# SLCO1B1: simvastatin 4055/4056

AUC = area under the concentration-time curve, BMI = body-mass index, CI = confidence interval, CTCAE = common terminology criteria for adverse events, HDL-cholesterol = high-density lipoprotein cholesterol, HR = 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 variant 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:**
Simvastatin is administered as a prodrug (lactone form). It is converted non-enzymatically and enzymatically in the body to the active metabolite simvastatin acid. The organic anion transporter 1B1 (SLCO1B1) plays an important role in simvastatin acid transport from the portal vein to liver cells, where simvastatin inhibits cholesterol production. Genetic variations in SLCO1B1 may reduce simvastatin acid transport to the liver and therefore increase simvastatin plasma concentrations. Higher simvastatin plasma concentrations increase the risk of myopathy.
Gene variant 521T>C:
All 6 meta-analyses and all 4 studies investigating myopathy risk found the risk to be increased in patients with a SLCO1B1 521C-allele compared to patients without a variant allele (Lu 2021, Turongkaravee 2021, Xiang 2021, Hopewell 2020, Xiang 2018, Jiang 2016, Hou 2015, Carr 2013, Brunham 2012 and SEARCH Collaborative Group 2008). In addition, Lu 2021 found this risk increase to extend to rhabdomyolysis, whereas Hopewell 2020 showed that the risk increase did not extend to muscle symptoms other than myopathy (i.e. pain or weakness but without creatine kinase elevations >10x upper limit of normal). Both studies investigating switch to another statin or early withdrawal from the study found the risk to be increased for patients with or homozygous for the 521C-allele (de Keyser 2014 and Voora 2009).
The only meta-analysis investigating effectiveness, only found a diminished cholesterol reduction in patients with a 521C-allele after exclusion of 1 of the 3 studies in the meta-analysis (Dou 2015). In addition, the size of the effect was small and unlikely to be clinically significant. Of 7 studies investigating effectiveness in patients, 3 found a diminished or slower cholesterol reduction in patients with a 521C-allele, 1 found a diminished cholesterol reduction, but significance disappeared after correction for multiple comparisons, and the other 3 found no effect of 521T>C on cholesterol reduction by simvastatin (Wu 2018, Hopewell 2013, SEARCH Collaborative Group 2008, Kitzmiller2017, Hu 2012, Sortica 2012 and Bailey 2010). All studies that found an effect, either found the effect to be so small that it was unlikely to be clinically relevant or found the effect to be temporary (i.e. a diminished reduction after 4 weeks, but not after 8 weeks of treatment).
Because of the increased myopathy risk, the KNMP Pharmacogenetics Working Group decided that there is a gene-drug interaction and that adjustment of therapy is recommended (yes/yes-interactions). As dose reduction is associated with a risk of reduced effectiveness, an alternative that is influenced to a lesser extent by gene variant 521C>T should be selected. Because the risk increase is modest for 521TC and because the majority of 521C-allele carriers do not develop myopathy, for 521TC it is recommended to try simvastatin at doses lower than the 80 mg dose, which is recommended against due to high myopathy risk in all patients, if an alternative is not possible.
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 might also have access to this background information text via your pharmacy or physician electronic decision support system.
Gene variant 388A>G:
One study found an increase in myopathy risk for patients with the 388G-allele (SEARCH Collaborative Group 2008). However, this increase was borderline significant and there was no study confirming this result.

Of the 5 studies investigating effectiveness, 2 found a diminished cholesterol reduction in patients with the 388G-allele, 1 found a diminished LDL-cholesterol reduction, but significance disappeared after correction for multiple comparisons, and the other 2 found no effect of 388A>G on cholesterol reduction by simvastatin (Wu 2018, SEARCH Collaborative Group 2008, Sortica 2012, Hopewell 2013 and Hu 2012). All studies that found an effect, found the effect to be so small that it was unlikely to be clinically relevant.
There were no studies investigating the effect of 388A>G on simvastatin 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:
One study found no increase in myopathy risk for patients with the 463A-allele (SEARCH Collaborative Group 2008).
