SLCO1B1: atorvastatin 4057/4058

AUC = area under the concentration-time curve, BMI = body mass index, CI = confidence interval, Cl_{or} = oral clearance, HDL-cholesterol = high-density lipoprotein cholesterol, HR = hazard ratio, HR_{adj} = adjusted hazard ratio, LDL-cholesterol = low-density lipoprotein cholesterol, OR = odds ratio, OR_{adj} = adjusted odds ratio, NS = non-significant, S = significant, SmPC = Summary of Product Characteristics, $t_{1/2}$ = half-life, 388AA = homozygous wild-type allele, 388AG = heterozygous (possibly reduced transporter activity), 388GG = homozygous mutant allele (possibly strongly reduced transporter activity), 463AA = homozygous variant allele (possibly strongly changed transporter activity), 463CA = heterozygous (possibly changed transporter activity), 463CC = homozygous wild-type allele, 521CC = homozygous variant allele (strongly reduced transporter activity), 521CT = heterozygous (reduced transporter activity), 521TT = homozygous wild-type allele.

Disclaimer: The Pharmacogenetics Working Group of the KNMP 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, the health care professional should consider the next best option.

Brief summary and justification of choices:
The organic anion transporter 1B1 (SLCO1B1) plays a role in atorvastatin transport from the portal vein to liver cells, where atorvastatin inhibits cholesterol production. Genetic variations in SLCO1B1 may reduce atorvastatin transport to the liver and therefore increase atorvastatin plasma concentrations. Higher atorvastatin plasma concentrations may increase the risk of myopathy.
Gene variant 521T>C:
Of the 5 studies investigating myopathy and/or atorvastatin intolerance, Voora 2022 (426x 521TC, 35x 521CC) and Puccetti 2010 (46 cases) found the 521C-allele to increase the risk. Turner 2020 (276x 521TC, 24x 521CC) found an increased risk before but not after correction for multiple comparisons, and Linskey 2020 (108x 521TC, 12x 521CC) and Voora 2009 (37x 521TC+CC).) did not find an increased risk. In addition, a meta-analysis of 3 studies with a total of 78x 521TC and 10x 521CC found an increased myopathy risk for 521TC and 521CC (Turongkaravee 2021). None of the other 4 meta-analyses and 5 other studies investigating myopathy risk found an increased risk in 521C-allele carriers (Xiang 2021 (meta-analysis of 4 studies with a total number of 545 patients), Lu 2021 (66 cases), Liu 2017 (98 cases), Jiang 2016 (maximum number of 5 studies with a total of 698 patients per meta-analysis), Hou 2015 (maximum number of 4 studies with 485 patients per meta-analysis), Carr 2013 (meta-analysis of 3 out of the 4 studies in Hou 2015), Brunham 2012 (10 cases), Santos 2012 (34x 521TC, 3x 521CC), and Hermann 2006 (13 cases)). De Keyser 2014 (126x 521TC, 15x 521CC) found the risk of an atorvastatin dose decrease or a switch to another statin to be increased for 521C-allele carriers, but only at an atorvastatin starting dose > 20 mg per day. There was no increase in the whole group, also not if meta-analysis with another group including 60x 521TC and 5x 521CC was performed. Lastly, Fukunaga 2016 (30 cases) did not find an increased risk of atorvastatin-induced liver injury in 521C-allele carriers.
Of the 6 studies investigating effectiveness in patients, 1 study found a difference in HDL-cholesterol elevation in patients homozygous for the 521C-allele (Thompson 2005 (1265 patients)) and 4 found no effect of 521T>C on cholesterol lowering by atorvastatin (Giannakopoulou 2014 (201 patients, including 57x 521TC and 4x 521CC), Fu 2013 (189 patients, including 49x 521TC and 7x 521CC), Rodriques 2011 (136 patients, including 26x 521TC, 2x 521CC), and Mega 2009 (686 patients, including approximately 192x 521CT and 13x 521CC)). The sixth study did not find an effect of the 521C-allele on major adverse cardiovascular events and all-cause mortality in 1081 atorvastatin users, including 276x 521TC and 24x 521CC (Turner 2020).
There is only limited evidence for an association between the 521T>C polymorphism and atorvastatin-induced myopathy or atorvastatin intolerance. Of the 5 rather small meta-analyses, only one found an effect (Turongkaravee 2021). In addition, of the 11 studies, only 4 found a significant effect before correction for multiple comparisons (Voora 2022 (426x 521TC, 35x 521CC), Puccetti 2010 (46 cases), Turner 2020 (276x 521TC, 24x 521CC). and De Keyser 2014 (126x 521TC, 15x 521CC)). In addition, for one of these studies this significant effect was only found in patients with an atorvastatin dose > 20 mg/day. Because the largest two studies (Voora 2022 (1627 patients, including 426x 521TC, 35x 521CC) and Turner 2020 (1081 patients, including 276x 521TC, 24x 521CC)) found an effect before correction for multiple comparisons and because of the effect found on atorvastatin AUC in kinetic studies (Pasanen 2007, He 2009, and Lee 2010), the KNMP Pharmacogenetics Working Group concluded that there seems to be a gene-drug interaction, but that the effect is relatively small and therefore generally not significant in small

clinical studies like most studies on atorvastatin and 521C>T. Based on this, the KNMP Pharmacogenetics Working Group decided to recommend an alternative or keeping the required dose low (for instance by adding ezetimibe), but only in patients with additional risk factors for myopathy or atorvastatin intolerance (yes/yes-interactions).
You can find a detailed overview of the observed kinetic and clinical effects per genotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background information text via your pharmacy or physician electronic decision support system.
Gene variant 388A>G:
None of the 3 studies and the small meta-analysis investigating myopathy risk found an increased risk in patients with the 388G-allele (Xiang 2021 (meta-analysis of 2 studies with a total of 380 patients), Liu 2017 (98 cases), Santos 2012 (142 patients, including 51x 388GA and 80x 388GG) and Hermann 2006 (13 cases)). In addition, Fukunaga 2016 (30 cases) did not find an increased risk of atorvastatin-induced liver injury in 388G-allele carriers.
Of 6 studies investigating effectiveness in patients, 1 found a decrease in LDL-cholesterol lowering in 388G-allele carriers (Kadam 2016 (177 patients, including- 87x 388AG and 57x 388GG)), 1 found an increase in LDL-cholesterol lowering in homozygotes for the 388G-allele (Rodrigues 2011 (136 patients, including 49x 388GG)) and the other 4 found no effect of 388A>G on cholesterol reduction by atorvastatin (Giannakopoulou 2014 (201 patients, including 99x 388AG and 38x 388GG), Fu 2013 (189 patients, including 4x 388GG), Mega 2009 (686 patients, including approximately 535x 388AG and 104x 388GG), and Thompson 2005 (1265 patients)). In the studies that found an effect, the effect was small and unlikely to be clinically relevant (a decrease with 9% in Kadam 2016 and an increase with 13% in Rodrigues 2011).
There were no studies investigating the effect of 388A>G on atorvastatin exposure.
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was insufficient evidence for a clinically relevant effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
Gene variant 463C>A:
Hermann 2006 (13 cases) did not find an increase in myopathy risk for patients with the 463A-allele.
None of the three studies investigating effectiveness, found an effect of 463C>A on cholesterol reduction by atorvastatin (Kadam 2016 (177 patients, including 10x 463CA), Rodrigues 2011 (136 patients, including 41x 463CA+AA), and Thompson 2005 (1265 patients)).
There were no studies investigating the effect of 463C>A on atorvastatin exposure.
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was insufficient evidence for a clinically relevant effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
Gene variants 411G>A, rs4149036C>A and rs4149080G>A:
For 411G>A, Giannakopoulou 2014 (201 patients, including 56x 411GA and 8x 411AA) found no effect on cholesterol lowering by atorvastatin.
For rs4149036C>A, Thompson 2005 (1265 patients) found a 51% decrease in triglyceride lowering in homozygotes for the A-allele compared to homozygotes for the C-allele. However, triglyceride lowering was not decreased in heterozygotes compared to homozygotes for the C-allele, arguing against a role of the A-allele and suggesting a chance finding,
For rs4149080G>A, Thompson 2005 (1265 patients) found a difference in HDL-cholesterol elevation in homozygotes for the A-allele, but not in heterozygotes.
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was insufficient evidence for a clinically relevant effect of these gene variants on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variants in the SLCO1B1 pharmacogenetic interactions.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting atorvastatin to be potentially beneficial for drug tolerance. Genotyping can be considered on an individual patient basis. If, how-ever, the genotype is available, the KNMP Pharmacogenetics Working Group recommends adhering to the gene-drug guideline.
The clinical implication of the gene-drug interaction scores 1 out of the maximum of 10 points (with pre-emptive genotyping considered to be potentially beneficial for scores ranging from 0 to 2 points) (see also the clinical implication score tables at the end of this risk analysis):
No severe clinical effects were observed in users of atorvastatin with a variant genotype. The maximum severity code was C corresponding to CTCAE grade 2. This results in a score of 0 out of the maximum of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (only points for CTCAE grade ≥ 3).
The lack of a severe clinical effect also results in a score of 0 of the maximum of 3 points for the second and third criterion of the clinical implication score: the level of evidence supporting an associated clinical effect grade ≥ 3 and the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect code ≥ D (grade ≥ 3).
The Summary of Product Characteristics (SmPC) of atorvastatin indicates that the SLCO1B1 521CC genotype increases atorvastatin exposure, but does not mention this genotype as a contra-indication and does not recommend pre-emptive genotyping. This results in 1 out of the maximum of 2 points for the fourth and last criterion of the

clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

The table below follows the KNMP nomenclature for SLCO1B1 polymorphisms. The nomenclature used in the table below may therefore differ from the nomenclature used by the authors in the article.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Voora D et al. SLCO1B1*5 allele is associated with atorvastatin discontinuation and adverse muscle symptoms in the context of routine care. Clin Pharmacol Ther 2022;111:1075-83.
PMID: 35034348.</td><td>4

