REVIEW ARTICLE

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Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between *SLCO1B1* and statins and *CYP2C9* and sulfonylureas

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Aligned with the mission of the Dutch Pharmacogenetics Working Group (DPWG) to promote the implementation of pharmacogenetics (PGx), this guideline is specifically designed to optimize pharmacotherapy of cholesterol lowering medication (statins) and glucose lowering medication (sulfonylureas). The *SLCO1B1* c.521 T > C variant reduces the activity of the SLCO1B1 transporter involved in statin transport out of the blood into the liver. High blood concentrations of statins increase the risk of serious myopathy. For simvastatin, the DPWG recommends choosing an alternative in homozygotes for these gene variant and to preferably choose an alternative in heterozygotes. For atorvastatin, the DPWG recommends to preferably choose an alternative in carriers of this gene variant having additional risk factors for myopathy. For rosuvastatin, the DPWG recommends keeping the dose as low as possible in carriers of this gene variant with additional risk factors. No therapy adjustment is required for fluvastatin and pravastatin in carriers of this gene variant. Gene variants can diminish the activity of the enzyme CYP2C9, that converts sulfonylurea to less effective metabolites. Although *CYP2C9* gene variants may lead to increased levels of glibenclamide, gliclazide, glimepiride, and tolbutamide, no therapy adjustments are required in patients with these variants. The main reason is that there was either no negative clinical effect or an increase in hypoglycemic, which is of less importance than the increase in effectiveness it signals. The DPWG classifies pre-emptive *SLCO1B1* testing as 'essential' for simvastatin 80 mg/day, 'beneficial' for simvastatin up to 40 mg/day, and 'potentially beneficial' for atorvastatin and rosuvastatin.

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INTRODUCTION

Pharmacogenetics, the study of how genetic variations influence an individual's response to medications, has emerged as a promising field in personalized medicine. Understanding the impact of genetic variations on drug efficacy and safety is crucial for optimizing treatment outcomes and minimizing adverse drug reactions. Although PGx is widely recognized as a valuable tool, implementation in daily clinical practice remains challenging [1]. Since 2005, the Dutch Pharmacogenetics Working Group (DPWG) has played a pivotal role in providing evidence-based guidelines for gene-drug interactions, aiding healthcare professionals in making informed decisions regarding medication selection and dosing [2]. The DPWG is a multidisciplinary group in which (clinical) pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists and toxicologists are represented. It aims to develop PGx informed therapeutic recommendations based on systematic literature review, and to assist physicians and pharmacists by integrating the recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance. This manuscript thus provides both the content required for enabling local translation of assay results into the distinguished genotype group or predicted phenotype and for programming therapeutic recommendations into local clinical decision support systems. With the objective of implementing PGx into routine care, the DPWG has additionally developed the clinical implication score, which is given to every gene-drug

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interaction requiring therapy adjustment [3]. The objective of this score is to direct clinicians on whether or not to order relevant PGx genotyping tests before initiating therapy. Recently, the DPWG guidelines were endorsed by the European Association of Clinical Pharmacology and Therapeutics and the European Association of Hospital Pharmacists [4, 5].

This article presents the DPWG guideline addressing the gene-drug interactions involving *SLCO1B1* and *CYP2C9* in the context of lipid and glucose lowering medication (statins and sulfonylurea). These groups of medication were combined because both decrease cardiovascular risk in high risk patients. The guideline describes the optimization of statin therapy to reduce side effect risk in patients with a *SLCO1B1* gene variant. In addition, the guideline indicated the absence of a need for adjustment of sulfonylurea treatment in patients with a *CYP2C9* gene variant. A summary of all references identified by the systematic review, which were used to develop this guideline, can be found in Supplementary Tables 1 and 2.

DRUGS

Statins

Statins, including simvastatin, atorvastatin, rosuvastatin, fluvastatin, and pravastatin, reduce the risk of cardiovascular events by decreasing circulating low-density lipoprotein (LDL) cholesterol and, to some extent, triglyceride levels, while also modestly increasing high-density lipoprotein (HDL) cholesterol levels. Statins block cholesterol synthesis by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase in the liver. The transporter SLCO1B1 has been shown to be involved in transport of statins from the blood into the liver.

Of particular concern in statin therapy are the adverse events of myopathy and rhabdomyolysis [6]. Myopathy refers to a spectrum of muscular disorders characterized by muscle pain, weakness, and elevated serum creatine kinase (CK) levels. Myopathy is reported in a significant amount of patients in daily practice (15–20%), but is mostly mild (CK <4x upper limit of normal) [7, 8]. Rhabdomyolysis, a more severe manifestation, represents the breakdown of muscle fibers with the release of myoglobin into the bloodstream, leading to potential renal injury and even acute kidney failure. Although rare (0.1–8.4 per 100,000 patient years), these adverse effects can be life-threatening and require prompt recognition and intervention [8].

