SLCO1B1: rosuvastatin 7740/7741

AUC = area under the concentration-time curve, CI = confidence interval, C_{max} = peak plasma concentration, CrI = credible interval, 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 rosuvastatin transport from the portal vein to liver cells, where rosuvastatin inhibits cholesterol production. Genetic variations in SLCO1B1 may reduce rosuvastatin transport to the liver and therefore increase rosuvastatin plasma concentrations. Higher rosuvastatin plasma concentrations may increase the risk of myopathy.
Gene variant 521T>C:
Of the 2 meta-analyses investigating myopathy, 1 found an increased risk for 521TC+CC, but not for 521TC and 521CC separately (Xiang 2018, number of studies and patients in the meta-analysis not mentioned). In contrast, the other found a decreased risk for 521CT and no effect for 521CC and 521TC+CC (Xiang 2021, 3 studies with a total number of 4394 patients). Of the 3 studies investigating myopathy, 2 found an increased risk for 521TC+CC (Merćep 2022 (81 myotoxicity cases either or not combined with 6 hepatotoxicity cases and 1 case with both myo- and hepatotoxicy) and Bai 2019 (including 130x 521TC and 54x 521CC)), whereas the 3rd and largest did not (Danik 2013 (including 1185x 521TC and 121x 521CC)).
Of the 2 studies investigating effectiveness in patients, the largest found a statistically, but not clinically significant percentual decrease in LDL-cholesterol in the first year for both 521TC and 521CC (Danik 2013, including 1185x 521TC and 121x 521CC) and the smallest found no effect on 3-month LDL-cholesterol level for 521TC+CC (Bailey 2010, including 72x 521TC and 7x 521CC).
Of the 4 studies investigating rosuvastatin kinetics, 3 did not show a (clear) difference in rosuvastatin exposure between 521CC and 521TC, including the study that showed a clearly higher atorvastatin exposure in 521CC in the same patients (Pasanen 2007, single dosing of 10 mg in healthy volunteers, including 12x 521TC and 4x 521CC). In Pasanen 2007, the AUC ratio for 521TT:521TC:521CC was 1:1.57:1.62 for rosuvastatin and 1:1.50:2.45 for atorvastatin. In Zhang 2020 (rosuvastatin 10 mg/day in patients, including 46x 521TC and 15x 521CC), the plasma concentration ratio was 1:1.74:1.90. In Bai 2019 (rosuvastatin 10 mg/day (87%), 20 mg/day (11%) or 5 mg/day (2%) in patients, including 130x 521TC and 54x 521CC), the dose-corrected plasma concentration ratio was 1:1.39:1.12 (difference between the genotypes significant before correction for multiple testing, but not significant after correction). In contrast, in Lehtisalo 2023 (single dosing of 40 mg (64%), 20 mg (21%) or 10 mg (15%) in healthy volunteers, including 63x 521TC and 12x 521CC), the difference between 521CC and 521TC was larger than expected with a dose-corrected AUC ratio of 1:1.21:2.09.
There is only very limited evidence for an association between the 521T>C polymorphism and rosuvastatin-induced myopathy with the two meta-analyses contradicting each other and the by far largest study showing no effect. 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 521CT is comparable between rosuvastatin and atorvastatin, the KNMP Pharmacogenetics Working Group decided to give a therapeutic recommendation. The kinetic effect of the 521T>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. For this reason, the KNMP Pharmacogenetics Working Group only recommends to keep the rosuvastatin dose as low as possible (e.g. by adding ezetimibe) in patients with additional risk factors for statin-induced myopathy (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 infor-