Of the two studies investigating effectiveness, one found an increased cholesterol reduction in patients with the 463A-allele and the other found no effect of 463C>A on cholesterol reduction by simvastatin (Hopewell 2013 and Sortica 2012). The size of the effect found by Hopewell 2013 was small and unlikely to be clinically significant.
There were no studies investigating the effect of 463C>A on simvastatin 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 rs4149081G>A, rs12372157T>G and rs35671512C>A:
For rs4149081G>A, one study found an increased cholesterol reduction in patients with the A-allele (Hu 2012). However, the size of the effect was small and unlikely to be clinically significant. In addition, there is strong linkage disequilibrium between 521T>C and rs4149081 in White patients, making an independent contribution of this gene variant unlikely in a predominantly White population like the Dutch population.
For rs12372157T>G, one study found no effect on the cholesterol reduction by simvastatin (Hopewell 2013).
For rs35671512C>A, one study found no effect on simvastatine-induced myopathy (SEARCH Collaborative Group 2008).
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 simvastatin 80 mg/day to be essential for drug tolerance. Genotyping must be performed before drug therapy has been initiated to guide drug selection. The KNMP Pharmacogenetics Working Group considers genotyping before starting simvastatin at a dose of 40 mg/day or lower to be beneficial for drug tolerance. It is advised to genotype the patient before (or directly after) drug therapy has been initiated to guide drug selection.
The clinical implication of the gene-drug interaction scores 7 out of the maximum of 10 points for 80 mg/day and 5 out of the maximum of 10 points for ≤ 40 mg/day (with pre-emptive genotyping considered to be essential for scores ranging from 6 to 10 points and considered to be beneficial for scores ranging from 3-5 points):
The risk of myopathy with creatine kinase ≥10 times the upper limit of normal (code D corresponding to CTCAE grade 3) and the risk of rhabdomyolysis (code E corresponding to CTCAE grade 4) are increased in patients with a genotype resulting in diminished SLCO1B1 activity (521CT and 521CC), both in patients using a mean dose of 30 mg/day (Brunham 2012) and in patients using 80 mg/day (SEARCH Collaborative Group 2008). This results in 1 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 (1 point for CTCAE grade 3 or 4).
The increased risk for serious myopathy (code D-E corresponding to grade 3-4) has been shown in 4 studies (Lu 2021, Hopewell 2020, Brunham 2012 and SEARCH Collaborative Group 2008) and 6 meta-analyses (Turongkaravee 2021, Xiang 2021, Xiang 2018, Jiang 2016, Hou 2015, Carr 2013). This results in the maximum score of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for three or more publications with level of evidence score ≥ 3).
For patients on simvastatin 80 mg/day, SEARCH Collaborative Group 2008 calculated the incidence of less serious and serious myopathy to be 0.6% for 521TT, 3% for 521TC and 18% for 521CC. Considering the proportion of patients with serious myopathy for each of the genotypes in this study, this would amount to 0.25% of 521TT, 1.3% of 521TC and 12% of 521CC with serious myopathy, so an excess risk of approximately 1.1% and 12% for 521TC and 521CC, respectively. The excess risk was calculated because other statins can also induce myopathy, so the myopathy risk does not drop to zero by switching the patient to another statin. Considering the prevalence of 521TC and 521CC in the Dutch population to be approximately 26% and 2.3% (521C-variant frequency of 15%), the percentage of patients with genotype attributable serious myopathy is 0.56%. This corresponds to a number needed to genotype of 178 to prevent one additional case of serious myopathy for patients on simvastatin 80 mg/day. For patients on simvastatin 40 mg/day, the mean myopathy incidence was 0.23% compared to 1.6% for 80 mg/day and the OR for myopathy was 2.6 per C-allele compared to 4.5 per C-allele for 80 mg/day (SEARCH Collaborative Group 2008). Based on the mean myopathy risk, the prevalence of the three

genotypes and the 2.6-fold higher risk per C-allele, this would amount to an incidence of less serious and serious myopathy of 0.15% for 521TT, 0.39% for 521TC and 1% for 521CC. Assuming the same proportion of patients with serious myopathy for 40 mg/day as for 80 mg/day, this would amount to 0.06% of 521TT, 0.17% of 521TC and 0.68% of 521CC with serious myopathy, so an excess risk of approximately 0.09% and 0.62% for 521TC and 521CC, respectively. Considering the prevalence of 521TC and 521CC in the Dutch population, the percentage of patients with genotype attributable serious myopathy is 0.035%. This corresponds to a number needed to genotype of 2860 to prevent one additional case of serious myopathy for patients on simvastatin 40 mg/day. For 80 mg/day, the calculated number needed to genotype of 178 results in 1 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (1 point for 100 < NNG ≤ 1000). For 40 mg/day, the calculated number needed to genotype of 2860 results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3 (only points for NNG ≤ 1000).