Sulfonylureas

Sulfonylureas, including glibenclamide, gliclazide, glimepiride, and tolbutamide, reduce the risk of cardiovascular events by lowering blood glucose levels in diabetes mellitus patients.

Sulfonylureas stimulate insulin secretion from pancreatic beta cells by binding to the sulfonylurea receptor (SUR) subunit of the adenosine triphosphate (ATP)-sensitive potassium channel, triggering subsequently the inhibition of the potassium efflux, cell depolarization, influx of calcium ions, and insulin granule exocytosis, enhancing insulin release into the bloodstream.

Sulfonylureas are metabolized predominantly by the liver into weakly effective (glibenclamide and glimepiride) or ineffective (gliclazide and tolbutamide) metabolites. The CYP2C9 enzyme has been shown to be involved in sulfonylurea metabolism. Glibenclamide inhibits CYP2C9 and thereby its own metabolism.

*GENE: solute carrier organic anion transporter family member 1B1 (*SLCO1B1*).* The *Solute Carrier Organic Anion Transporter Family Member 1B1* (*SLCO1B1*) gene is located on chromosome 12p12.1 and contains 15 exons [9]. The gene encodes the transporter SLCO1B1, which has the alternative names organic anion transporter polypeptide 1B1 (OATP1B1) or OATP-C. This transporter plays an important role in the transport of statins from the blood into the liver cells. Polymorphisms that reduce the activity of this transporter may lead to increased plasma levels of the statin, increasing the risk of myopathy [10, 11]. Although many polymorphisms have been found in the *SLCO1B1* gene, only one was found to be associated with the risk of myopathy. This polymorphism is c.521 T > C, which is present in two alleles (*5 and *15). The HGVS nomenclature of the polymorphism c.521 T > C is included in the legend of Table 1.

Table 1. Distinguished genotypes and genotype groups or predicted phenotypes (pharmacogenetic contraindications) for *SLCO1B1* and *CYP2C9*.

Gene	Assigned genotype (group)/predicted phenotype (pharma-cogenetic contraindication) name	Genotype group description	Examples of genotypes
SLCO1B1	521 TT (wild type)	Homozygous wildtype for c.521 T > C	
	521 TC	Heterozygous for c.521 T > C	
	521CC	Homozygous for c.521 T > C	
CYP2C9	*1/*1	two alleles with normal enzyme activity	*1/*1, *1/*9
	*1/*2	*2 and one allele with normal enzyme activity	*1/*2
	*1/*3	*3 and one allele with normal enzyme activity	*1/*3
	IM OTHER (intermediate metaboliser, other genotype)	one allele with decreased enzyme activity other than *2 and *3 and one allele with normal enzyme activity	*1/*8, *1/*11
	*2/*2	two *2 alleles	*2/*2
	*2/*3	one *2 and one *3 allele	*2/*3
	*3/*3	two *3 alleles	*3/*3
	PM OTHER (poor metaboliser, other genotype)	two alleles with decreased enzyme activity, of which at least one other than *2 or *3	*2/*8, *3/*11, *8/*11

The gene variants and alleles mentioned in the table above are characterized by the following sequence variations:
SLCO1B1 c.521T>C: rs-number: rs4149056; NM_006446.4: c.521T>C; NP_006437.3: p.(Val174Ala); NC_000012.11: g.21331549 T > C.
*CYP2C9**1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*CYP2C9**2: rs-number: rs1799853; NM_000771.4: c.430 C > T; NP_000762.2: p.(Arg144Cys); NC_000010.11: g.94942290 C > T.
*CYP2C9**3: rs-number: rs1057910; NM_000771.4: c.1075 A > C; NP_000762.2: p.(Ile359Leu); NC_000010.11: g.94981296 A > C.
*CYP2C9**8: rs-number: rs7900194; NM_000771.4: c.449 G > A; NP_000762.2: p.(Arg150His); NC_000010.11: g.94942309 G > A.
*CYP2C9**9: rs-number: rs2256871; NM_000771.4: c.752 A > G; NP_000762.2: p.(His251Arg); NC_000010.11: g.94949217 A > G
*CYP2C9**11: rs-number: rs28371685; NM_000771.4: c.1003 C > T; NP_000762.2: p.(Arg335Trp); NC_000010.11: g.94981224 C > T.