mation text via your pharmacy or physician electronic decision support system.
Gene variant 388A>G:
Neither the meta-analysis nor the study investigating myopathy risk found an increased risk in patients with the 388G-allele (Xiang 2021 (meta-analysis of 2 studies with a total number of 842 patients) and Bai 2019 (including 262x 388AG and 444x 388GG). In addition, Bai 2019 did not find a difference in dose-corrected rosuvastatin plasma concentration between 388AA, 388AG and 388GG.
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was no evidence for an 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 463C>A and 1929A>C:
Lehtisalo 2023 (single dosing in healthy volunteers) found a lower dose-corrected AUC for 4x 463AA, 1929CC or 463CA-1929AC (i.e. 2 alleles considered to result in higher than normal function), but no significant difference in 44x 463CA or 1929AC (i.e. 1 allele considered to result in higher than normal function),
Because a lower systemic exposure due to a higher transport into the liver where rosuvastatin inhibits cholesterol production, is unlikely to lead to either an increased risk of myopathy or a decrease in LDL-cholesterol lowering, the KNMP Pharmacogenetics Working Group decided that these data provide no reason for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
Gene variant rs4363657T>C
Neither of the 2 studies investigating myopathy found an increased risk for patients with the rs4363657C-allele (Bai 2019 (including 358x rs4363657TC and 180x rs4363657CC) and (Danik 2013 (including 1211x rs4363657TC and 135x rs4363657CC)). Danik 2013 found a statistically, but not clinically significant percentual decrease in LDL-cholesterol in the first year for both rs4363657TC and rs4363657CC.
In addition, the first study to report rs4363657 found this intronic gene variant to be in almost complete linkage disequilibrium with 521T>C ($r^2 > 0.95$).in a White patient group (SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy -- a genomewide study. N Engl J Med 2008;359:789-99. PubMed PMID: 18650507).
Based on the above, the KNMP Pharmacogenetics Working Group decided that there was no evidence for an independent effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.

Recommendation concerning pre-emptive genotyping, including justification of choices:
The KNMP Pharmacogenetics Working Group considers genotyping before starting rosuvastatin 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 rosuvastatin with a variant phenotype. 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 rosuvastatin indicates that the SLCO1B1 521CC genotype increases rosuvastatin 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.

Source	Code	Effect	Comments
ref. 1 Lehtisalo M et al. A comprehensive pharmacogenomic study indicates roles for SLCO1B1,	3	247 healthy volunteers received a single dose rosuvastatin. 88 of these volunteers were derived from 4 previous studies, including the 32 volunteers from Pasanen 2007. The dose of rosuvastatin was 40 mg in 159 volunteers, 20 mg in 51 volunteers and 10 mg in 37 volunteers. Relevant co-medication was excluded. Effect sizes (estimated marginal means) were determined by analysis of variance, adjusting for covariates (body weight, SLCO2B1 1457C >	Authors' conclusion: "These data suggest roles for SLCO1B1, ABCG2 and SLCO2B1 in rosuvastatin

<table>
<tr>
<td>ABCG2 and SLCO2B1 in rosuvastatin pharmacokinetics.
Br J Clin Pharmacol.
2023;89:242-52.
PMID:
35942816.

ref. 1, continuation</td>
<td>463AA +1929 CC+ 463CA-1929 AC: A

463CA +1929AA AA

521TC: AA

521CC: A</td>
<td>T genotype and ABCG2 421C>A genotype). Genome-wide association and candidate gene analyses were performed with a stepwise linear regression analysis fixed for significant demographic covariates.

Genotyping:
- 4x 463AA, 1929CC or 463CA-1929AC (i.e. 2 alleles considered to result in higher than normal function)
- 44x 463CA or 1929AC (i.e. 1 allele considered to result in higher than normal function)
- 124x no variant allele
- 63x 521TC
- 12x 521CC