The Summary of Product Characteristics (SmPC) of simvastatin indicates that 521TC and 521CC have an increased risk of myopathy. In addition, the SmPC recommends genotyping before starting simvastatin 80 mg/day. For 80 mg/day, this results in the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (2 points for a recommendation to genotype in the SmPC). For ≤ 40 mg/day, 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 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<br>Lu B et al. Effect of SLCO1B1 T521C on statin-related myotoxicity with use of lovastatin and atorvastatin. Clin Pharmacol Ther 2021;110:733-40.<br>PMID: 34114646.</td>
<td>4</td>
<td>82 cases with simvastatin-induced myopathy or rhabdomyolysis were compared to 748 controls matched on age (within 5 years of case age), sex, and simvastatin dose. Only patients with a simvastatin dose ≥ 40 mg/day were selected from the health care database. 43 cases (52%) used a simvastatin dose of 80 mg/day, the other 48% a dose of 40 mg/day. In a secondary analysis, 77 cases with simvastatin-induced rhabdomyolysis were compared to 695 matched controls.<br>Simvastatin-induced myopathy was defined as ≥1 creatine kinase level >5x the upper limit of normal within six months after receiving a simvastatin 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 diagnosis were excluded from analysis. Simvastatin-induced rhabdomyolysis was defined as ≥1 diagnosis of rhabdomyolysis (via ICD-9 (International Classification of Diseases 9th Revision) code) within six months after receiving a simvastatin prescription.<br>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.<br>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.<br><br>Genotyping (myopathy or rhabdomyolysis case-control analysis):<br>cases:<br>- 47x 521TT<br>- 29x 521TC<br>- 6x 521CC<br>controls:<br>- 537x 521TT<br>- 195x 521TC<br>- 16x 521CC<br><br>Results:
<table>
<tr><td colspan="3">Risk compared to 521TT:</td></tr>
<tr><td></td><td>521TC</td><td>521CC</td></tr>
<tr><td>myopathy or</td><td>OR = 1.8 (95% CI:</td><td>OR = 4.6 (95% CI:</td></tr>
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</td>
<td>Author’s conclusion:<br>”We replicated the previously-established association between rs4149056 genotype and simvastatin-induced myotoxicity. In particular, compared to homozygous T allele carriers, there was a significantly increased risk of simvastatin-induced myopathy + rhabdomyolysis in homozygous carriers of the C allele.”</td>
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<tr><td>ref. 1, continuation</td><td>521TC: E<br><br>521CC: E</td><td>
<table>
<tr><td rowspan="4">rhabdomyolysis</td><td>1.08-2.91) (S)</td><td>1.58-11.9) (S)</td></tr>
<tr><td colspan="2">The 521C-allele frequency was higher in cases than in controls (25% versus 15%) (S).</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="3">rhabdomyolysis</td><td>OR = 2.0 (95% CI: 1.20-3.45) (S)</td><td>OR = 4.2 (95% CI: 1.46-10.9) (S)</td></tr>
<tr><td colspan="2">The 521C-allele frequency was higher in cases than in controls (25% versus 15%) (S).</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 2<br>Turongkaravee S et al.<br>A systematic review and meta-analysis of genotype-based and individualized data analysis of SLCO1B1 gene and statin-induced myopathy.<br>Pharmacogenomics J 2021;21:296-307.<br>PMID: 33608664.</td><td>3<br><br>521TC: C<br><br>521CC: C<br><br>521TC +CC: C</td><td>Meta-analysis investigating the effect of gene variant 521T>C on risk of myopathy (defined by muscle weakness after simvastatin use with/without confirming by creatine kinase levels ≥3x the upper limit of normal) in Whites. 5 studies with a total number of 3199 patients (2208x 521TT, 896x 521TC, and 95x 521CC) were included in the meta-analysis. Because the two largest included studies did not report results separately for simvastatin, 899 patients (28%) in the meta-analysis used another statin than simvastatin. Studies were performed in either the United Kingdom (4 studies) or the Netherlands (1 study).<br>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. 