The polymorphism c.521 T > C has a high frequency in Whites (14–22%), East-Asians (8–16%) and Latin-Americans (11%), and a lower frequency in Africans (1–8%) and South Asians (5%) (Supplementary Table 3A).

Distinguished genotype groups

Three genotypes/genotype groups are distinguished: heterozygotes and homozygotes of c.521 T > C and wildtype genotypes (see Table 1). A genotype to distinguished genotype (group) translation table, which can be used to program this translation in laboratory information systems, can be found in Supplementary Table 3B.

*GENE: cytochrome P450 family 2 subfamily C member 9 (*CYP2C9*). CYP2C9* has previously been described elsewhere as a part of published DPWG guidelines [12]. A detailed explanation of the gene and its variants can be found in Supplementary Material 1, and Supplementary Table 4A through 4C. The allocation of genotypes to distinguished genotypes, genotype groups and predicted phenotypes is summarized in Table 1. Allelic variants of *CYP2C9* result in a reduced or absent metabolic capacity of CYP2C9. The DPWG distinguishes three metaboliser phenotypes: normal metaboliser (wildtype, two alleles resulting in normal enzyme activity), intermediate metaboliser (one allele resulting in reduced enzyme activity), and poor metaboliser (two alleles resulting in reduced enzyme activity). Because the metabolic capacity of the two most common variant alleles, *2 and *3, differs significantly, the intermediate and poor metabolisers are further subdivided based on the presence of these alleles or of other alleles with reduced activity, like *8 and *11 (Table 1).

GENE-DRUG INTERACTION

SLCO1B1 is involved in transport of statins from the blood into the liver. The *SLCO1B1* c.521 T > C polymorphism results in reduced SLCO1B1 activity. For this reason, the statin concentration in blood plasma is expected to be higher and the statin concentration in liver cells is expected to be lower in patients with the *SLCO1B1* c.521 T > C polymorphism. This might result in a higher incidence of adverse events, like myopathy, and a lower effectiveness, respectively.

CYP2C9 is involved in the metabolism of sulfonylureas into metabolites with reduced or absent effectiveness. *CYP2C9* gene variants result in reduced or absent CYP2C9 metabolic activity. For this reason, the sulfonylurea plasma concentration is expected to be higher in patients with *CYP2C9* gene variants. This might result in a higher incidence of adverse events and/or a higher effectiveness.

SUPPORTING BODY OF EVIDENCE

The description of the methods that were used for this guideline, including an extensive literature search, assessment and the therapeutic recommendations have been described previously [2, 13]. In short, a systematic review of the literature was performed followed by selection and summarizing of the relevant articles by a scientist of the Royal Dutch Pharmacists Association (mainly MN) after which they were scored for level of evidence and clinical relevance. After summarizing the manuscripts, therapeutic recommendations were formulated.

Supplementary Material 2 contains the details of the literature searches conducted for this study.

For the level of evidence, a five-point scale was utilized, with 0 representing the lowest quality, such as data on file, and 4 indicating the highest quality, such as high-quality meta-analyses or studies. The clinical impact of the findings was assessed using a seven-point scale ranging from AA# to F. AA# suggests a positive effect, while F indicates the most negative effect. This clinical impact scale (AA#-F) is aligned with the Common Terminology Criteria for Adverse Events (CTCAE), where CTCAE grade 5 severity corresponds to the clinical relevance score F (indicating death), and CTCAE grade 1 severity aligns with clinical relevance score B. The clinical relevance score further comprises the scores AA#, AA, and A, which signify a positive clinical effect, no kinetic or clinical effect, and a kinetic effect or not clinically relevant effect, respectively. Detailed summaries and scores of the articles can be found in Supplementary Table 1A–E (statins) and 2A-2D (sulfonylureas). The summary and scores of each article were checked by two independent DPWG members. The DPWG made the final decision on the therapeutic recommendations.

GENERAL CONCLUSIONS OF EVIDENCE

SLCO1B1 and statins

SLCO1B1-*simvastatin*. In the systematic review performed for simvastatin and *SLCO1B1*, all 6 meta-analyses and 4 studies investigating myopathy risk found an increased risk for patients with the *SLCO1B1* 521C-allele compared to those without the variant (see Supplementary Tables 1A and 5A). One study also found this risk increase to extend to rhabdomyolysis, while another study showed it did not extend to muscle symptoms without significant creatine kinase elevations (i.e. pain or weakness but without creatine kinase elevations >10x upper limit of normal). Both studies investigating switch to another statin or early withdrawal from the study found an increased risk for patients carrying or homozygous for c.521 T > C.