521CC: C

521TC: C</td><td>1627 patients were treated with atorvastatin. Follow-up was for a maximum of 12 years. 56% of patients discontinued atorvastatin and 18% developed atorvastatin-associated muscle symptoms.
Muscle symptoms were defined as a composite variable: creatine kinase level > 3 times the upper limit of normal, International Classification of Diseases 10th Revision (ICD-10) diagnosis codes for myalgia, myopathy, or rhabdomyolysis, and/or a new atorvastatin allergy in the electronic medical record.
Relevant comedication was not excluded, but was adjusted for.
Analysis of association with atorvastatin discontinuation was by univariate and multivariate logistic regression, the latter adjusting for age, sex, ethnicity, the indication for statin therapy, relevant comorbidities such as thyroid disease, concomitant medications, relevant lab data, and atorvastatin dose. Cox proportional hazards model was used to illustrate the association of the 521C carrier status with time to atorvastatin discontinuation, as well as time to onset of muscle symptoms.

Genotyping:
- 1166x 521TT
- 426x 521TC
- 35x 521CC

Results:
<table>
<tr><td colspan="4">Risk compared to 521TT:</td></tr>
<tr><td></td><td>521CC</td><td>521TC</td><td>incidence for 521TT</td></tr>
<tr><td rowspan="3">atorvastatin discontinuation</td><td>x 1.21 (S)</td><td>x 1.10 (trend for an increase (NS))</td><td rowspan="3">54%</td></tr>
<tr><td colspan="2">The 521C-allele was associated with atorvastatin discontinuation (S).</td></tr>
<tr><td colspan="2">OR_{adj} per 521C-allele = 1.2 (95% CI: 1.005-1.472) (S)</td></tr>
<tr><td rowspan="2">time to atorvastatin discontinuation</td><td colspan="2">HR_{adj} = 1.2 (95% CI: 1.1-1.4) (S)</td><td rowspan="2"></td></tr>
<tr><td colspan="2">The 521C-genotype explained 8.8% of the variance in atorvastatin discontinuation.</td></tr>
<tr><td>muscle symptoms</td><td colspan="2">x 1.11 (NS (significance not determined))</td><td>18%</td></tr>
<tr><td>time to muscle symptoms</td><td colspan="2">HR_{adj} = 1.4 (95% CI: 1.1-1.7) (S)</td><td></td></tr>
</table></td><td>Author’s conclusion:
”A univariate model revealed that SLCO1B1*5 increased the likelihood that patients would stop atorvastatin during routine care. A multivariate Cox proportional hazards model further demonstrated that this same variant was associated with time to atorvastatin discontinuation. Additional time-to-event analyses also revealed that SCLO1B1*5 was associated with statin-associated musculoskeletal symptoms.”</td></tr>
<tr><td>ref. 2
Lu B et al. Effect of SLCO1B1 T521C on statin-related myotoxicity with use of lovastatin and atorvastatin. Clin Pharmacol Ther 2021;110:733-</td><td>4</td><td>66 cases with atorvastatin-induced myopathy or rhabdomyolysis were compared to 693 controls matched on age (within 5 years of case age), sex, and atorvastatin dose. Only patients with a atorvastatin dose ≥ 40 mg/day were selected from the health care database. 33 cases (50%) used a atorvastatin dose of 80 mg/day, the other 50% a dose of 40 mg/day. In a secondary analysis, 38 cases with atorvastatin-induced rhabdomyolysis were compared to 407 matched controls.
Atorvastatin-induced myopathy was defined as ≥1 creatine kinase level >5x the upper limit of normal within six months after receiving an atorvastatin prescription. The upper limit of normal for creatine kinase utilised was 336 units/L for males and 176 units/L for females. Creatine kinase levels reported within 7 days of myocardial infarction diag-</td><td>Author’s conclusion:
”Our findings suggest that the association of rs4149056 with simvastatin-related myotoxicity may also extend to lovastatin. More data is needed to determine the extent</td></tr>
</table>

<table>
<tr>
<td>40.
PMID:
34114646.

ref. 2, continuation</td>
<td>521TC:
AA

521CC:
AA</td>
<td>nosis were excluded from analysis. Atorvastatin-induced rhabdomyolysis was defined as ≥1 diagnosis of rhabdomyolysis (via ICD-9 (International Classification of Diseases 9th Revision) code) within six months after receiving an atorvastatin prescription.
Cases with a dispensing history of any interacting non-statin medication within one year prior to the outcome were excluded from analysis. Analysis was by multivariate logistic regression, adjusting for self-reported ethnicity.
Based a conservative effect size of 3.0 per 521C allele, 521C allele frequency of 0.15, log additive mode of inheritance, and a conservative population risk of 5% for statin-induced myopathy based on prior studies, it was calculated that at least 21 cases would be needed to have greater than 80% power to determine an association between 521T>C and statin-induced myopathy.

Genotyping (myopathy or rhabdomyolysis case-control analysis):
cases: controls:
- 47x 521TT - 514x 521TT
- 16x 521TC - 164x 521TC
- 3x 521CC - 15x 521CC

Results:
<table>
<tr><td colspan="3">Risk compared to 521TT:</td></tr>
<tr><td></td><td>521TC</td><td>521CC</td></tr>
<tr><td rowspan="3">myopathy or rhabdomyolysis</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">The 521C-allele frequency did not differ in cases and controls (NS).</td></tr>
<tr><td colspan="2">Inclusion of matching criteria for race or obesity/ diabetes status each yielded similar results to that of the primary analysis.</td></tr>
<tr><td rowspan="2">rhabdomyolysis</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">The 521C-allele frequency was similar in cases and controls (NS, p = 0.08).</td></tr>
</table>
</td>
<td>of the association in atorvastatin users.”</td>
</tr>
<tr>
<td>ref. 3
Turongkaravee S et al.
A systematic review and meta-analysis of genotype-based and individualized data analysis of SLCO1B1 gene and statin-induced myopathy.
Pharmacogenomics J 2021;21:296-307.
PMID:
33608664.</td>
<td>3</td>
<td>Meta-analysis investigating the effect of gene variant 521T>C on risk of myopathy (defined by muscle weakness after atorvastatin use with/without confirming by creatine kinase levels ≥3x the upper limit of normal) in Caucasians. 3 studies with a total number of 315 patients (227x 521TT, 78x 521TC, and 10x 521CC) were included in the meta-analysis. Studies were performed in the United Kingdom, Croatia and the Netherlands Risk of bias for genetic association studies was assessed considering four domains: information bias (3 items), confounding bias (2 items), selective outcome report, and Hardy–Weinberg equilibrium assessment. 1 of the 3 included studies had low/no risk on bias for all 7 items, 1 had unclear or insufficient information to assess the risk of bias for ascertainment of genotyping examination (1 of the 3 information bias items) and the 3rd study had possible/high risk of bias for Hardy-Weinberg equilibrium assessment.
Of the 3 publications included in the meta-analysis, 1 was also included in our risk analysis separately (Brunham 2012). Of a 2nd publication (Carr 2013), we only included the meta-analysis data.
The systematic review protocol was prospectively registered with PROSPERO, the International prospective register of systematic reviews. For the per genotype approach, OR1 (aa vs AA) and OR2 (Aa vs AA) were estimated using mixed-effect logistic regression and a random-effects model irrespective of heterogeneity between the studies. This suggests that also the statistical method was chosen prospectively. The search and selection strategy was transparent and the data extraction was standardised.
Quality of the included studies was judged and reported, but not by a generally accepted study quality scale.
Publication bias was assessed by funnel plot and Egger’s test. However, Egger’s test was only assessed for all statins (10 studies), not for atorvastatin separately.</td>
<td>Author’s conclusion:
”CC and TC genotypes also suggested a higher risk of myopathy in simvastatin users and in atorvastatin users, than those who carried TT genotype.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 3, continuation</td>
<td>521TC: C