Results:
<table>
<tr><td colspan="2">Dose-corrected rosuvastatin AUC compared to no variant allele (value for no variant allele = 3.73 ng.h/ml per mg):</td></tr>
<tr><td>463AA, 1929CC or 463CA-1929AC</td><td>x 0.56 (90% CI: 0.38-0.84) (S)</td></tr>
<tr><td>463CA or 1929AC</td><td>x 0.95 (NS)</td></tr>
<tr><td>521TC</td><td>x 1.21 (NS)</td></tr>
<tr><td>521CC</td><td>x 2.09 (90% CI: 1.56-2.81) (S)</td></tr>
<tr><td colspan="2">In a genome wide association assay, 521T>C was the only gene variant showing genome-wide significance (S). Other variants also did not show genome-wide significance after adjusting for 521T>C. The AUC of rosuvastatin was 42% higher per copy of the 521C allele.</td></tr>
<tr><td colspan="2">In a candidate gene analysis, 521T>C was the only gene variant showing significance after Bonferroni correction for multiple testing (S). The AUC of rosuvastatin was 52% higher per copy of the 521C allele.
388A>G showed a significant effect before but not after Bonferroni correction for multiple testing (NS).</td></tr>
<tr><td colspan="2">521C>T was also associated with C_{max}, but not with $t_{1/2}$.</td></tr>
</table>
</td>
<td>pharmacokinetics. Poor SLCO1B1 or ABCG2 function genotypes may increase the risk of rosuvastatin-induced myotoxicity. Reduced doses of rosuvastatin are advisable for patients with these genotypes.”</td>
</tr>
<tr>
<td>ref. 2
Merćep I et al.
Loss of function polymorphisms in SLCO1B1 (c.521T>C, rs4149056) and ABCG2 (c.421C>A, rs2231142) genes are associated with adverse events of rosuvastatin: a case-control study.
Eur J Clin Pharmacol
2022;78:227-36.
PMID:
34668025.</td>
<td>4</td>
<td>88 cases with rosuvastatin-induced myotoxicity (n = 82) and/or hepatotoxicity (n = 7) were compared to 129 age-matched controls using rosuvastatin for more than 3 months and longer than the case. One of the cases had both myotoxicity (myalgia) and hepatotoxicity. The rosuvastatin dose was 10 mg/day in 47.7% of cases, 15-20 mg/day in 31.8%, 5 mg/day in 19.3% and 30-40 mg/day in 1.1% of cases.
Rosuvastatin-induced myotoxicity was defined as myalgia (muscle pain without an increase in serum creatinine kinase or with an increase ≤ 3 times the upper limit of normal), myopathy (increased creatine kinase > 3 times the upper limit of normal accompanied with muscle symptoms) or rhabdomyolysis. Of the cases with myotoxicity, 56% had myalgia, 43% had myopathy, and 1.2% (1 patient) had rhabdomyolysis. Hepatotoxicity was defined as a new-onset increase in serum levels of liver transaminases ≥ 3 times the upper limit of normal, or an increase to > 20% of the pre-treatment levels in subjects with pre-existing elevated transaminases.
69.3% of cases developed myotoxicity and/or hepatotoxicity within the first 3 months of treatment, 20.5% between 3 and 6 months of treatment, 4.6% between 8 and 11 months, and 5.7% between 13 and 15 months.
Familiar dyslipidemia occurred less often and chronic liver disease more often in cases than in controls.
Relevant comedication was not excluded, but was adjusted for.
Analysis was by (frequentist) multivariate logistic regression, adjusting for factors reported to be associated with the risk of statin-induced muscular/hepatic adverse events: age, sex, CYP2C9 phenotype (NM or IM/PM), CYP2C19 phenotype (NM, RM/UM, or IM/PM), comorbidities (hypertension and, cumulatively, diabetes or chronic kidney or liver disease (viral hepatitis, alcoholic, or non-alcoholic fatty liver disease)), and the use of CYP2C9/2C19 and/or OATP1B1/ABCG2</td>
<td>Author’s conclusion:
”Loss of function polymorphisms in SLCO1B1 c.521 T>C and ABCG2 c.421C>A genes are associated with the presence of rosuvastatin related myotoxicity and/or hepatotoxicity.”</td>
</tr>
</table>

<table>
<tr><td>ref. 2, continuation</td><td>521TC +CC: C</td><td>inhibitors.
Based on a 521C allele carrier frequency of 0.30, a study size of 90 cases and 135 controls, was calculated to provide 80% power to detect a relevant effect size (i.e. >2.0, range 2.1-2.5).