The only meta-analysis investigating effectiveness only found a diminished cholesterol reduction in patients carrying c.521 T > C after exclusion of 1 of the 3 studies in the meta-analysis. In addition, the effect size was small and unlikely to be clinically significant (see Supplementary Tables 1A and 5A). Among the 7 studies investigating effectiveness in patients, all 4 studies that found an effect, either found the effect to be so small that it was unlikely to be clinically relevant or found the effect to be temporary (i.e. a diminished reduction after 4 weeks, but not after 8 weeks of treatment).

Because of the increased myopathy risk, the DPWG decided to recommend adjustment of simvastatin therapy in *SLCO1B1* c.521 T > C carriers.

SLCO1B1-*atorvastatin*. For the systematic review performed for atorvastatin and *SLCO1B1*, found 2 of the 5 included studies investigating myopathy and/or atorvastatin intolerance, that the c.521 T > C increased the risk (one study including 461 c.521 T > C carriers and one study including 46 cases) (see Supplementary Tables 1B and 5B). One study including 300 c.521 T > C carriers found an increased risk before but not after correcting for multiple comparisons. Two studies with 120 and 37 c.521 T > C carriers, respectively, did not find an increased risk. A meta-analysis of 3 studies showed an increased myopathy risk for c.521 T > C carriers. However, 4 other meta-analyses and 5 additional studies did not find a significant effect.

Regarding effectiveness, one study with 1265 patients found a difference in HDL-cholesterol elevation in patients homozygous for c.521 T > C (see Supplementary Tables 1B and 5B). Four studies with 686, 201, 189, and 136 patients, respectively, did not find an effect of c.521 T > C on cholesterol lowering by atorvastatin. A study in 1081 atorvastatin users did not find an effect on major adverse cardiovascular events and all-cause mortality.

Based on the above and because of the effect of c.521 T > C found on atorvastatin exposure in the 3 included kinetic studies, the DPWG concluded that there seems to be a gene-drug interaction, but that the effect on myopathy and/or intolerance is relatively small and therefore generally not significant in small

clinical studies like most studies on atorvastatin and c.521 C > T. Although the evidence is not strong, the DPWG concluded the evidence to be sufficient to consider adjustment of atorvastatin therapy in c.521 T > C carriers.

SLCO1B1-*rosuvastatin*. In the systematic review performed for rosuvastatin and *SLCO1B1*, one of the two meta-analyses investigating rosuvastatin-induced myopathy found an increased risk for c.521 T > C carriers, but not for c.521 T > C heterozygotes and homozygotes separately, while the other found an decreased risk for heterozygotes and no effect for homozygotes and carriers. Of the 3 studies investigating myopathy, 2 found an increased risk for c.521 T > C carriers, whereas the 3rd and largest did not (see Supplementary Tables 1C and 5C). Neither of two studies found c.521 T > C to result in a clinically significant reduction of LDL-cholesterol lowering.

Data on rosuvastatin kinetics were inconsistent in that three out of the four studies did not show a clear difference in rosuvastatin exposure between c.521 T > C heterozygotes and homozygotes (see Supplementary Tables 1C and 5C). However, a study investigating exposure of rosuvastatin and atorvastatin in the same individuals showed a similar exposure increase for rosuvastatin and atorvastatin in c.521 T > C heterozygotes (exposure ratios for c.521 T > C homozygotes:c.521 T > C heterozygotes:c.521 T > C wild type homozygotes of 1:1.57:1.62 and 1:1.50:2.45, respectively).

So, there is very limited evidence for an association between the c.521 T > C polymorphism and rosuvastatin-induced myopathy. In addition, there is no evidence for a clinically significant negative effect on LDL-cholesterol lowering. However, because in a side-by-side comparison, the exposure difference in c.521 C > T heterozygotes was comparable between rosuvastatin and atorvastatin, the DPWG decided that there is sufficient evidence to conclude that there is a gene-drug interaction present and to consider adjustment of rosuvastatin therapy in c.521 T > C carriers.

SLCO1B1-*fluvastatin*. Two small studies, including 9 and 16 c.521 T > C carriers, respectively, found no impact of gene variant c.521 T > C on fluvastatin plasma levels after single dosing, but a larger study, including 78 c.521 T > C carriers, showed an increase in levels with each additional c.521 T > C gene variant (see Supplementary Tables 1D and 5D). Another study revealed an increase in fluvastatin levels after repeated dosing in 7 c.521 T > C heterozygotes, but only when using an extended-release formulation, not when using an immediate release formulation. In addition, although the exposure-increase was relatively high (69%), the resulting exposure remained lower than for the (clinically slightly less efficient) immediate-release formulation (which was still 139% higher).