3 of the 5 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 5th study had possible/high risk of bias for Hardy-Weinberg equilibrium assessment.<br>Of the 5 publications included in the meta-analysis, 2 were also included in our risk analysis separately (Brunham 2012 and SEARCH Collaborative Group 2008). Of a 3rd publication (Carr 2013), we only included the meta-analysis data.<br>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.<br>Quality of the included studies was judged and reported, but not by a generally accepted study quality scale.<br>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 simvastatin separately.<br><br>Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>OR = 1.78 (95% CI: 1.15-2.77) (S)</td><td rowspan="2">OR = 2.2 (95%CI: 1.2-2.4) (S)</td></tr>
<tr><td>521CC</td><td>OR = 2.81 (95% CI: 1.17-6.77) (S)</td></tr>
<tr><td colspan="3">Heterogeneity between the studies was high for all comparisons. Analysis for all statins suggested mean age, percent of females, and duration of therapy as possible sources of heterogeneity.</td></tr>
<tr><td colspan="3">Funnel plots showed no indication for publication bias.<br>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>
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<tr><td>ref. 3<br>Xiang Q et al.<br>Correlation between single-nucleotide polymorphisms and</td><td>3</td><td>Meta-analysis investigating the effect of gene variant 521T>C on risk of myopathy. 4 studies with a total number of 573 patients were included in the meta-analysis. The identity of the included studies is not indicated. Studies investigating simvastatin and SLCO1B1 scored 7-9 of the 9 points on the Newcastle-Ottawa Scale for study quality.</td><td>Author’s conclusion:<br>”An increased risk of statin-induced myopathy was predicted</td></tr>
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<td>statin-induced myopathy: a mixed-effects model meta-analysis.<br>Eur J Clin Pharmacol 2021;77:569-81.<br>PMID: 33150478.<br><br>ref. 3, continuation</td>
<td>521TC: D<br><br>521CC: D<br><br>521TC +CC: D</td>
<td>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.<br>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.<br>According to the methods section, publication bias was assessed by Egger’s and Begg’s test. However, since no results are mentioned for the simvastatin meta-analysis, it is unclear whether publication bias was also assessed for this meta-analysis.<br><br>Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>OR = 2.80 (95% CI: 1.81-4.31) (S)</td><td rowspan="2">OR = 3.10 (95%CI: 2.11-4.55) (S)</td></tr>
<tr><td>521CC</td><td>OR = 9.27 (95% CI: 4.04-21.22) (S)</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>
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<td>for carriers of the rs4149056 C allele among simvastatin-treated patients.”</td>
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<td>ref. 4<br>Hopewell JC et al.<br>Independent risk factors for simvastatin-related myopathy and relevance to different types of muscle symptom.<br>Eur Heart J 2020;41:3336-42.<br>PMID: 32702748.</td>
<td>3</td>
<td>130 cases with simvastatin-induced myopathy were compared to 9109 non-matched controls (the study population included all genotyped patients). Data on muscle symptoms other than myopathy (i.e. pain or weakness but without creatine kinase elevations >10x upper limit of normal) were available for 9109 patients (3035 cases and 6074 controls). Patients were derived from three large trial populations: 8538 UK patients from the Heart Protection Study (HPS) trial allocated 40 mg simvastatin daily for ~5 years, 167 UK patients from the SEARCH trial allocated simvastatin 80 mg daily for ~7 years, and 534 Chinese patients from the HPS2-THRIVE trial given simvastatin 40 mg daily (and randomly allocated niacin-laropiprant or matching placebo) for ~4 years: This indicates that the patient group in this study overlaps with both the patient group in Hopewell 2013 (Heart Protection Study, myopathy risk not investigated) and that in SEARCH Collaborative Group 2008 (myopathy investigated for the SEARCH patients in the case-control study and the Heart Protection Study patients in the replication study).