521CC: C

521TC +CC: C</td>
<td>Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>OR = 1.98 (95% CI: 1.11-3.52) (S)</td><td rowspan="2">OR = 2.1 (95% CI: 1.2-3.8) (S)</td></tr>
<tr><td>521CC</td><td>OR = 3.95 (95% CI: 1.23-12.63) (S)</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was absent for all comparisons.</td></tr>
<tr><td colspan="3">Funnel plots showed no indication for publication bias.
Neither did Egger’s test for all statins (10 studies) for the comparison 521CC versus 521TT. However, Egger’s test for all statins for the comparison 521TC versus 521TT showed a trend for publication bias (p = 0.069) (NS).</td></tr>
</table></td>
<td></td>
</tr>
<tr>
<td>ref. 4
Xiang Q et al. Correlation between single-nucleotide polymorphisms and statin-induced myopathy: a mixed-effects model meta-analysis.
Eur J Clin Pharmacol 2021;77:569-81.
PMID: 33150478.</td>
<td>3

521TC: AA

521CC: AA

388AG: AA

388GG: AA</td>
<td>Meta-analyses investigating the effect of gene variants 521T>C and 388A>G on risk of myopathy. 4 studies with a total number of 545 patients were included in the meta-analysis for 521T>C and 2 studies with a total number of 380 patients in the meta-analysis for 388A>G. The identity of the included studies is not indicated. Studies investigating atorvastatin and SLCO1B1 scored 6-9 of the 9 points on the Newcastle-Ottawa Scale for study quality.
Prospective registration of the meta-analysis protocol was not mentioned, but the meta-analysis was performed with a mixed-effects model. This indicates that the statistical method was chosen prospectively. The data extraction was standardised, but transparency of the search and selection strategy was severely hampered by the selected studies not being identified.
Quality of the included studies was judged with a generally accepted study quality scale, but since the included studies were not identified, the exact scores of the included studies are not known.
According to the methods section, publication bias was assessed by Egger’s and Begg’s test. However, since no results are mentioned for the atorvastatin meta-analyses, it is unclear whether publication bias was also assessed for these meta-analyses.

Results:
<table>
<tr><td colspan="3">Myopathy risk compared to homozygous wild-type allele carriers (521TT or 388AA):</td></tr>
<tr><td></td><td>heterozygous variant allele carriers</td><td>homozygous variant allele carriers</td></tr>
<tr><td rowspan="2">521T>C</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">NS</td></tr>
<tr><td rowspan="2">388A>G</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">NS</td></tr>
<tr><td colspan="3">Presence or absence of heterogeneity between the studies and publication bias were not reported and probably not assessed.</td></tr>
</table></td>
<td>Author’s conclusion:
”The correlation of SLCO1B1 rs4149056 and GATM rs9806699 with the risk of statin-induced myopathy may depend on the use of simvastatin and rosuvastatin, respectively.”</td>
</tr>
<tr>
<td>ref. 5
Linskey DW et al. Association of SLCO1B1 c.521T>C (rs4149056) with discontinuation of atorvastatin due to statin-associated muscle symptoms.
Pharmacogenet Genomics 2020;30:208-11.
PMID: 32453264.</td>
<td>3</td>
<td>379 patients were treated with atorvastatin for 12 months. 80% of patients was treated with an atorvastatin dose ≤ 20 mg/day. 61% of all patients and 43% of the 76 patients on an atorvastatin dose > 20 mg/day discontinued atorvastatin due to atorvastatin-associated muscle symptoms.
Muscle symptoms were defined as any symptom specific to muscle that was stated by the patient 12 months after treatment start: muscle symptoms (e.g., pain, weakness, cramps) and/or elevated creatinine kinase levels. The secondary outcome was discontinuation of atorvastatin specifically due to (patient reported) elevation of creatine kinase levels.
Relevant comedication was not excluded, but a previous analysis showed that there was no significant difference in the number of medications that could impact statin exposure (i.e. CYP3A4 inducers/inhibitors) between those experiencing atorvastatin-associated muscle symptoms and atorvastatin tolerant individuals.
Analysis of association with atorvastatin discontinuation due to atorvastatin-associated muscle symptoms was by univariate and multivariate logistic regression, the latter adjusting for family history of heart disease, obesity, hypertension, and smoking. No adjustment was</td>
<td>Author’s conclusion:
”SLCO1B1 c.521T>C was not significantly associated with discontinuation of atorvastatin therapy due to statin-associated muscle symptoms.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>521TC +CC: AA</td>
<td>made for inflammatory muscle disease despite a higher percentage of inflammatory muscle disease in patients discontinuing atorvastatin due to atorvastatin-associated muscle symptoms.
80% power was estimated to detect an odds ratio ≥1.9 for SLCO1B1 521T>C-carrier status.

Genotyping:
- 259x 521TT
- 108x 521TC
- 12x 521CC

Results:
<table>
<tr><td colspan="3">Therapy discontinuation due to patient reported atorvastatin-associated muscle symptoms for 521TC+521CC compared to 521TT:</td></tr>
<tr><td rowspan="2">all muscle symptoms</td><td>all doses</td><td>NS</td></tr>
<tr><td>dose > 20 mg/day</td><td>NS</td></tr>
<tr><td>elevated creatine kinase levels</td><td>all doses</td><td>NS</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Turner RM et al.
A genome-wide association study of circulating levels of atorvastatin and its major metabolites.
Clin Pharmacol Ther 2020;108:287-97.
PubMed PMID: 32128760.</td>
<td>4</td>
<td>1081 White patients with a recent non-ST elevation acute coronary syndrome were treated with 80 mg or 40 mg atorvastatin daily.
For 580 patients, atorvastatin and metabolite concentrations were measured after 1 month. For 146 patients, treated with 80 mg daily, atorvastatin and metabolite concentrations were measured after 12 months. Patients were on the same dose of atorvastatin for at least 1 month. The mean sampling time was 14 hours after the last dose, assuming the last dose to be at 22.00 hour on the preceding day. Exclusion criteria were low outlier participants with two or more analytes <0.5ng/mL (i.e. less than the lower limit of quantification) (to exclude non-compliant patients) and high outlier participants with atorvastatin ≥31ng/mL or ≥15.5ng/mL if prescribed atorvastatin 80mg or 40mg, respectively (to exclude patients with recent atorvastatin administration). Prior to GWAS, multivariable linear regression was used for clinical covariate selection. A Bonferroni multiple testing-corrected genome-wide statistical significance threshold of $p<5.0x10^{-8}/8$ tests = $6.25x10^{-9}$ was applied. The proportion of observed variability explained by the gene variant was assessed by multivariable linear regression. Results after 12 months were assessed by multivariable linear regression analysis adjusted for age, sex, time since last dose, and sample storage duration, if applicable ($p<0.05$ taken to be significant). For 1081 patients, who were discharged from hospital on atorvastatin (at any dose), clinical effectiveness was determined. Median follow up from discharge was 17 months. For 870 of these patients, adverse events and atorvastatin intolerance were determined after 1 month. Major adverse cardiovascular event was defined as a composite of myocardial infarction, ischaemic stroke or cardiovascular death. Atorvastatin intolerance was defined as atorvastatin discontinuation, atorvastatin dose reduction, switching to a different statin of lower equivalent dose and/or atorvastatin non-adherence (self-reported missing at least one atorvastatin pill in the last week). Associations were tested by regression analysis. The multiple testing-corrected significance threshold was $p<0.05/16$ tests = 0.003.
13% of patients had a major adverse cardiovascular event, 8.6% died, 6.1% had an adverse event, 1.5% had muscular symptoms, and 14% were intolerant to atorvastatin.
Relevant co-medication was not excluded, but results were adjusted for co-medication.

