes compared to other groups.	Rosuvastatin-lactone PK were similar among the three groups.
(120)	N=11 healthy Korean volunteers	Pravastatin 40 mg or Pitavastatin 4 mg	Pitavastatin AUC and Cmax increased more than pravastatin for compound N130D + V174A homozygotes compared with WT	Uptake into oocytes overexpressing the compound N130D + V174A allele was decreased for pitavastatin more so than pravastatin. Fluvastatin was unaffected.
(78)	N=10 healthy Japanese volunteers	Pravastatin 10 mg (+ olmesartan 10 mg)	Pravastatin PK not significantly affected for N130D homozygotes, versus carriers of the compound N130D + V174A variant and/or versus N130D + V174A homozygotes	Co-administration of olmesartan + pravastatin did not affect PK based on *SLCO1B1* genotype.
(107)	N=16 healthy Chinese volunteers	Atorvastatin 40 mg (+ rifampicin 600 mg)	When combined with concomitant rifampicin, Atorvastatin AUC increased among V174A carriers and WT patients compared to V174A homozygotes	Rifampicin PK not affected by variation in *SLCO1B1* genotype.
(70)	N=57 healthy Japanese male volunteers	Pravastatin	Relative bioavailability F(rel) increased for pravastatin in carriers of the compound N130D + V174A variant, and in homozygotes, versus WT.	Since compound N130D + V174A genotype alters $F_{(rel)}$, *SLCO1B1* is one of the determinants of systemic exposure to pravastatin.
(119)	N=18 healthy Chinese volunteers	Pitavastatin 2 mg	Pitavastatin AUC, C_{max} increased with N130D carriers compared to wild type (WT).	Pitavastatin CL was reduced in N130D carriers. No differences according to genotype were observed in $T_{1/2}$ and $T_{max.}$
(144)	N=290 Korean volunteers	Atorvastatin 20 mg	Mean AUC of atorvastatin and 2-hydroxyatorvastatin was larger for compound N130D + V174A homozygotes (n = 3), than for N130D + V174A carriers (n = 8), and also larger than patients with WT. No PK difference with atorvastatin lactone was found.	This study showed the compound N130D + V174A variant may be associated with individual difference in the AUC of atorvastatin.
(7)	185 cases of rhabdomyolysis compared to 732 controls	Cerivastatin at various doses	Permutation test results suggested an association between cerivastatin-associated rhabdomyolysis and *SLCO1B1* variants (P=0.002), but not *CYP2C8* variants (P=0.073) or *UGTs* (P=0.523). The V174A allele was associated with risk of rhabdomyolysis (odds ratio: 1.89; 95% confidence interval: 1.40-2.56).	In transfected cells, V174A allele reduced cerivastatin transport by 40% compared with the reference transporter (P<0.001).