<br>Scheduled follow-up visits were conducted at least 6-monthly after initiation of simvastatin and additional visits conducted when patients reported muscle symptoms. At each visit, participants were asked a directed question about any new unexplained muscle pain or weakness and alanine transaminase (ALT) was measured. Creatine kinase was measured: if muscle symptoms were reported in HPS; at each follow-up visit irrespective of symptoms in SEARCH; and if muscle symptoms were reported or routinely measured ALT was >1.5x upper limit of normal in HPS2-THRIVE.<br>Myopathy was defined as unexplained muscle pain or weakness with creatine kinase >10x upper limit of normal (within 28 days). The rate of myopathy was low: 9 per 10 000 person-years of simvastatin therapy in the 3 trials (1 per 10 000 person-years for Europeans on simvastatin 20 mg/day, 2 per 10 000 person-years for Europeans on simvastatin 40 mg/day. 13 per 10 000 person-years for Europeans on simvastatin 80 mg/day, and 26 per 10 000 person-years for Chinese on simvastatin 40 mg/day). The mean time from initiation of study simvastatin to myopathy was 18 months, with 36% of cases occurring in the first 6 months of treatment. The rate of myopathy per 10 000 person-years was 19 in the first year of treatment versus 5 in later years (mean treatment period 3.4 years). The rate of rhabdomyolysis was 0.7 per 10 000 person-years. Muscle symptoms other than myopathy (i.e. pain or weakness but without creatine kinase elevations >10x upper limit of normal) were very common, occurring at least</td>
<td>Author’s conclusion:<br>”Although SLCO1B1 genotype was associated with myopathy, it was not associated with other muscle symptoms.”</td>
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<td>ref. 4, continuation</td>
<td>521TC + 521CC: D<br><br>521TC: D</td>
<td>once during follow-up in 26% of patients, with an overall rate of 981 events per 10 000 person-years (the rate was similar for different simvastatin doses and ethnicities).<br>Comedication with amiodarone was excluded, other relevant comedication was not.<br>Associations of 521T>C genotype with myopathy were estimated using logistic regression models adjusted for ethnicity and simvastatin dose.<br><br>Genotyping (myopathy case-control analysis):<br>cases: - 69x 521TT - 43x 521TC - 18x 521CC<br>controls: - 6603x 521TT - 2306x 521TC - 200x 521CC<br><br>Results:
<table>
<tr><td colspan="3">Risk for 521TC+521CC to 521TT:</td></tr>
<tr><td></td><td>ethnicity and simvastatin dose</td><td></td></tr>
<tr><td rowspan="6">myopathy</td><td rowspan="2">all participants, 40 or 80 mg</td><td>$OR_{adj}$ = 3.10 (95% CI: 2.09-4.59) (S)</td></tr>
<tr><td>$OR_{adj}$ per C-allele (I.e. compared to T-allele) was 2.94 (95% CI: 2.15-4.03) (S)</td></tr>
<tr><td>European, 40 mg</td><td>NS</td></tr>
<tr><td>European, 80 mg</td><td>OR = 6.03 (95% CI: 2.73-13.94) (S)</td></tr>
<tr><td>Chinese, 40 mg</td><td>OR = 2.47 (95% CI: 1.52-4.00) (S)</td></tr>
<tr><td colspan="2">Note: The authors indicate that the association was consistent in Chinese and European patients (p for heterogeneity = 0.75), probably because the value of the non-significant OR for Europeans receiving 40 mg/day was 2.58.</td></tr>
<tr><td rowspan="4">muscle symptoms other than myopathy</td><td>all participants</td><td>NS</td></tr>
<tr><td>European, 40 mg</td><td>NS</td></tr>
<tr><td>European, 80 mg</td><td>NS</td></tr>
<tr><td>Chinese, 40 mg</td><td>NS</td></tr>
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<tr>