Genotyping (estimated based on allele frequency):
- 781x 521TT
- 276x 521TC
- 24x 521CC

Results:</td>
<td>Author’s conclusion:
’In summary, both novel and recognised genetic associations have been identified with circulating levels of atorvastatin and its major metabolites. Further study is warranted to determine the clinical utility of genotyping rs4149056 (SLCO1B1 521 C>T) in patients on high dose atorvastatin.’’</td>
</tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td>521TC: A
521CC A</td><td>
<table>
<tr><td colspan="4">Results compared to 521TTor to the 521T-allele:</td></tr>
<tr><td colspan="2"></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td rowspan="3">median atorvastatin plasma concentration</td><td>month 1</td><td>x 2.32</td><td>x 1.34</td><td>4.7 ng/ml</td></tr>
<tr><td colspan="3">For the C-allele versus the T-allele, there was no genome-wide significance (NS), but there was a nominal significance (p = 2.21x10^{-6}).</td></tr>
<tr><td colspan="3">Clinical factors explained 16.9% of variation in atorvastatin plasma concentration, clinical factors together with 521T>C explained 20.2% (S).</td></tr>
<tr><td></td><td>month 12</td><td colspan="3">S for an increase with increasing number of 521C-alleles</td></tr>
<tr><td rowspan="2">median 2-hydroxy atorvastatin plasma concentration</td><td>month 1</td><td colspan="3">For the C-allele versus the T-allele, there was no genome-wide significance (NS), but there was a nominal significance (p = 1.09x10^{-6}).</td></tr>
<tr><td>month 12</td><td colspan="3">trend for an increase with increasing number of 521C-alleles (p = 0.057) (NS)</td></tr>
<tr><td>median atorvastatin lactone plasma concentration</td><td>month 1</td><td colspan="3">NS</td></tr>
<tr><td>median 2-hydroxy atorvastatin lactone plasma concentration</td><td>month 1</td><td colspan="3">NS</td></tr>
<tr><td colspan="2">all adverse events</td><td colspan="3">NS</td></tr>
<tr><td colspan="2">muscular symptoms</td><td colspan="3">OR = 2.32 (95% CI: 1.01-5.33) for the C-allele versus the T-allele (S, but NS after correction for multiple comparisons).
OR = 3.97 (95% CI: 1.29-12.27) for 521TC+CC versus 521TT (S, but NS after correction for multiple comparisons).</td></tr>
<tr><td colspan="2">atorvastatin intolerance</td><td colspan="3">OR = 1.55 (95% CI: 1.09-2.19) for the C-allele versus the T-allele (S, but NS after correction for multiple comparisons).</td></tr>
<tr><td colspan="2">major adverse cardiovascular events</td><td colspan="3">NS</td></tr>
<tr><td colspan="2">all-cause mortality</td><td colspan="3">NS</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 7
Liu JE et al. SLCO1B1 521T > C polymorphism associated with rosuvastatin-induced myotoxicity in Chinese coronary artery disease patients: a nested case-control study. Eur J Clin Pharmacol</td><td>3

521TC</td><td>98 cases with muscle-related adverse symptoms (pain, soreness, weakness, or twitches) during atorvastatin treatment for at least 6 months were compared to 139 age and sex matched controls without muscle-related adverse symptoms from the same cohort. All patients had percutaneous coronary intervention for coronary artery disease. For a larger group including also patients on other statins (148 cases and 255 controls), BMI and HDL-cholesterol were higher in cases than in controls.
Relevant co-medications was not excluded. In the larger group, use of β-blockers, ACE-inhibitors, calcium channel blockers and proton pump inhibitors did not differ between cases and controls.

Genotyping:
521T>C: 388A>G:
- 180x 521TT - 21x 388AA</td><td>Author’s conclusion:
‘’Non-significant association was observed between 521C mutant allele and risk of myotoxicity in patients that received atorvastatin and simvastatin.’’</td></tr>
</table>

<table>
<tr><td>2017;73:1409-16.
PubMed PMID: 28812116.

ref. 7, continuation</td><td>+CC: AA

388GG: AA

388AG: AA</td><td>- 57x 521TC or 521CC
- 79x 388AG
- 137x 388GG

Results:<table><tr><td colspan="2">Myopathy risk:</td></tr><tr><td>521T>C</td><td>NS for TC+CC versus TT</td></tr><tr><td>388A>G</td><td>NS for GG versus AG versus AA</td></tr></table></td><td></td></tr>
<tr><td>ref. 8
Jiang J et al.
Association between SLCO1B1 -521T>C and -388A>G polymorphisms and risk of statin-induced adverse drug reactions: a meta-analysis.
Springerplus 2016;5:1368.
PubMed PMID: 27606156.</td><td>4

521TC: AA

521CC: AA

521TC +CC: AA</td><td>Meta-analysis of studies investigating the effect of gene variant 521T>C on myopathy risk. 5 publications with 6 independent studies and a total number of 1065 patients were included in the meta-analysis. 4 of the included studies were cohort studies and the other two were case-control studies. All studies included mainly white patients. For TC versus TT and CC versus TT 3 studies with a total of 532 patients were included, for TC+CC versus TT 5 studies with a total of 698 patients, and for CC versus TC versus TT and for the C- versus the T-allele 2 studies with a total of 165 patients were included. The included studies scored 7-9 of the maximum of 9 points on the Newcastle-Ottawa Quality scale. Follow-up in the included studies was at least 1 year.
Of the 5 publications included in the meta-analysis, 2 were also included in the meta-analysis of Turongkaravee 2021 (Brunham 2012 and Carr 2013).
Of the 5 publications included in the meta-analysis, 4 were also included in our risk analysis separately (Voora 2009, Brunham 2012, Santos 2012, and De Keyser 2014). Of the 5th publication (Carr 2013), we only included the meta-analysis data.
The effect estimates (OR or HR) of the studies were pooled. If available, adjusted effect estimates were used.
Meta-analyses were performed with a random-effects model in case of moderate to high heterogeneity between the studies and with a fixed-effects model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Publication bias was assessed by Begg’s and Egger’s test.

Results:<table><tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr><tr><td>521TC</td><td>NS</td><td rowspan="2">NS for TC+CC versus TT.
NS for CC versus CT versus TT.</td></tr><tr><td>521CC</td><td>NS</td></tr><tr><td colspan="3">There was no increased risk for the 521C-allele compared to the 521T-allele (NS).</td></tr><tr><td colspan="3">For all comparisons, there was no heterogeneity observed between the studies.</td></tr><tr><td colspan="3">For all comparisons with at least 3 studies, there were no indications of publication bias. Publication bias was not assessed for comparisons with 2 studies.</td></tr></table></td><td>Author’s conclusion:
”Subgroup analysis by statin type showed that the adverse drug reaction risk was significantly elevated among simvastatin users, but not among atorvastatin users.”</td></tr>
<tr><td>ref. 9
Fukunaga K et al.
ABCB1 polymorphism is associated with atorvastatin-induced liver injury in Japanese population.
BMC Genet 2016;17:79.
PubMed PMID: 27296832.</td><td>3</td><td>30 cases with atorvastatin-induced liver injury were compared to 414 controls without liver injury on atorvastatin therapy.
The Bonferroni multiple testing-corrected significance threshold was p<0.05/17 = 0.0029.
Relevant co-medication was not excluded.

Genotyping:
521T>C:
- 324x 521TT
- 106x 521TC
- 14x 521CC
388A>G:
- 54x 388AA
- 191x 388AG
- 199x 388GG

Results:<table><tr><td colspan="3">% of patients with liver injury for gene variant carriers compared to non-carriers:</td></tr><tr><td></td><td></td><td>value</td></tr></table></td><td>Author’s conclusion:
‘’ABCB1 rs2032582 was found to be associated with an increased risk of atorvastatin-induced liver injury by genotyping 444 Japanese subjects for 15 functional SNPs in eight candidate genes that reportedly affect</td></tr>
</table>

<table>
<tr><td>ref. 9, continuation</td><td>521TC +CC: AA

388AG +GG: AA</td><td>
<table>
<tr><td></td><td></td><td>for non-carriers</td></tr>
<tr><td rowspan="2">521TC+CC compared to 521TT</td><td>NS</td><td rowspan="2">5.6%</td></tr>
<tr><td>Results were also NS for the 521C-allele compared to 521T-allele.</td></tr>
<tr><td rowspan="2">388AG+GG compared to 388AA</td><td>NS</td><td rowspan="2">7.4%</td></tr>
<tr><td>Results were also NS for the 388G-allele compared to 388A-allele.</td></tr>
</table>
</td><td>the pharmacokinetics of atorvastatin. No other polymorphisms showed a significant association with atorvastatin-induced liver injury.’’</td></tr>
<tr><td>ref. 10
Kadam P et al. Genetic determinants of lipid-lowering response to atorvastatin therapy in an Indian population. J Clin Pharm Ther 2016;41:329-33.
PubMed PMID: 26932749.</td><td>3

388AG +GG: A

463CA: AA</td><td>177 patients were treated with atorvastatin 10 mg/day for 8 weeks.
Poor responders were defined as patients with a reduction of <30% in LDL-cholesterol levels.
30% of patients was poor responder. None of the patients reported any side effects.
Multiple regression analysis was used to elucidate the association between gene variants and lipid-lowering response. Age, gender, smoking status and alcohol intake were included as covariates, but none of these parameters was associated with response to atorvastatin in this study.
Co-medication that could affect lipid levels was excluded, but co-medication with influence on atorvastatin was not.

