Editorial Commentary

Should we test for SLCO1B1 genotype before prescribing statins?—a discussion of clinical trial results

Yitian Zhou[1], **Volker M. Lauschke**[1,2,3]

[1]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; [2]Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany; [3]University of Tuebingen, Tuebingen, Germany

Correspondence to: Volker M. Lauschke. Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77, Stockholm, Sweden.
Email: volker.lauschke@ki.se.

Comment on: Vassy JL, Gaziano JM, Green RC, *et al.* Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol: A Randomized Clinical Trial. JAMA Netw Open 2020;3:e2027092.

Submitted Sep 29, 2022. Accepted for publication Oct 19, 2022.
doi: 10.21037/atm-2022-70
View this article at: https://dx.doi.org/10.21037/atm-2022-70

Genetic biomarkers that allow prediction of drug response or toxicity hold promise for the personalization of pharmacological treatment. By now, more than 120 drugs have received pharmacogenetic drug labels by FDA or EMA that provide guidance regarding indications, contraindications or dosage recommendations in relation to patient genotype (1,2). One of those pharmacogenetic associations regards statins, which are widely used as cholesterol-lowering drugs for the prevention and treatment of cardiovascular disease in high-risk patients. Specifically, there is strong genetic as well as mechanistic evidence for a link between statin-induced myopathy and rhabdomyolysis with the presence of the variant rs4149056 (c.521T>C; p.V174A) in *SLCO1B1* (3), the gene encoding the hepatic statin transporter OATP1B1. Rs4149056 has been shown experimentally to result in reduced transporter function (4) and has been repeatedly associated with elevated statin plasma concentrations due to impaired hepatic uptake (5,6). As a consequence of this available evidence, *SLCO1B1*5* and **15*, the main alleles containing rs4149056, are included in guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) to mitigate statin-related myotoxicity (7). Of note however, this guideline only refers to the interpretation and implementation of test results if available, not whether pharmacogenetic testing should be conducted.

The decision of whether preemptive pharmacogenetic testing should be conducted is complex and requires the evaluation of a multitude of factors, including the prevalence and predictive power of the pharmacogenetic biomarker, costs of genetic testing, the severity and costs associated with the adverse event, as well as safety, cost, and efficacy of alternative therapies. Moreover, there are important concerns regarding the effects of genotyping on prescribing practices and patient adherence. Specifically, the presence of a risk genotype might discourage prescription of recommended statin levels or adversely affect adherence, which might result in a worsening of hypercholesterolemia and, accordingly, negative impacts on public health. This concern is of particular importance as previous evaluations of the clinical validity, utility and cost-effectiveness of preemptive *SLCO1B1* genotyping for statin risk have remained controversial (8-10).

Recently, Vassy and colleagues presented the results of a multicenter randomized non-inferiority trial to test whether preemptive genotyping of statin-naive patients at high risk of atherosclerotic cardiovascular disease would not have negative effects on low density lipoprotein cholesterol (LDL-C) reduction (11). The study was conducted over the course of 3.5 years across eight primary care practices in the Veterans Affairs Boston Healthcare System, randomizing a total of 408 patients. Importantly, patients in the intervention group experienced LDL-C reductions at 12 months that was not significantly lower compared to the control group (mean change in LDL-C in intervention *vs.* control group, –1.1 *vs.* –2.2 mg/dL; difference, –1.1 mg/dL; 90% CI, –4.1 to 1.8 mg/dL; P<0.001). Furthermore, while the fraction of patients receiving statin therapy in agreement

with the guidelines by the American College of Cardiology-American Heart Association (ACC-AHA) was overall low in both groups, the number in the intervention group was noninferior compared to the control group [12 patients (6.2%) in the intervention group *vs.* 14 patients (6.5%) in the control group; 90% CI, –0.038 to 0.032; P<0.001]. Only few muscle-related adverse events were registered in any of the groups [2 cases (1%) in the intervention group *vs.* 3 cases (1.4%) in controls]. Notably, none of these were related to CPIC guideline-discordant prescriptions, neither in the control nor the intervention group, suggesting that the slightly higher adverse event rates in the control group would not have been prevented by genetically-guided prescribing.

Besides variants in *SLCO1B1*, also variability in *ABCG2* (rs2231142), encoding the export transporter protein BCRP, has been implicated in statin pharmacokinetics, specifically of rosuvastatin (12-14). While impacts of rs2231142 in *ABCG2* are overall markedly lower than for rs4149056 in *SLCO1B1*, it remains to be investigated whether incorporation of this variant in pharmacogenetic guidance might contribute to avoiding the remaining safety events in individuals with normal *SLCO1B1* phenotypes. Furthermore, both *SLCO1B1* as well as *ABCG2* harbor a plethora of other, mostly rare variations, which have been estimated to account for a total of 5–10% of the overall genetically encoded functional variability of OATP1B1 and BCRP (15,16). Analogously to the incorporation of additional genes, consideration of these additional variations using sequencing approaches might provide further refinements for the optimization of personalized prescribing.