Genotyping:
cases: controls:
- 37x 521TT - 83x 521TT
- 41x 521TC - 42x 521TC
- 10x 521CC - 4x 521CC

Results:
Risk of myotoxicity and/or hepatotoxicity for 521TC+521CC compared to 521TT:
OR_{adj} = 2.45 (95% CI: 1.34-4.48) (S)
Similar results were obtained after adjusting for ABCG2 variant allele carriage (OR_{adj} = 2.45 (95% CI: 1.23-4.91) (S)), by Bayesian multivariate logistic regression (OR_{adj} = 2.59 (95% CrI: 1.42-4.90) (S)), including only patients with myotoxicity (OR_{adj} = 2.72 (95% CI: 1.46-5.07) (S)), and after full matching of cases and controls (OR_{adj} = 2.20 (95% CI: 1.10-4.42) (S)). The estimated risk was somewhat higher after accounting for approximated time of exposure to rosuvastatin (OR_{adj} = 3.08 (95% CI: 1.65-5.73) (S)).
Bayesian analysis showed the effect estimate to be fairly resistant to unmeasured confounding (E-value 4.62).</td><td></td></tr>
<tr><td>ref. 3
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

521TC +CC: AA

388AG: AA</td><td>Meta-analysis investigating the effect of gene variant 521T>C on risk of myopathy. 3 studies with a total number of 4394 patients were included in the meta-analysis for 521T>C and 2 studies with a total number of 842 patients in the meta-analysis for 388A>G. The identity of the included studies is not indicated, except for a reference to the study of Bai 2018 for 521T>C. Studies investigating rosuvastatin and SLCO1B1 scored 6-9 of the 9 points on the Newcastle-Ottawa Scale for study quality.
The only study mentioned to be included in the meta-analyses (Bay 2018 in the meta-analysis for 521C>T) was also included in our risk analysis separately.
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. In addition, Bai 2018 is mentioned as possible cause of the decreased risk found for 521TC, but this study found a 1.7 higher incidence of myopathy in 521TC than in 521TT. This raises the question whether data extraction was correct.
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 rosuvastatin meta-analyses, it is unclear whether publication bias was also assessed for these meta-analyses.

Results:
Myopathy risk compared to homozygous wild-type allele carriers (521TT or 388AA):
<table><tr><td></td><td>heterozygous variant allele carriers</td><td>homozygous variant allele carriers</td></tr><tr><td rowspan="2">521T>C</td><td>OR = 0.82 (95% CI: 0.70-0.95) (S)</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></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>
</table>

<table>
<tr><td>ref. 3, continuation</td><td>388GG: AA</td><td>Presence or absence of heterogeneity between the studies and publication bias were not reported and probably not assessed.</td><td></td></tr>
<tr><td>ref. 4
Zhang D et al. Effects of ABCG2 and SLCO1B1 gene variants on inflammation markers in patients with hypercholesterolemia and diabetes mellitus treated with rosuvastatin. Eur J Clin Pharmacol 2020;76:939-46.
PMID: 32361904.</td><td>3

521TC +CC: A</td><td>269 patients were treated with rosuvastatin 10 mg/day for more than 4 weeks.
Trough plasma concentrations were determined.
Relevant comedication was not excluded.
Logistic regression analysis was performed.

Genotyping:
- 208x 521TT
- 46x 521TC
- 15x 521CC

Results:
<table>
<tr><td colspan="3">Rosuvastatin plasma concentration compared to 521TT (value for 521TT = 8.83 ng/ml):</td></tr>
<tr><td>521TC</td><td>x 1.74</td><td rowspan="2">S</td></tr>
<tr><td>521CC</td><td>x 1.90</td></tr>
</table>
</td><td>Author’s conclusion:
”ABCG2 421C > A (rs2231142) and SLCO1B1 521 T > C (rs4149056) genetic variants affect rosuvastatin concentration significantly.”</td></tr>
<tr><td>ref. 5
Bai X et al. Effects of SLCO1B1 and GATM gene variants on rosuvastatin-induced myopathy are unrelated to high plasma exposure of rosuvastatin and its metabolites. Acta Pharmacol Sin 2019;40:492-99.
PMID: 29950617.</td><td>3