Genotyping (estimated based on gene variant frequencies):
388A>G:
- 33x 388AA
- 87x 388AG
- 57x 388GG
463C>A:
- 167x 463CC
- 10x 463CA

Results:
<table>
<tr><td colspan="3">Reduction in LDL-cholesterol levels compared to non-carriers of the gene variant:</td></tr>
<tr><td></td><td></td><td>value for non-carriers</td></tr>
<tr><td rowspan="3">388AG+388GG compared to 388AA</td><td>approximately x 0.91 (S)</td><td>approximately 34%</td></tr>
<tr><td colspan="2">The frequency of the 388G-allele was significantly higher in atorvastatin poor responders compared to responders (S).</td></tr>
<tr><td colspan="2">Gene variants in the CYP3A4, SLCO1B1 and ABCB1 region explained only 2% of the variation in LDL-cholesterol lowering.</td></tr>
<tr><td>463CA compared to 463CC</td><td>NS</td><td></td></tr>
</table>
</td><td>Author’s conclusion:
‘’In our study, patients with wild-type genotypes of CYP7A1 (rs3808607), CYP3A4 (rs2740574), SLCO1B1 (rs2306283) and variant allele-carrying genotype of ABCB1 (rs2032582, rs-1045642) showed significantly greater LDL-cholesterol reductions in response to atorvastatin therapy.’’</td></tr>
<tr><td>ref. 11
Hou Q et al. Association between SLCO1B1 gene T521C polymorphism and statin-related myopathy risk: a meta-analysis of case-control studies.
Medicine (Baltimore) 2015;94:e1268.
PubMed PMID: 26376374.</td><td>3</td><td>Meta-analysis of case-control studies investigating the effect of gene variant 521T>C on myopathy risk. Four studies with a total number of 485 patients (68 cases and 417 controls) were included in the meta-analysis. For the comparison of the C- with the T-allele 2 studies with a total of 163 patients (21 cases and 144 controls) were included. All studies included mainly white patients. The included studies scored 6-9 points on the Newcastle-Ottawa Quality scale. The authors report that the distribution of genotypes in the control group deviated from Hardy–Weinberg equilibrium in Brunham 2012 with a P value 0.04.
All 4 studies included in the meta-analysis, were also included in the meta-analysis of Jiang 2016 and 2 were also included in the meta-analysis of Turongkaravee 2021 (Brunham 2012 and Carr 2013).
Of the 4 studies included in the meta-analysis, 3 were also included in our risk analysis separately (Voora 2009, Santos 2012 and Brunham 2012). Of the 4th publication (Carr 2013), we only included the meta-analysis data.
Meta-analyses were performed with a random-effects model in case of moderate to high heterogeneity between the studies and with a fixed-effects model in case of low heterogeneity between the studies. This</td><td>Author’s conclusion:
”When stratified by statin type, the association was significant in individuals receiving simvastatin, but not in those receiving atorvastatin.”</td></tr>
</table>

<table>
<tr>
<td>ref. 11, continuation</td>
<td>521TC +CC: AA</td>
<td>indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the data extraction was standardised.
Analysis publication bias was not performed for atorvastatin. Neither was sensitivity analysis.

Results:
<table>
<tr><td colspan="2">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC+CC</td><td>NS</td></tr>
<tr><td colspan="2">Results were also NS for the 521C-allele compared to the 521T-allele.</td></tr>
<tr><td colspan="2">For both comparisons, no heterogeneity was observed between the studies.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 12
Giannakopoulou E et al.
No impact of SLCO1B1 521 T>C, 388A>G and 411G>A polymorphisms on response to statin therapy in the Greek population.
Mol Biol Rep 2014;41:4631-8.
PubMed PMID: 24668570.</td>
<td>3

521TC +CC: AA

388AG: AA

388GG: AA

411GA +AA: AA</td>
<td>201 patients were treated with atorvastatin (5-80 mg/day; mean 21.0 mg/day) for 6 months. The dose of atorvastatin was adjusted according to the National Cholesterol Education Program Adult Treatment Panel III treatment goal for LDL-cholesterol based on risk category (LDL-cholesterol <3,4, <2.6 or <1.8 mmol/l).
Atorvastatin treatment reduced total cholesterol with 34.5% and LDL-cholesterol with 42.2% in this study.
Associations were tested with multivariable linear regression, adjusted for age, sex, BMI, statin dose and baseline cholesterol levels.
Relevant co-medication was not excluded.

Genotyping (based on the relative frequencies for patients on either atorvastatin or simvastatin):
521T>C:
- 140x 521TT
- 57x 521TC
- 4x 521CC
388A>G:
- 64x 388AA
- 99x 388AG
- 38x 388GG
411G>A:
- 137x 411GG
- 56x 411GA
- 8x 411AA

Results:
<table>
<tr><td colspan="6">Results compared to 521TT or 411GG, or for 388GG versus 388AG versus 388AA :</td></tr>
<tr><td></td><td></td><td>521TC +CC</td><td>388GG</td><td>388AG</td><td>411GA +AA</td></tr>
<tr><td rowspan="5">% reduction in total cholesterol</td><td>all</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>5-10 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>20 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>≥ 40 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>female</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>male</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td rowspan="5">% reduction in LDL-cholesterol</td><td>all</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>5-10 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>20 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>≥ 40 mg/day</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>female</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td>male</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
<tr><td colspan="2">mean atorvastatin dose</td><td>NS</td><td colspan="2">NS</td><td>NS</td></tr>
</table>
Note: 388A>G and 411G>A were in high linkage disequilibrium. In addition, 411G>A is a synonymous gene variation, which means that it does not change the encoded amino acid (137 Ser).</td>
<td>Author’s conclusion:
‘‘SLCO1B1 521 T>C, 388A>G and 411G>A polymorphisms were not associated with lipid-lowering response to atorvastatin or simvastatin.’’</td>
</tr>
<tr>
<td>ref. 13
de Keyser CE et al.
The SLCO1B1 c.521T>C polymorphism is associated with dose de-</td>
<td>3</td>
<td>477 patients from a population-based cohort, aged 55 years or older (mean 70.6 years), and 244 patients with hypercholesterolemia and/or hypertension from a myocardial infarction case-control study were treated with atorvastatin. Follow-up started at the date of first atorvastatin prescription and ended at the date of dose reduction, the end of the last prescription, or after 3 years. Patients having a gap of at least 180 days between two prescriptions were excluded. A fixed effect inverse variance meta-analysis was performed to combine the results</td>
<td>Author’s conclusion:
‘‘For atorvastatin, an association was found in users with a starting dose of more than 20 mg.’’</td>
</tr>
</table>

<table>
<tr>
<td>crease or switching during statin therapy in the Rotterdam Study. Pharmacogenet Genomics 2014;24:43-51. PubMed PMID: 24263182.

ref. 13, continuation</td>
<td>521CC: AA

521TC: AA

521TC +CC: C</td>
<td>of both groups.
In the largest group, the dose was decreased in 17% of patients, and a switch to another cholesterol-lowering drug was performed for 6% of patients. In the smallest group, this was 11% and 7%, respectively.
The reason for dose reduction or switch to another cholesterol-lowering drug was established for 63 patients on simvastatin or atorvastatin to be an adverse drug reaction in 68% of patients, a too strong reduction in cholesterol level in 27% of patients, and a response to a cholesterol measurement (most likely because of ineffectiveness) in 5% of patients.
Relevant co-medication was not excluded.
Hazard ratios were adjusted for age, sex, and starting dose.
The authors estimated a power of 90.0% to find an HR of 2.0 and a power of 51.7% to find an HR of 1.5 in the largest group, and a power of 56.0% and 29.0%, respectively, in the smallest group.

Genotyping:
Largest group:
- 336x 521TT
- 126x 521TC
- 15x 521CC

Smallest group:
- 179x 521TT
- 60x 521TC
- 5x 521CC

Results:
<table>
<tr><td colspan="4">Risk of dose decrease of switch to another cholesterol-lowering drug compared to 521TT:</td></tr>
<tr><td colspan="2"></td><td>521CC</td><td>521TC</td></tr>
<tr><td rowspan="7">largest group</td><td>all</td><td>NS</td><td>NS</td></tr>
<tr><td>men</td><td>NS</td><td></td></tr>
<tr><td>women</td><td>NS</td><td></td></tr>
<tr><td>starting dose ≤ 20 mg/day</td><td>NS</td><td></td></tr>
<tr><td>starting dose > 20 mg/day</td><td colspan="2">HR = 3.26 (95% CI:1.47-7.25) (S)</td></tr>
<tr><td>< 70 years</td><td>NS</td><td></td></tr>
<tr><td>≥ 70 years</td><td>NS</td><td></td></tr>
<tr><td colspan="2">smallest group</td><td colspan="2">NS</td></tr>
<tr><td colspan="2">meta-analysis of both groups</td><td colspan="2">NS</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 14
Fu Q et al. Lack of association between SLCO1B1 polymorphism and the lipid-lowering effects of atorvastatin and simvastatin in Chinese individuals. Eur J Clin Pharmacol 2013;69:1269-74. PubMed PMID: 23263738.</td>
<td>4

521CC: AA

521TC: AA</td>
<td>189 patients were treated with atorvastatin 20 mg/day for 4 weeks.
Blood samples were collected after a 12-hours fast.
None of the patients showed any elevation in aminotransferase or creatine phosphokinase, and no patients reported skeletal muscle abnormalities or other notable safety concerns.
Co-medication was excluded. Poor adherence (reported or calculated intake of <80% of the prescribed number of tablets) was excluded.
Carriage of CYP3A4*1G, CYP3A5*3 and CYP3AP1*3 was excluded.
P values were adjusted by age, BMI and pretreatment lipid levels.