Regarding clinical effects, none of the included studies investigated myopathy. Four studies did not find any influence of c.521 T > C on LDL-cholesterol lowering or cholesterol synthesis/absorption in fluvastatin users (see Supplementary Tables 1D and 5D). A meta-analysis of two studies showed a decrease in LDL-cholesterol lowering for c.521 T > C carriers. However, the authors probably strongly overestimated the weight of the study showing the largest effect in this meta-analysis. One study found a lower fluvastatin dose in c.521 T > C carriers. However, this study did not correct for confounders like the baseline cholesterol plasma concentration and coronary heart disease risk. One study showed a lower increase in HDL-cholesterol in c.521 T > C carriers.

Because of the observed pharmacokinetic effect, the DPWG concluded that there is a *SLCO1B1*-fluvastatin interaction. However, the DPWG concluded that there is insufficient evidence for a clinical effect that makes therapy adjustment useful and therefore decided to give no therapeutic recommendation for *SLCO1B1* c.521 T > C carriers planned to be treated with fluvastatin.

SLCO1B1-*pravastatin*. Of the 2 studies investigating myopathy and/or pravastatin intolerance, none found a significant effect of the c.521 T > C gene variant (see Supplementary Tables 1E and 5E). In addition, 3 case reports also did not provide strong evidence for a role of gene variants leading to reduced SLCO1B1 transporter activity in the development of myopathy. So, the risk of pravastatin-induced myopathy seems low, even in patients with risk factors. This is confirmed by the SmPC Pravastatine Na STADA 21-7-2019, stating that there was no difference in the rates of myalgia, muscle weakness, and the incidence of creatine kinase level >3 and >10 times the upper limit of normal compared to placebo in three pravastatin trials, including the one from which the data of one of the two studies were derived.

Regarding effectiveness, one study including 769 c.521 T > C carriers found a small decrease in LDL-cholesterol lowering with increasing number of c.521 T > C gene variants, but no evidence of clinical significance. Two studies, including 177 and 9 c.521 T > C carriers, respectively, found no effect of c.521 T > C on LDL-cholesterol levels.

Of the 5 included studies investigating pravastatin exposure, the only study with daily dosing in patients did not find an effect of c.521 T > C on median pravastatin acid and lactone plasma concentrations (see Supplementary Tables 1E and 5E). Of 4 single-dose studies in healthy volunteers, 3 showed an effect of c.521 T > C on pravastatin levels, with the effect in c.521 T > C homozygotes even being considerable (increase with 91–256%).

Because the majority of single dosing studies in healthy volunteers showed an effect of c.521 T > C on pravastatin exposure, the DPWG concluded that there is a *SLCO1B1*-pravastatin interaction. However, the DPWG considered the evidence for a clinically significant effect of c.521 T > C, i.e. an increase in adverse events like myopathy or a clinically significant decrease in cholesterol lowering, to be insufficient to recommend therapy adjustment. So, the DPWG decided to give no therapeutic recommendation for *SLCO1B1* c.521 T > C carriers planned to be treated with pravastatin.

CYP2C9 and sulfonylurea derivates

In carriers of *CYP2C9* gene variants, the only clinical effect observed was an increase in efficacy for glibenclamide (in 4 studies), gliclazide (in 2 studies), and tolbutamide (in 2 studies) (see Supplementary Tables 2A, B, D and 6A, B, D). Because there is only a positive effect, the DPWG decided that no action, and thus no therapeutic recommendation, is necessary for these gene-drug interactions.

For glimepiride, 2 studies showed an increase in efficacy and 1 study an increased risk of hypoglycemic in *CYP2C9* gene variant carriers (see Supplementary Tables 2C and 6C). Because a lack of effectiveness is a much more common problem with sulfonylurea derivates than the occurrence of hypoglycemic, the DPWG decided that the favorable effect on efficacy is more important than the unfavorable effect on the risk of hypoglycemic. Therefore, the DPWG recommends no action for this gene-drug interaction.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

The DPWG recommendations for simvastatin, atorvastatin, and rosuvastatin in *SLCO1B1* c.521 T > C hetero- and homozygotes, and the absence of recommendations for the other investigated gene-drug combinations is summarized in Table 2. A brief description of the rationale for the therapeutic recommendation for simvastatin, atorvastatin, and rosuvastatin in *SLCO1B1* c.521 T > C hetero- and homozygotes is indicated below. More details are available in the third column of Supplementary Tables 5A through 5C.

Table 2. Pharmacotherapeutic recommendations for the different genotype group-drug combinations (if present).