521TC +CC: C

388AG +GG:</td><td>752 patients were treated with rosuvastatin. 87% of patients was treated with an rosuvastatin 10 mg/day, 11% with 20 mg/day and 2% with 5 mg/day.
Myopathy was defined as new and inexplicable muscle-related symptoms, including myalgia, weakness, stiffness, spasms, or twitches (irrespective of creatine kinase values), rhabdomyolysis, and inexplicable creatine kinase elevations of > 4 times the upper limit of normal (irrespective of symptoms).
Relevant comedication was not excluded. For the whole patient group, no significant associations between comedication and myopathy were found.
Analysis of association with (logarithmically transformed) dose-corrected plasma concentrations and myopathy was by linear and univariate logistic regression analysis, respectively. Linear regression analysis adjusted for clinical baseline characteristics showing a significant effect on the dose-corrected concentrations (plasma aspartate aminotransferase levels and concomitant angiotensin-converting enzyme inhibitors for rosuvastatin, creatinine levels for rosuvastatin lactone and age and heart failure for N-desmethylrosuvastatin). The false discovery rate (FDR) due to multiple testing (analysis of 9 variants in 6 genes) was controlled by using the Sas Proc Multtest with the FDR option to correct multiple comparisons in the genetic factors analysis.

Genotyping:
<table>
<tr><td>521T>C</td><td>388A>G</td><td>rs4363657T>C</td></tr>
<tr><td>- 568x TT</td><td>- 46x AA</td><td>- 214x TT</td></tr>
<tr><td>- 130x TC</td><td>- 262x AG</td><td>- 358x TC</td></tr>
<tr><td>- 54x CC</td><td>- 444x GG</td><td>- 180x CC</td></tr>
</table>
Results:
<table>
<tr><td colspan="5">Results compared to homozygous wildtype (521TT, 388AA or rs4363657TT):</td></tr>
<tr><td></td><td>gene variant</td><td>homozygous variant</td><td>heteroozygous variant</td><td>value for homozygous wildtype</td></tr>
<tr><td rowspan="4">% of patients with myopathy</td><td rowspan="2">521T>C</td><td>x 2.71</td><td>x 1.69</td><td rowspan="2">5.46%</td></tr>
<tr><td colspan="2">OR = 1.74 (95% CI: 1.18-2.57) (S)</td></tr>
<tr><td>388A>G</td><td colspan="2">NS</td><td>8.70%</td></tr>
<tr><td>rs43636</td><td colspan="2">NS</td><td>6.54%</td></tr>
</table>
</td><td>Author’s conclusion:
”SLCO1B1 and GATM genetic variants are potential biomarkers for predicting rosuvastatin-induced myopathy, and their effects on rosuvastatin-induced myopathy are unrelated to the high plasma exposure of rosuvastatin and its metabolites.”</td></tr>
</table>

<table>
<tr><td>ref. 5, continuation</td><td>AA

rs4363657TC+CC: AA</td><td>
<table>
<tr><td></td><td>57T>C</td><td colspan="2"></td><td></td></tr>
<tr><td rowspan="2">dose-corrected rosuvastatin plasma concentration (ng/L per mg)</td><td>521T>C</td><td>x 1.12</td><td>x 1.39</td><td>321</td></tr>
<tr><td colspan="3">S for the difference between the genotypes before correction for multiple testing, but NS after correction</td></tr>
<tr><td rowspan="3">dose-corrected rosuvastatin lactone plasma concentration (ng/L per mg)</td><td>388A>G</td><td>NS</td><td>NS</td><td>371</td></tr>
<tr><td>rs4363657T>C</td><td>NS</td><td>NS</td><td>353</td></tr>
<tr><td>521T>C</td><td>NS</td><td>NS</td><td>45</td></tr>
<tr><td rowspan="3">dose-corrected N-desmethyl rosuvastatin plasma concentration (ng/L per mg)</td><td>388A>G</td><td>NS</td><td>NS</td><td>70</td></tr>
<tr><td>rs4363657T>C</td><td>NS</td><td>NS</td><td>52</td></tr>
<tr><td>521T>C</td><td>NS</td><td>NS</td><td>45</td></tr>
<tr><td>388A>G</td><td>NS</td><td>NS</td><td>54</td></tr>
<tr><td>rs4363657T>C</td><td>NS</td><td>NS</td><td>51</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 6
Xiang Q et al. Association between SLCO1B1 T521C polymorphism and risk of statin-induced myopathy: a meta-analysis. Pharmacogenomics J 2018;18:721-9. PubMed PMID: 30250148.</td><td>3