Genotyping:
- 133x 521TT
- 49x 521TC
- 7x 521CC

Results:
<table>
<tr><td colspan="4">% reduction in fasting lipid levels compared to 521TT:</td></tr>
<tr><td></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td>total cholesterol</td><td>NS</td><td>NS</td><td>17.5%</td></tr>
<tr><td>LDL-cholesterol</td><td>NS</td><td>NS</td><td>27.8%</td></tr>
<tr><td>HDL-cholesterol</td><td>NS</td><td>NS</td><td>0.8%</td></tr>
<tr><td>triglyceride</td><td>NS</td><td>NS</td><td>22.7%</td></tr>
</table>
</td>
<td>Author’s conclusion: ’’SLCO1B1 521T > C and 388A > G polymorphisms may not be associated with the lipid-lowering effects of atorvastatin and simvastatin.’’</td>
</tr>
</table>

ref. 14, continuation	388GG: AA	Results were also NS for patients with both 521CC and 388GG (n = 4) compared to patients with both 521TT and 388AA (n = 4), suggesting also a lack of effect of 388GG.	
ref. 15 Carr DF et al. SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the Clinical Practice Research Datalink. Clin Pharmacol Ther 2013;94:695-701. PubMed PMID: 23942138.	3 521TC +CC: AA	11 patients with myopathy (atorvastatin discontinuation due to serum creatine kinase > 4x upper limit of normal) were compared to 110 patients receiving atorvastatin for at least 3 months without above normal serum creatine kinase measurements. A meta-analysis was performed of the study above and 2 other studies investigating the effect of gene variant 521T>C on myopathy. All studies included in the meta-analysis, were also included in the meta-analyses of Jiang 2016 and Hou 2015, and 2 were also included in the meta-analysis of Turongkaravee 2021 (Brunham 2012 and the study above). All other studies in the meta-analysis were also included in our risk analysis separately (Brunham 2012 and Voora 2009). Meta-analyses were performed with a random-effects model in case of moderate to high heterogeneity between the studies and with a fixed-effects model in case of low heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent, but the data extraction method was not specified. Analysis of study quality and publication bias was not performed. Results: Myopathy risk compared to 521TT: 521TC+CC: NS	Author's conclusion: ''Our meta-analysis of studies in Caucasians, including our data, also shows that there was a higher risk with simvastatin (OR = 3.25 (1.72–6.12)) than with atorvastatin (OR = 1.54 (0.80–2.97)), regardless of daily dose, in carriers of the SLCO1B1 polymorphism.''
ref. 16 Francesca Notarangelo M et al. Genetic predisposition to atorvastatin-induced myopathy: a case report. J Clin Pharm Ther 2012;37:604-6. PubMed PMID: 22582980.	2 521CC: B 521TC: B	A 48-year-old Italian man developed myalgia and weakness of the limbs two weeks after initiation of atorvastatin 40 mg/day. The creatine kinase plasma concentration was moderately increased to 300 IU/L. Co-medication consisted of acetylsalicylic acid, clopidogrel, metoprolol and ramipril. None of these drugs are known CYP3A4 or SLCO1B1 inhibitors. The risk factors hypothyroidism and renal dysfunction were excluded. The symptoms and creatine kinases elevation resolved within a few days of discontinuation of atorvastatin. The 65-year-old father of the patient had myalgia in the upper limbs while using atorvastatin 40 mg/day. The creatine kinase plasma concentration was only slightly increased. The symptoms and creatine kinases elevation resolved within a few days of discontinuation of atorvastatin. The 48-year-old man was a homozygous variant and his father a heterozygous variant for the rs4363657 polymorphism in SLCO1B1. This polymorphism is in linkage disequilibrium with 521T>C.	Authors' conclusion: "The two cases of atorvastatin-induced myopathy reported here emphasize the impact of genetic factors on the risk of myopathy with statins. Although genotyping all patients before initiating therapy is not recommended at present, pharmacogenetic testing may be useful for new patients who have a family history of statin induced myopathy."
ref. 17 Brunham LR et al. Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin. Pharmacoge-	3 521TC +CC: AA	10 Dutch cases with severe atorvastatin-associated myopathy and 35 age and gender-matched controls using the same atorvastatin dose. The mean atorvastatin dose was approximately 30 mg/day. Myopathy was defined as creatine kinase plasma concentrations exceeding 10 times the upper limit of normal (150 U/L). Relevant co-medication was not excluded. Cases versus controls: - There was no difference in the frequency of the 521C allele (from 0.19 to 0.20) (NS) - No increased risk of myopathy (OR = 1.06 (NS; 95% CI: 0.22-4.80)) The authors stated that the sample size was too small to exclude a relationship between the 521C allele and atorvastatin-associated	Authors' conclusion: "When subjects were stratified by statin type, the SLCO1B1 rs4149056 genotype was significantly associated with myopathy in patients who received simvastatin, but not in

nomics J 2012;12:233-7. PubMed PMID: 21243006.		myopathy with certainty.	patients who received atorvastatin."
ref. 18 Santos PC et al. SLCO1B1 haplotypes are not associated with atorvastatin-induced myalgia in Brazilian patients with familial hypercholesterolemia. Eur J Clin Pharmacol 2012;68:273-9. PubMed PMID: 21928084.	4 521TC +CC: AA 388AG +GG: AA	143 Brazilian patients with familial hypercholesterolaemia used atorvastatin for at least 1 year. The initial doses were 20 mg/day (n=11), 40 mg/day (n=49), 60 mg/day (n=3) and 80 mg/day (n=80). The dose was increased for 9 patients. CYP450 and SLCO1B1 inhibitors were excluded. Similar results were found when the data were analysed by dose or after correction for dose, age and gender. 14 patients developed myalgia, including 1 with creatine kinase elevation up to 3 times the upper limit of normal. 16 patients had creatine kinase elevation exceeding 3 times the upper limit of normal. No patients had creatine kinase elevation exceeding 10 times the upper limit of normal or rhabdomyolysis. The mean dose was approximately 60 mg/day in both patients with and without myalgia. Genotyping: 521T>C: 106x TT, 34x TC, 3x CC 388A>G: 12x AA, 51x GA, 80x GG (521TC + 521CC) versus 521TT: - No significant difference in the percentage of patients with myalgia (5.4% versus 11.3%) (NS) - No significant difference in creatine kinase plasma concentration (137.0 versus 142.1 U/L) (NS) - No significant difference in the percentage of patients with creatine kinase exceeding 3 times the upper limit of normal (10.8% versus 11.3%) (NS) - No significant difference in the percentage of patients with myalgia and/or creatine kinase exceeding 3 times the upper limit of normal (NS) (388AG + 388GG) versus 388AA: - No significant difference in the percentage of patients with myalgia (6.3% versus 12.5%) (NS) - No significant difference in creatine kinase plasma concentration (147.8 versus 135.5 U/L) (NS) - No significant difference in the percentage of patients with creatine kinase exceeding 3 times the upper limit of normal (12.7% versus 10.0%) (NS) - No significant difference in the percentage of patients with myalgia and/or creatine kinase exceeding 3 times the upper limit of normal (NS) The authors stated that the sample size was too small to exclude a less than 4-fold elevation of the risk of myalgia.	Authors' conclusion: "Our findings reaffirm that the SLCO1B1 genetic risk appears to be greater in those patients receiving simvastatin compared with those receiving atorvastatin."
ref. 19 Rodrigues AC et al. Pharmacogenetics of OATP transporters reveals that SLCO1B1 c.388A>G variant is determinant of increased atorvastatin response. Int J Mol Sci 2011;12:5815-27. PubMed PMID:	3 521TC +CC: AA	136 Brazilian patients with moderate hypercholesterolaemia and risk factors for cardiovascular disease used atorvastatin 10 mg/day for 4 weeks. Co-medication with CYP3A4 substrates or inhibitors did not have a significant effect on cholesterol lowering. Adverse events did not occur. Alanine-aminotransferase plasma concentrations increased after treatment but hepatotoxicity did not occur. Genotyping: 521T>C: 108x TT, 26x TC, 2x CC 388A>G: 82x (GA + AA), 49x GG 463C>A: 95x CC, 41x (CA + AA) (521TC + 521CC) versus 521TT: - No difference in LDL-cholesterol before initiation of therapy (193 versus 192 mg/dL) (NS) - No significant difference in atorvastatin-induced lowering of LDL-cholesterol (40.9% versus 38.1%) (NS)	Authors' conclusion: "SLCO1B1 c.388A>G polymorphism causes significant increase in atorvastatin response and may be an important marker for predicting efficacy of lipid-lowering therapy."