A main limitation of the study is the considerable heterogeneity in statin prescriptions with fewer patients with decreased or poor *SLCO1B1* function genotypes in the intervention group than in the control group combined with a relatively small cohort size. Specifically, only 24 and 26 patients received statin prescriptions in the control and intervention groups, respectively, and of these only less than one-third were heterozygous or homozygous for rs4149056. Moreover, among these patients with decreased or poor transporter genotype only one patient in the control group received a prescription discordant with the CPIC guidelines for the respective genotype (20 mg simvastatin); however, the patient was not among those experiencing an adverse event. Despite those limitations, the presented results are encouraging and ameliorate concerns that preemptive genotyping for risk variations of statin-related myopathy might reduce adherence or worsen patient outcomes. While we believe that the current data is not sufficient to endorse the implementation of *SLCO1B1* testing to guide statin therapy in primary care, such a strategy does at the very least not seem to negatively impact atherosclerotic cardiovascular disease prevention, thus paving the way for further evaluations of the cost-effectiveness and patient benefits of genotype-guided prescribing in larger dedicated trials.

Acknowledgments

Funding: The work in the authors' laboratory was funded by the Swedish Research Council [2019-01837, 2021-02801], by the EU/EFPIA/OICR/McGill/KTH/Diamond Innovative Medicines Initiative 2 Joint Undertaking (EUbOPEN grant number 875510), by the European Union's Horizon 2020 research and innovation program Ubiquitous Pharmacogenomics (grant agreement number 668353) and by the Robert Bosch Foundation, Stuttgart, Germany.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-70/coif). YZ and VML are co-founders and shareholders of PersoMedix AB. In addition, VML is CEO and shareholder of HepaPredict AB and discloses consultancy work for Enginzyme AB. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Shekhani R, Steinacher L, Swen JJ, et al. Evaluation of Current Regulation and Guidelines of Pharmacogenomic Drug Labels: Opportunities for Improvements. Clin Pharmacol Ther 2020;107:1240-55.
2. Lauschke VM, Zhou Y, Ingelman-Sundberg M. Novel genetic and epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity. Pharmacol Ther 2019;197:122-52.
3. SEARCH Collaborative Group; Link E, Parish S, et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med 2008;359:789-99.
4. Kiander W, Vellonen KS, Malinen MM, et al. The Effect of Single Nucleotide Variations in the Transmembrane Domain of OATP1B1 on in vitro Functionality. Pharm Res 2021;38:1663-75.
5. Pasanen MK, Neuvonen M, Neuvonen PJ, et al. SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 2006;16:873-9.
6. Pasanen MK, Fredrikson H, Neuvonen PJ, et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82:726-33.
7. Cooper-DeHoff RM, Niemi M, Ramsey LB, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther 2022;111:1007-21.
8. Vassy JL, Chun S, Advani S, et al. Impact of SLCO1B1 Pharmacogenetic Testing on Patient and Healthcare Outcomes: A Systematic Review. Clin Pharmacol Ther 2019;106:360-73.
9. Jansen ME, Rigter T, Rodenburg W, et al. Review of the Reported Measures of Clinical Validity and Clinical Utility as Arguments for the Implementation of Pharmacogenetic Testing: A Case Study of Statin-Induced Muscle Toxicity. Front Pharmacol 2017;8:555.
10. Brunette CA, Dong OM, Vassy JL, et al. A Cost-Consequence Analysis of Preemptive SLCO1B1 Testing for Statin Myopathy Risk Compared to Usual Care. J Pers Med 2021;11:1123.
11. Vassy JL, Gaziano JM, Green RC, et al. Effect of Pharmacogenetic Testing for Statin Myopathy Risk vs Usual Care on Blood Cholesterol: A Randomized Clinical Trial. JAMA Netw Open 2020;3:e2027092.
12. Birmingham BK, Bujac SR, Elsby R, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. Eur J Clin Pharmacol 2015;71:329-40.
13. Lee HK, Hu M, Lui SSh, et al. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. Pharmacogenomics 2013;14:1283-94.
14. Keskitalo JE, Zolk O, Fromm MF, et al. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2009;86:197-203.
15. Zhang B, Lauschke VM. Genetic variability and population diversity of the human SLCO (OATP) transporter family. Pharmacol Res 2019;139:550-9.
16. Xiao Q, Zhou Y, Lauschke VM. Ethnogeographic and inter-individual variability of human ABC transporters. Hum Genet 2020;139:623-46.

Cite this article as: Zhou Y, Lauschke VM. Should we test for SLCO1B1 genotype before prescribing statins?—a discussion of clinical trial results. Ann Transl Med 2022;10(23):1293. doi: 10.21037/atm-2022-70