521TC+CC: C

521TC: AA

521CC: AA</td><td>Meta-analysis of studies investigating the effect of gene variant 521T>C on myopathy risk. The number of studies and patients in the rosuvastatin meta-analysis is not stated, nor was the identity of the included studies. The authors mention rosuvastatin as intervention in 2 studies: Danik 2013 (1282 cases and 3122 controls) and 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 2017;73:1409-16 (148 cases and 255 controls), scoring respectively 6 and 7 out of the maximum of 9 points on the Newcastle-Ottawa Scale for study quality. Danik 2013 is also included in our risk analysis separately.
Summary risk differences were calculated based on event numbers in each group in individual studies.
Prospective registration of the meta-analysis protocol was not mentioned, but a random effect model was used for the meta-analysis, so the statistical method could have been 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.
Analysis of publication bias was not performed for rosuvastatin separately. Neither were analyses of heterogeneity between studies and sensitivity.

Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>NS</td><td rowspan="2">OR = 1.69 (95%CI: 1.07-2.67) (S); risk difference = 0.13 (95%CI: 0.01-0.25) (S)</td></tr>
<tr><td>521CC</td><td>NS</td></tr>
</table>
</td><td>Author’s conclusion:
”The findings of this study indicated that SLCO1B1 T521C was associated with a significantly higher risk of statin-induced myopathy, especially for simvastatin, rosuvastatin, and cerivastatin.”</td></tr>
<tr><td>ref. 7
Danik JS et al. Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. Am Heart J</td><td>3</td><td>4399 persons without prior vascular disease or diabetes and with low LDL-cholesterol levels (< 3,4 mmol/L) and elevated C-reactive protein levels (≥ 2 mg/L) were treated with rosuvastatin 20 mg/day for a median of 1.9 years for prevention of first-ever cardiovascular events.
Follow-up was 3 and 6 months after treatment start, followed by every 6 months thereafter.
Adverse events included self-reported symptoms that were categorized using the Medical Dictionary for Regulatory Activities classifications. In case of serious adverse events, investigators were asked to complete a detailed serious adverse event form.
Clinical myalgia occurred at a rate of 4.1 events per 100 persons-</td><td>Author’s conclusion:
”There appears to be no increased risk of myalgia among users of rosuvastatin who carry the rs4363657C or the rs4149056C allele in</td></tr>
</table>

2013;165:1008-14.
PMID: 23708174.

ref. 7, continuation

years (in 9.5% of patients), which did not differ significantly from the rate in 4378 persons on placebo, although there was a trend for an increase (p = 0.09). Muscle weakness, stiffness, or pain occurred at a rate of 9.3 events per 100 persons-years (in 16.9% of patients) and rhabdomyolysis, myopathy, or myositis at a rate of 0.03 per 100 persons-years (in 0.03% of patients), Both rates did not differ from the rates in persons on placebo.
There were no differences across 521T>C and rs4363657 genotypes in the distribution of clinical covariates that have been shown to affect incidence of myopathy with statin use, such as age, gender, body mass index or renal function as measured by creatinine. Immunosuppressants were excluded, but other relevant comedication was not.
Analysis of association with myopathy was by Cox proportional hazard models. Analysis of association with change in LDL-cholesterol was by linear regression. Both analyses assumed an additive relationship between allele dose and clinical outcome.

Genotyping:

521T>C	rs4363657T>C
- 3093x TT	- 2931x TT
- 1185x TC	- 1211x TC
- 121x CC	- 135x CC

Results:

Results compared to homozygous wildtype (521TT or rs4363657TT):

	gene variant	homozygous variant	heteroozygous variant	value for homozygous wildtype
% of patients with myalgia	521T>C	NS	NS	9.7%
		Also NS for homozygous variant versus heterozygous variant versus homozygous wildtype.		
	rs4363657T>C	NS	NS	9.8%
		Also NS for homozygous variant versus heterozygous variant versus homozygous wildtype.		
% of patients with muscle weakness, stiffness, or pain	521T>C	NS	trend for a lower risk (p = 0.06) (NS)	20.3%
		Trend for a lower risk (p = 0.09) (NS) for homozygous variant versus heterozygous variant versus homozygous wildtype.		
	rs4363657T>C	NS	NS	20.4%
		Also NS for homozygous variant versus heterozygous variant versus homozygous wildtype.		
% of patients with rhabdomyolysis, myopathy, or myositis	521T>C	not determined	not determined	0.1%
		None of the C-allele carriers had rhabdomyolysis, myopathy, or myositis.		
	rs4363657T>C	not determined	not determined	0.1%
		None of the C-allele carriers had rhabdomyolysis, myo-		

SLCO1B1."

<table>
<tr><td>ref. 7, continuation</td><td>521CC: A

521TC: A

rs4363657CC: A

rs4363657TC: A</td><td>
<table>
<tr><td></td><td></td><td colspan="2">pathy, or myositis.</td><td></td></tr>
<tr><td rowspan="2">creatine kinase levels</td><td>521T>C</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td>rs4363657T>C</td><td>NS</td><td>NS</td><td></td></tr>
<tr><td rowspan="2">% decrease in LDL-cholesterol in the first 1 year</td><td>521T>C</td><td>x 0.91 (S)</td><td>x 0.97 (S)</td><td>52.1%</td></tr>
<tr><td colspan="3">Also S for homozygous variant versus heterozygous variant versus homozygous wildtype.</td></tr>
<tr><td rowspan="2">rs4363657T>C</td><td>x 0.91 (S)</td><td>x 0.97 (S)</td><td>52.1%</td></tr>
<tr><td colspan="3">Also S for homozygous variant versus heterozygous variant versus homozygous wildtype.</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 8
Bailey KM et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. Circ Cardiovasc Genet 2010;3:276-85. PMID: 20207952.</td><td>3

521TC+CC: AA</td><td>310 patients were treated with rosuvastatin 10 mg/day for 3 months.
Comedication associated with rhabdomyolysis in combination with statins or other concomitant drugs with special warnings or precautions (as per summary of product characteristics for both drugs) were excluded, but comedication affecting SLCO1B1 was not.
Mean age was significantly higher in the 521C allele carriers than in the non-carriers (63.50 versus 61.46 years).
Bonferroni correction for 4 variant genotypes (2 transporters with two genotypes each) was applied.
A power calculation showed the study to have 77.8% power to detect a 10% difference in mean 3-month LDL-cholesterol levels between the 521T>C genotypes..

Genotyping:
- 231x 521TT
- 72x 521TC
- 7x 521CC

Results:
<table>
<tr><td colspan="2">3- month LDL-cholesterol level compared to 521TT (value for 521TT = 1.89 mmol/L):</td></tr>
<tr><td>521TC+CC</td><td>NS</td></tr>
</table>
</td><td>Author’s conclusion:
’There were no differences for patients with variants of CYP-2C9, CYP2C19, or SLCO1B1 in comparison with their respective wild types.’’</td></tr>
<tr><td>ref. 9
Pasanen MK et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82:726-33. PMID: 17473846.</td><td>3

521CC: A

521TC: AA</td><td>32 volunteers received a single dose of 10 mg rosuvastatin.
Co-medication and CYP3A5 expressers were excluded.
On the basis of previous data on the pharmacokinetics of rosuvastatin, the number of subjects in each genotype group was estimated to be sufficient to detect a 50% larger AUC of rosuvastatin in subjects with the 521TC genotype than in those with the 521TT genotype, and a 100% larger AUC in subjects with the 521CC genotype than in those with the 521TT genotype with a power of at least 80%.

Genotyping:
- 16x 521TT
- 12x 521TC
- 4x 521CC.