22016628. **ref. 19, continuation**	388GG: AA[#] 463CA +AA: AA	388GG versus (388GA + 388AA): - No difference in LDL-cholesterol before initiation of therapy (193 versus 191 mg/dL) (NS) - Atorvastatin-induced lowering of LDL-cholesterol increased by 4.7 percentage points (from 36.6% to 41.3%) (S; OR = 3.23 (95% CI: 1.30-8.04)) (463CA + 463AA) versus 463CC: - No significant difference in LDL-cholesterol before initiation of therapy (184 versus 196 mg/dL) (NS) - No significant difference in atorvastatin-induced lowering of LDL-cholesterol (38.0% versus 38.4%) (NS)	
ref. 20 Puccetti L et al. Genetic involvement in statins induced myopathy. Preliminary data from an observational case-control study. Atherosclerosis 2010;211:28-9. PubMed PMID: 20347093.	3 521TC +CC: C	A case-control study including 46 patients who had discontinued atorvastatin due to adverse events or who developed muscle symptoms and/or creatine kinase elevation exceeding 3 times the upper limit of normal were compared to controls without intolerance or muscle symptoms. Relevant co-medication was not excluded. The risk of intolerance increased with the atorvastatin dose (OR = 3.3 (95% CI: 1.7-5.6)). 14 cases used atorvastatin 20 mg/day, 26 cases 40 mg/day. Case-control study: - The 521C allele was associated with intolerance or muscle symptoms with OR = 2.7 (95% CI: 1.3-4.9) (S) The allele frequency was 0.13 in the controls and 0.48 in the cases.	Authors' conclusion: "In the cohort of both intolerant and matched tolerant subjects, the study showed no association between the C-allele of rs4149056 SNP in SLCO1B1 and myopathy in rosuvastatin-treated subjects whereas it was confirmed for atorvastatin."
ref. 21 Lee YJ et al. Effects of SLCO1B1 and ABCB1 genotypes on the pharmacokinetics of atorvastatin and 2-hydroxyatorvastatin in healthy Korean subjects. Int J Clin Pharmacol Ther 2010;48:36-45. PubMed PMID: 20040338.	3 521TC: A 521CC: A	28 Korean volunteers were given a single dose of 20 mg atorvastatin. Co-medication was excluded. Genotyping: 521T>C: 17x TT, 8x TC, 3x CC. 521TC versus 521TT: - The atorvastatin AUC increased by 22% from 66.3 to 80.7 ng.hour/mL (NS) - The atorvastatin lactone AUC increased by 2.5% from 40.0 to 41.0 ng.hour/mL (NS) - The AUC of the active metabolite 2-hydroxyatorvastatin increased by 36% from 57.9 to 78.8 ng.hour/mL (S) - The AUC of 2-hydroxyatorvastatin lactone increased by 19% from 79.5 to 94.4 ng.hour/mL (NS) - The atorvastatin $t_{1/2}$ and those of the metabolites did not change significantly (NS) 521CC versus 521TT: - The atorvastatin AUC increased by 124% from 66.3 to 148.2 ng.hour/mL (S) - The atorvastatin lactone AUC increased by 28% from 40.0 to 51.2 ng.hour/mL (NS) - The AUC of the active metabolite 2-hydroxyatorvastatin increased by 81% from 57.9 to 104.7 ng.hour/mL (S) - The AUC of 2-hydroxyatorvastatin lactone increased by 6.5% from 79.5 to 84.7 ng.hour/mL (NS) - The atorvastatin $t_{1/2}$ and those of the metabolites did not change significantly (NS)	Authors' conclusion: "This study shows that the SLCO1B1 *15 allele may be associated with the individual difference in the AUC of atorvastatin."
ref. 22 Voora D et al. The SLCO1B1*5 genetic variant	3	146 American patients used atorvastatin 10 mg/day for 8 weeks, followed by atorvastatin 80 mg/day for 8 weeks. Relevant co-medication was not excluded. Genotyping: 521T>C: 109x TT, 37x (TC + CC).	Authors' conclusion: "Subjects who carried at least 1 allele of SLCO-

is associated with statin-induced side effects. J Am Coll Cardiol 2009;54:1609-16. PubMed PMID: 19833260. **ref. 22, continuation**	521TC +CC: AA	(521TC + 521CC) versus 521TT: - There was a 1.4-fold increase from 19% to 27% in the percentage of patients who either withdrew from the study early due to an adverse event, developed myalgia or muscle cramps or had creatine kinase elevation exceeding 3 times the upper limit of normal (NS).	1B1*5 and were assigned to simvastatin had a greater incidence of the composite adverse event, and those assigned to atorvastatin showed a similar trend when compared with those with no alleles."
ref. 23 Mega JL et al. Identification of genetic variants associated with response to statin therapy. Arterioscler Thromb Vasc Biol 2009;29:1310-5. PubMed PMID: 19667110.	3 521TC: AA 521CC: AA 388AG: AA 388GG: AA	686 Caucasian patients with recent acute coronary syndrome used atorvastatin 80 mg/day for 1 month. Relevant co-medication was not excluded. Genotyping: 521T>C: C-allele frequency was 0.14 388A>G: G-allele frequency was 0.39 521TT versus 521TC versus 521CC: - No difference in LDL-cholesterol before initiation of therapy (NS) - No significant difference in atorvastatin-induced lowering of LDL-cholesterol (49.24% versus 47.83% versus 47.50%) (NS) 388AA versus 388AG versus 388GG: - No difference in LDL-cholesterol before initiation of therapy (NS) - No significant difference in atorvastatin-induced lowering of LDL-cholesterol (49.50% versus 48.82% versus 47.05%) (NS)	Authors' conclusion: "None of the other pharmacokinetic SNPs (among which the SNPs in SLCO1B1) were significantly related to the percent reduction in LDL-C in either treatment arm."
ref. 24 He YJ et al. Rifampicin alters atorvastatin plasma concentration on the basis of SLCO1B1 521 T>C polymorphism. Clin Chim Acta 2009;405:49-52. PubMed PMID: 19374892.	3 521TC: A 521CC: A	16 Chinese volunteers were given a single dose of 40 mg atorvastatin. Co-medication, smoking, alcohol and drugs were excluded. Genotyping: 521T>C: 6x TT, 6x TC, 4x CC. 521TC versus 521TT: - The atorvastatin AUC increased by 15% from 27.4 to 31.6 ng.hour/mL (S for the trend) - The $t_{1/2}$ decreased by 11% from 12.0 to 10.7 hours (S for the trend) - Cl_{cr} decreased by 19% from 1580.8 to 1282.4 L/hour (S for the trend) 521CC versus 521TT: - The atorvastatin AUC increased by 108% from 27.4 to 56.9 ng.hour/mL (S for the trend) - The $t_{1/2}$ decreased by 27% from 12.0 to 8.8 hours (S for the trend) - Cl_{cr} decreased by 44% from 1580.8 to 882.9 L/hour (S for the trend)	
ref. 25 Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6. PubMed PMID: 18794729.	3 521TC: AA 521CC: AA	32 Caucasian volunteers were given a single dose of 20 mg atorvastatin. Co-medication, CYP3A5 expressers and carriers of the ABCC2 1446C>G and CYP2C9*3 polymorphisms were excluded. Genotyping: 521T>C: 16x TT, 12x TC, 4x CC 521TT versus 521TC versus 521CC: - No differences in the mean and maximum percentage decrease in cholesterol precursor/cholesterol ratio after administration of atorvastatin The cholesterol precursors investigated were lathosterol and desmosterol. - No differences in the mean and maximum percentage decrease in cholesterol absorption marker/cholesterol ratio after administration of atorvastatin The cholesterol absorption marker investigated was the plant sterol avenasterol. - No difference in total cholesterol before administration of atorvastatin	Authors' conclusion: "The short-term effects of statins on cholesterol homeostasis were not associated with the SLCO1B1 polymorphism."