Drug	Gene	Predicted phenotype (based on genotype) or assigned genotype (group) name	Pharmacotherapeutic recommendation (if present)[a]
Simvastatin	*SLCO1B1*	521TC	- choose an alternative - Consider any additional risk factors for statin-induced myopathy. Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of atorvastatin is not recommended for patients with additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors. - if an alternative is not an option: - avoid simvastatin doses exceeding 40 mg/day (e.g. by adding ezetimibe) - advise the patient to report muscle symptoms
		521CC	- choose an alternative - Consider any additional risk factors for statin-induced myopathy. Atorvastatin is affected less severely by the SLCO1B1 gene variation, but is also affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Use of atorvastatin is not recommended for patients with additional risk factors for statin-induced myopathy. Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not significantly influenced by the SLCO1B1 gene variation or CYP3A4 inhibitors.
Atorvastatin	*SLCO1B1*	521TC	Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy: - choose an alternative Rosuvastatin and pravastatin are influenced to a similar extent by the SLCO1B1 gene variation, but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced significantly by the SLCO1B1 gene variation or CYP3A4 inhibitors. - if an alternative is not an option: - keep the atorvastatin dose as low as possible (e.g. by adding ezetimibe) - advise the patient to report muscle symptoms Patient has NO additional significant risk factors for statin-induced myopathy: - advise the patient to report muscle symptoms
		521CC	Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy: - choose an alternative Rosuvastatin and pravastatin are influenced to a lesser extent by the SLCO1B1 gene variation and are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced significantly by the SLCO1B1 gene variation or CYP3A4 inhibitors. - if an alternative is not an option: - keep the atorvastatin dose as low as possible (e.g. by adding ezetimibe) - - advise the patient to report muscle symptoms Patient has NO additional significant risk factors for statin-induced myopathy: - advise the patient to report muscle symptoms
Rosuvastatin	*SLCO1B1*	521TC	Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy: - keep the rosuvastatin dose as low as possible (e.g. by adding ezetimibe) - advise the patient to report muscle symptoms Patient has NO additional significant risk factors for statin-induced myopathy: - advise the patient to report muscle symptoms
		521CC	Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy: - keep the rosuvastatin dose as low as possible (e.g. by adding

Table 2. continued

Drug	Gene	Predicted phenotype (based on genotype) or assigned genotype (group) name	Pharmacotherapeutic recommendation (if present)[a]
			ezetimibe) - advise the patient to report muscle symptoms Patient has NO additional significant risk factors for statin-induced myopathy: - advise the patient to report muscle symptoms
Fluvastatin	*SLCO1B1*	521TC	—
		521CC	—
Pravastatin	*SLCO1B1*	521TC	—
		521CC	—
Glibenclamide	*CYP2C9*	All variant genotypes and phenotypes[b]	—
Gliclazide	*CYP2C9*	All variant genotypes and phenotypes[b]	—
Glimepiride	*CYP2C9*	All variant genotypes and phenotypes[b]	—
Tolbutamide	*CYP2C9*	All variant genotypes and phenotypes[b]	—

[a]: – = no pharmacotherapeutic recommendation: no genotype group-drug interaction has been found.
[b]: *1/*2, *1/*3, IM OTHER, *2/*2, *2/*3, *3/*3, and PM OTHER.

SLCO1B1-simvastatin

As dose reduction is associated with reduced effectiveness, the DPWG indicates that an alternative less affected by the c.521 C > T variant should be chosen in c.521 T > C carriers. Because the risk increase is modest for c.521 T > C heterozygotes and because the majority of c.521 T > C carriers do not develop myopathy, for c.521 T > C heterozygotes, it is recommended to try simvastatin at lower doses than 80 mg/day if an alternative is not possible. Doses of 80 mg/day are recommended against in all patients due to high risk of myopathy and are rarely used in clinical practice. Because of the higher risk in c.521 T > C homozygotes, the DPWG recommends to always avoid simvastatin in these patients.

SLCO1B1-atorvastatin

Because the systematic review points to a relatively small effect of c.521 T > C polymorphism on atorvastatin-induced myopathy or atorvastatin intolerance, the DPWG decided to recommend adjustment of therapy only in c.521 T > C carriers with additional risk factors for statin-induced myopathy. As dose reduction is associated with reduced effectiveness, the DPWG indicates that choosing an alternative less affected by the c.521 C > T variant is preferred. If an alternative is not possible, it is recommended to keep the required dose as low as possible (e.g., by adding ezetimibe).

SLCO1B1-rosuvastatin

The systematic review revealed only very limited evidence for an association between the c.521 T > C polymorphism and rosuvastatin-induced myopathy, but a similar kinetic effect of this polymorphism for rosuvastatin and atorvastatin. For this reason, the DPWG decided to also recommend adjustment of rosuvastatin therapy only in c.521 T > C carriers with additional risk factors for statin-induced myopathy. The kinetic effect of the c.521 T > C polymorphism has only been shown to be weaker for fluvastatin, which is not a high potency statin like rosuvastatin and therefore is not a good alternative. Therefore, the recommendation is to keep the rosuvastatin dose as low as possible (e.g., by adding ezetimibe).