Results:
<table>
<tr><td colspan="4">Results compared to 521TT:</td></tr>
<tr><td></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td>AUC rosuvastatin</td><td>x 1.62 (S)</td><td>x 1.57 (trend, p = 0.053) (NS)</td><td>35.0 ng/h/ml</td></tr>
<tr><td>$t_{1/2}$ rosuvastatin</td><td>x 0.80 (NS)</td><td>x 0.83 (NS)</td><td>13.7 h</td></tr>
<tr><td colspan="4">Note: The difference in AUC for 521CC compared to 521TT was 1.5 fold higher for atorvastatin (x 2.45) than for rosuvastatin (S). However, this seems to be mainly due to the lack of a clear gene dose effect for rosuvastatin, because the difference in AUC for 521TC compared to 521TT was similar for atorvastatin (x 1.50) and rosuvastatin.</td></tr>
</table>
</td><td>Authors’ conclusion:
“These results indicate that, unexpectedly, SLCO1B1 polymorphism has a larger effect on the AUC of atorvastatin than on the more hydrophilic rosuvastatin.”</td></tr>
</table>

ref. 10 SmPC Crestor (rosuvastatin) 13-10-22.	0 521CC: A	Pharmacokinetics: Pharmacogenetic polymorphism Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, concerns OATP1B1 and BCRP transporter proteins. A risk of higher rosuvastatin exposure is present in patient with SLCO1B1 (AOTP1B1) and/or ABCG2 (BCRP) genetic polymorphisms. Individual polymorphism of SLCO1B1 c.521CC and ABCG2c.421AA is associated with a higher rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC genotypes. This specific genotype has not been clinically established, but a lower daily Crestor dose is recommended for patients known to have these polymorphisms.	
ref. 11 SmPC Crestor (rosuvastatin), USA, 13-01-23.	0 521CC: A	Pharmacokinetics: Pharmacogenomics Disposition of rosuvastatin, involves OATP1B1 and other transporter proteins. Higher plasma concentrations of rosuvastatin have been reported in very small groups of patients (n=3 to 5) who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO-1B1 521T > C). The frequency of this genotype (i.e., SLCO1B1 521 C/C) is generally lower than 5% in most racial/ethnic groups. The impact of this polymorphism on efficacy and/or safety of Crestor has not been clearly established.	

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

Comments:

- For the clinical outcomes, only studies and meta-analyses with more than 300 patients or more than 30 cases were included. The study of Chasman 2012 was not included, because it investigates the effect on LDL-cholesterol lowering in the same patients as Danik 2013. For the kinetic outcomes, only studies repor-ting data per genotype, and with either more than 3 521CC and more than 10 521CT and direct comparison with other statins or with more than 10 521CC and more than 40 521CT were included. Other studies did not add enough to the evidence to be included.
- 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 three single-dose studies, the plasma AUC of rosuvastatin has been 117% higher at a dose of 40 mg/day and 65-72% higher at a dose of 10 mg/day in 521CC than in 521TT (Pasanen 2007; Lee E et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005;78: 330-41; and Choi JH et al. Influence of OATP1B1 genotype on the pharmacokinetics of rosuvastatin in Koreans. Clin Pharmacol Ther 2008;83:251-7). In single-dose studies, the effect of 521T>C on statin pharmacokinetics is third strongest for rosuvastatin 40 mg/day (after simvastatin and atorvastatin) and fourth strongest for rosuvastatin 10 mg/day (after simvastatin, atorvastatin and pravastatin).
  Recommendation per genotype group:

Genotype group	Implications	Recommendation[a]	Classification of recommendation[b]	Considerations
521TC	Typical myopathy risk with doses ≤20 mg. Increased rosuvastatin exposure as compared with normal function.	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry should be evaluated

		possible increased risk for myopathy especially for doses >20 mg.		prior to initiating a statin. The effects of drug-drug interactions may be more pronounced, resulting in a higher risk of myopathy.
521CC	Typical myopathy risk with doses ≤20 mg. Increased rosuvastatin exposure as compared with normal function and 521TC.	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function and Asian ancestry 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.
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: 13 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 rosuvastatin transport from the portal vein to liver cells, where rosuvastatin inhibits cholesterol production, although transport of rosuvastatin by other transporters (SLCO1B3, SLCO2B1, and SLC10A1, and the efflux transporter ABCG2) has been reported. Genetic variations in SLCO1B1 may reduce rosuvastatin transport to the liver and therefore increase rosuvastatin plasma concentrations. Higher rosuvastatin 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.	6-10 +

	Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	

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