ref. 25, continuation		(NS) The authors stated that the sample size was too small to exclude differences in statin response smaller than 40%.	
ref. 26 Pasanen MK et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82:726-33. PubMed PMID: 17473846.	3 521TC: A 521CC: A	32 Caucasian volunteers were given a single dose of 20 mg atorvastatin. Co-medication and CYP3A5 expressers were excluded. Genotyping: 521T>C: 16x TT, 12x TC, 4x CC. 521TC versus 521TT: - The atorvastatin AUC increased by 50% from 24.2 to 36.2 ng.hour/mL (S) - The atorvastatin lactone AUC increased by 26% from 4.3 to 5.4 ng.hour/mL (NS) - The AUC of the active metabolite 2-hydroxyatorvastatin increased by 40% from 1.0 to 1.4 ng.hour/mL (NS) - The AUC of 2-hydroxyatorvastatin lactone increased by 33% from 3.6 to 4.8 ng.hour/mL (NS) - The atorvastatin $t_{1/2}$ and those of the metabolites did not change significantly (NS) - No significant differences in the AUCs of atorvastatin and 2-hydroxyatorvastatin in different haplotypes (different 388A>G, -11187G>A and/or -10499A>C SNPs) 521CC versus 521TT: - The atorvastatin AUC increased by 145% from 24.2 to 59.3 ng.hour/mL (S) - The atorvastatin lactone AUC increased by 105% from 4.3 to 8.8 ng.hour/mL (NS) - The AUC of the active metabolite 2-hydroxyatorvastatin increased by 100% from 1.0 to 2.0 ng.hour/mL (S) - The AUC of 2-hydroxyatorvastatin lactone increased by 61% from 3.6 to 5.8 ng.hour/mL (NS) - The atorvastatin $t_{1/2}$ and those of the metabolites did not change significantly (NS)	Authors' conclusion: "These results indicate that, unexpectedly, SLCO1B1 polymorphism has a larger effect on the AUC of atorvastatin than on the more hydrophilic rosuvastatin."
ref. 27 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 2006;79:532-9. PubMed PMID: 16765141.	4 521TC +CC: AA 463CA +AA: AA 388AG +GG: AA	13 Norwegian cases with reversible atorvastatin-associated myalgia and 15 healthy controls using atorvastatin 10 mg/day for 1 week without myalgia. Co-medications that can interact with atorvastatin were excluded. Cases versus controls: - There was no difference in the frequency of the 521C allele (haplotypes *5 and *15) (0.00 versus 0.07) (NS) - There was no difference in the frequency of the 463A allele (haplotype *14) (0.27 versus 0.23) (NS) - There was no difference in the frequency of the 388G allele (haplotypes *1b and *15) (0.38 versus 0.40) (NS)	Authors' conclusion: "There were no differences in frequencies of SLCO1B1 polymorphisms between patients with atorvastatin-related myopathy and healthy control subjects."
ref. 28 Thompson JF et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin	3 rs4149036 AA: A rs4149080: A 521CC:	1265 Caucasian patients used atorvastatin 10 mg/day for 6 weeks. Relevant co-medication was not excluded. Possible associations were determined for 43 SNPs in 16 genes. - Triglycerides decreased to a lesser extent in homozygotes for the rs4149036A allele (decrease by 9.5% versus 20.1% for AC and 19.2% for CC) (S without correction for multiple tests; p = 0.0024) - There was a difference in HDL-cholesterol elevation in homozygotes for the rs4149080 and 521C variant alleles (S without correction for	Authors' conclusion: "None of the associations found here predict atorvastatin LDL-C lowering in a manner sufficient to

response. Pharmacogenomics J 2005;5:352-8. PubMed PMID: 16103896.	A 388AG +GG: AA 463CA +AA: AA	multiple tests; p = 0.026 and p = 0.037) - The 388A>G, 463C>A, -540C>T, Phe73Leu, rs2291073, Gly488Ala and Leu643Phe SNPs were not associated with reductions in cholesterol and triglyceride concentrations	impact decisions on treatment."
ref. 29 SmPC Lipitor (atorvastatin) 17-01-22.	0 521CC: A	Pharmacokinetics: SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure to atorvastatin, which may lead to an increased risk of rhabdomyolysis. Polymorphism in the gene encoding OATP1B1 (SLCO-1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the effectiveness are unknown.	

Risk group	High doses and factors that increase the atorvastatin plasma concentration (hepatic or renal impairment, co-medication with CYP3A4 inhibitors, co-medication with SLCO1B1 inhibitors such as gemfibrozil), female gender, advanced age, hypothyroidism

Comments:

- For the period after October 2012, only studies and meta-analyses with more than 160 patients were included. Other studies did not contribute enough to the evidence.
- Existing guideline:
  Cooper-DeHoff RM 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. PMID: 35152405.
  CPIC distinguishes the following SLCO1B1 genotype groups: poor function (521CC), decreased function (521TC), normal function (521TT, excluding homozygotes for the *14-allele (which has both gene variants 388A>G and 463C>A)), and increased function (homozygotes for the *14-allele). However, CPIC does not recommend therapy adjustment for SLCO1B1 increased function.
  CPIC indicates that, although the association of gene variant 521T>C with myopathy varies by statin, there is evidence supporting the role of SLCO1B1 variants in the systemic clearance of all statins. CPIC mentions that in the single-dose study Pasanen 2007, the plasma AUC of atorvastatin has been 144% higher in 521CC than in 521TT. In single-dose studies, the effect of 521T>C on statin pharmacokinetics is second strongest for atorvastatin (after simvastatin).
  Recommendation per genotype group:

Genotype group	Implications	Recommendation[a]	Classification of recommendation[b]	Considerations
521TC	Increased atorvastatin exposure as compared with normal function, which may translate to increased myopathy risk.	Prescribe ≤40 mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for 40-mg dose. If dose >40 mg needed for desired efficacy, consider combination therapy (i.e., atorvastatin plus nonstatin guideline-directed medical therapy).	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug-drug interactions may be more pronounced, resulting in a higher risk of myopathy.
521CC	Increased atorvastatin exposure as compared with normal function and 521TC, which may	Prescribe ≤20 mg as a starting dose and adjust doses of atorvastatin based on disease-specific guidelines. If dose >20 mg is nee-	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evalua-

	translate to increased myopathy risk.	ded for desired efficacy, consider rosuvastatin or combination therapy (i.e., atorvastatin plus nonstatin guideline-directed medical therapy).		ted prior to initiating a statin. The effects of drug-drug interactions may be more pronounced, resulting in a higher risk of myopathy.
388GG+ 463AA	Typical myopathy risk and statin exposure.	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated prior to initiating a statin.

[a]: Recommendations are for adult patients only. CPIC indicates that at the time of writing the guideline, no data were available regarding SLCO1B1 genotype effects on statin response or myopathy in paediatric patients. How-ever, pharmacokinetic data showed that gene variant 521T>C may affect the disposition of simvastatin more in children compared with adults, and the variant had equivalent impact on pravastatin and rosuvastatin pharmaco-kinetics between children and adults (Wagner JB et al. Impact of SLCO1B1 genetic variation on rosuvastatin systemic exposure in pediatric hypercholesterolemia. Clin Transl Sci 2020;13:628-37; Wagner JB et al. Impact of genetic variation on pravastatin systemic exposure in pediatric hypercholesterolemia. Clin Pharmacol Ther 2019; 105:1501-12; and Wagner JB et al. Impact of SLCO1B1 genotype on pediatric simvastatin acid pharmacokine-tics. J Clin Pharmacol 2018;58:823-33).

[b]: Strong = the evidence is high quality and the desirable effects clearly outweigh the undesirable effects. Moderate = there is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

On 7-4-2023, there was not a more recent version of the recommendations present on the CPIC-site.

Date of literature search: 8 March 2023.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetic Working Group decision	521TC	4 C	yes	yes	16 May 2023
	521CC	4 C	yes	yes	

Mechanism:
The organic anion transporter 1B1 (SLCO1B1) plays an important role in atorvastatin transport from the portal vein to liver cells, where atorvastatin inhibits cholesterol production, although transport of atorvastatin by other organic anion transporters (SLCO1A2, SLCO1B3, and SLCO2B1) has been reported. Genetic variations in SLCO1B1 may reduce atorvastatin transport to the liver and therefore increase atorvastatin plasma concentrations. Higher atorvastatin plasma concentrations may increase the risk of myopathy.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	Possible Score	Given Score
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	
• CTCAE Grade 5 (clinical effect score F)	++	

Level of evidence supporting the associated clinical effect grade ≥ 3 • One study with level of evidence score ≥ 3 • Two studies with level of evidence score ≥ 3 • Three or more studies with level of evidence score ≥ 3	 + ++ +++	
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 • 100 < NNG ≤ 1000 • 10 < NNG ≤ 100 • NNG ≤ 10	 + ++ +++	
PGx information in the Summary of Product Characteristics (SmPC) • At least one genotype/phenotype mentioned OR • Recommendation to genotype OR • At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	 + ++ ++	 +
Total Score:	10+	1+
Corresponding Clinical Implication Score:		Potentially beneficial