Supplementary Tables 7 and 8 present an overview of suggested pop-up or look-up texts for electronic prescribing systems for pharmacists and physicians. These can be used to program alerts into the clinical decision support system (CDSS). The guidelines and background information are available on KNMP.nl [14].

IMPLICATIONS FOR CLINICAL PRACTICE

The ongoing debate on the implementation of single gene-drug pairs in routine care is centered around the evidence required for pre-therapeutic genotyping effectiveness, the cost-effectiveness of PGx guided therapy, and reimbursement challenges [15, 16]. Consequently, gene-drug pairs ready for implementation face obstacles in clinical practice uptake [1].

To diminish this inconclusiveness and guide clinicians in ordering relevant PGx genotyping tests before initiating therapy, the DPWG has devised the clinical implication score [3]. This score categorizes pre-therapeutic PGx results as essential, beneficial, or potentially beneficial based on four criteria: the clinical effect associated with the gene-drug interaction, the level of evidence supporting the clinical effect, the effectiveness of the intervention in preventing the clinical effect (number needed to genotype), and the PGx information in the drug-label. The criteria of the clinical implication score and the scores provided for each of these criteria by the DPWG can be found in Supplementary Table 9.

Based on the clinical implication score, the DPWG considers genotyping of *SLCO1B1* before starting simvastatin at a dose of 80 mg/day to be "essential" for drug safety. This score indicates that genotyping must be performed before simvastatin 80 mg/day is initiated to guide drug selection. For simvastatin at a dose of 40 mg/day or lower, the DPWG concluded the clinical implication score to be "beneficial" for drug safety. This score means that it is advised to consider genotyping *SLCO1B1* before or directly after drug therapy initiation to guide drug selection.

For both atorvastatin and rosuvastatin, the DPWG concluded the clinical implication score to be "potentially beneficial" for the prevention of side effects in patients with additional significant risk factors for statin-induced myopathy. This indicates that genotyping of *SLCO1B1* can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline.

Because therapeutic recommendations are lacking for the other gene-drug combinations in this guideline, pre-emptive genotyping offers no benefit. For this reason, the clinical implication score (with scores ranging from potentially beneficial to essential) is not applicable to these gene-drug combinations.

DIFFERENCES BETWEEN AVAILABLE GUIDELINES

To the best of our knowledge, there are no guidelines available for the *CYP2C9*-sulfonylurea gene-drug combinations. Only the

DPWG and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have formulated pharmacogenetics guidelines for *SLCO1B1* and statins. Differences between CPIC and DPWG methodology have previously been described in detail [17].

CPIC published its guideline on *SLCO1B1* gene variants and statins [18]. For simvastatin and c.521 T > C carriers, the only difference between the CPIC and DPWG recommendations is that CPIC recommends a simvastatin dose < 20 mg/day and DPWG a simvastatin dose ≤ 40 mg/day in c.521 T > C heterozygotes if an alternative is not possible. For atorvastatin and rosuvastatin, CPIC recommends therapy adjustment in all patients, while DPWG recommends therapy adjustment only in patients with additional significant risk factors for statin-induced myopathy. For atorvastatin, CPIC recommends keeping the dose low, while DPWG indicates an alternative statin to be the preferred option and recommends to keep the dose low only when an alternative statin is not possible. In addition, CPIC recommends concrete dose boundaries (≤ 40 mg/day for c.521 T > C heterozygotes and ≤ 20 mg/day for c.521 T > C homozygotes), whereas DPWG recommends to keep the dose as low as possible. For rosuvastatin, CPIC recommends keeping the dose ≤ 20 mg/day for c.521 T > C homozygotes and gives no dose recommendations for c.521 T > C heterozygotes, only a warning for a possible increased myopathy risk for doses > 20 mg/day, whereas DPWG recommends to keep the dose as low as possible for both homozygotes and heterozygotes. For fluvastatin and pravastatin, CPIC recommends to preferably keep the dose ≤ 40 mg/day for c.521 T > C homozygotes but indicates higher doses or an alternative statin to be an option if this is not possible. For c.521 T > C heterozygotes, CPIC gives no dose recommendations, only a warning for a possible increased myopathy risk for doses > 40 mg/day. In contrast, DPWG concluded the absence of a need for therapy adjustment for fluvastatin and pravastatin in c.521 T > C carriers.

CPIC considers homozygotes for the *SLCO1B1* *14 allele (containing both the polymorphisms c.388 A > G and c.463 C > A) to have increased SLCO1B1 transporter function but does not recommend therapy adjustment for any statin in these patients, because experimental data show strong evidence for a typical myopathy risk and statin exposure in these patients. This confirms the DPWG conclusion that the only *SLCO1B1* polymorphism for which a clinically significant effect has been found, is c.521 T > C.

DATA AVAILABILITY

All data and material are either included in the supplementary information or publicly available (i.e. the published articles, PubMed). The guidelines and background information are available on KNMP.nl [14] and will be available on PharmGKB.org.

REFERENCES

1. Swen JJ, Huizinga TW, Gelderblom H, de Vries EG, Assendelft WJ, Kirchheiner J, et al. Translating pharmacogenomics: challenges on the road to the clinic. PLoS Med. 2007;4:e209.
2. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte-an update of guidelines. Clin Pharm Ther. 2011;89:662–73.
3. Swen JJ, Nijenhuis M, van Rhenen M, de Boer-Veger NJ, Buunk AM, Houwink EJF, et al. Pharmacogenetic information in clinical guidelines: the European perspective. Clin Pharm Ther. 2018;103:795–801.
4. European Association for Clinical Pharmacology and Therapeutics (EACPT). Available from: https://www.eacpt.eu/.
5. European Association of Hospital Pharmacists (EAHP). Available from: https://www.eahp.eu/.
6. Vinci P, Panizon E, Tosoni LM, Cerrato C, Pellicori F, Mearelli F, et al. Statin-associated myopathy: emphasis on mechanisms and targeted therapy. Int J Mol Sci. 2021;22:11687.
7. Vrablik M, Zlatohlavek L, Stulc T, Adamkova V, Prusikova M, Schwarzova L, et al. Statin-associated myopathy: from genetic predisposition to clinical management. Physiol Res. 2014;63:S327–34.
8. Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, et al. Phenotype standardization for statin-induced myotoxicity. Clin Pharm Ther. 2014;96:470–6.
9. National Center for Biotechnology Information (NCBI). SLCO1B1 solute carrier organic anion transporter family member 1B1 [Homo sapiens (human)]; Available from: https://www.ncbi.nlm.nih.gov/gene/10599.
10. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharm Rev. 2011;63:157–81.
11. Romaine SP, Bailey KM, Hall AS, Balmforth AJ. The influence of SLCO1B1 (OATP1B1) gene polymorphisms on response to statin therapy. Pharmacogenomics J. 2010;10:1–11.
12. Manson LEN, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk AM, Houwink EJF, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of CYP2C9, HLA-A and HLA-B with anti-epileptic drugs. Eur J Hum Genet. 2024;32:903–11.
13. Swen JJ, Wilting I, de Goede AL, Grandia L, Mulder H, Touw DJ, et al. Pharmacogenetics: from bench to byte. Clin Pharm Ther. 2008;83:781–7.
14. Royal Dutch Pharmacists Association (KNMP). Pharmacogenetic Recommendation Text. Available from: https://www.knmp.nl/.
15. Karamperis K, Koromina M, Papantoniou P, Skokou M, Kanellakis F, Mitropoulos K, et al. Economic evaluation in psychiatric pharmacogenomics: a systematic review. Pharmacogenomics J. 2021;21:533–41.
16. Simeonidis S, Koutsilieri S, Vozikis A, Cooper DN, Mitropoulou C, Patrinos GP. Application of economic evaluation to assess feasibility for reimbursement of genomic testing as part of personalized medicine interventions. Front Pharm. 2019;10:830.
17. Bank PCD, Caudle KE, Swen JJ, Gammal RS, Whirl-Carrillo M, Klein TE, et al. Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the Dutch pharmacogenetics working group. Clin Pharm Ther. 2018;103:599–618.
18. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharm Ther. 2022;111:1007–21.

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AUTHOR CONTRIBUTIONS

DFGJW drafted the manuscript. EJHF supervised drafting of the manuscript and contributed to conceiving the work and interpretation of the results. MN performed most of the literature searches and article summaries and suggested clinical decision support texts. BS had the clinical decision support texts translated in English and published them. NBV, AB, HJG, AR, GAR, RHNS, JJS, DT, and RW contributed to conceiving the work and interpretation of the results. VHMD led the meetings in which the DPWG decided about the article summaries and clinical decision supports texts and contributed to conceiving the work and interpretation of the results. In addition, all authors revised the manuscript and approved the final version.

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COMPETING INTERESTS

The Pharmacogenetics Working Group of the KNMP (DPWG) formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-024-01769-7.

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