<td>ref. 5<br>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</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 simvastatin meta-analysis is not stated, nor was the identity of the included studies. The authors mention simvastatin as intervention in 2 studies: SEARCH Collaborative Group 2008 (85 cases and 90 controls) and Hubáček JA et al. SLCO1B1 polymorphism is not associated with risk of statin-induced myalgia/myopathy in a Czech population. Med Sci Monit 2015;21:1454-9. PubMed PMID: 25992810 (286 cases and 707 controls), scoring respectively 9 and 7 out of the maximum of 9 points on the Newcastle-Ottawa Scale for study quality. SEARCH Collaborative Group 2008 is also included in our risk analysis separately. Hubáček 2015 is not included in our risk analysis, because only 41% of patients received simvastatin (59% received atorvastatin) and results were not investigated for simvastatin separately. So, the statement of Xiang et al. that Hubáček 2015 concerns a simvastatin intervention is wrong.<br>Of the 2 studies known to be included in this meta-analysis, 1 was also included in the meta-analysis of Turongkaravee 2021 (SEARCH Collaborative Group 2008).<br>Summary risk differences were calculated based on event numbers in</td>
<td>Author’s conclusion:<br>”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>
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<td>ref. 5, continuation</td>
<td>521TC +CC: D<br><br>521TC: AA<br><br>521CC: AA</td>
<td>each group in individual studies.<br>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.<br>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.<br>Analysis of publication bias was not performed for simvastatin separately. Neither were analyses of heterogeneity between studies and sensitivity.<br><br>Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>trend for an increased risk (p = 0.055) (NS)</td><td rowspan="2">OR = 2.35 (95%CI: 1.08-5.12) (S);<br>risk difference = 0.17 (95%CI: 0.01-0.33) (S)</td></tr>
<tr><td>521CC</td><td>NS</td></tr>
<tr><td colspan="3">There was a trend for an increased risk for the 521C-allele compared to the 521T-allele (p = 0.099) (NS).</td></tr>
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<td>ref. 6<br>Wu X et al. Associations of the SLCO1B1 polymorphisms with hepatic function, baseline lipid levels, and lipid-lowering response to simvastatin in patients with hyperlipidemia. Clin Appl Thromb Hemost 2018;24:240S-247S.<br>PubMed PMID: 30336686.</td>
<td>4<br><br>521CC: B<br><br>521TC: A<br><br>388GG: A</td>
<td>542 patients were treated with simvastatin 20 mg/day for 8 weeks.<br>Co-medication that could lower plasma lipid levels or otherwise affect the blood lipid profile was excluded from at least 1 week prior to the study. SLCO1B1-inhibitors before the study were not excluded, but the study was preceded by a washout period of 7 to 10 days.<br>Lipid levels results were adjusted for BMI, age, alcohol consumption and smoking. Creatine kinase levels results were adjusted for sex, BMI, age, alcohol consumption and smoking.<br><br>Genotyping:<br>521T>C:<br>- 425x TT<br>- 113x TC<br>- 4x CC<br><br>388A>G:<br>- 47x AA<br>- 212x AG<br>- 283x GG<br><br>Results:
<table>
<tr><td colspan="5">Changes in lipid and creatine kinase levels compared to 521TT:</td></tr>
<tr><td></td><td>treatment period</td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td>total cholesterol</td><td>4 weeks</td><td>x 0.68 (S)</td><td>x 0.94 (S)</td><td>-31.9%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-30.2%</td></tr>
<tr><td>LDL-cholesterol</td><td>4 weeks</td><td>trend for a smaller change (p = 0.06) (NS)</td><td>x 0.93 (S)</td><td>-41.2%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-35.9%</td></tr>
<tr><td>triglycerides</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-22.8%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-20.7%</td></tr>
<tr><td>HDL-cholesterol</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-10.1%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-13.8%</td></tr>
<tr><td>creatine kinase</td><td>4 weeks</td><td>NS</td><td>NS</td><td>+26.8%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>+62.8%</td></tr>
</table>
<table>
<tr><td colspan="5">Changes in lipid and creatine kinase levels compared to 388AA:</td></tr>
<tr><td></td><td>treatment period</td><td>388GG</td><td>388AG</td><td>value for 388AA</td></tr>
<tr><td>total cholesterol</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-31.6%</td></tr>
<tr><td></td><td>8 weeks</td><td>x 0.91 (S)</td><td>NS</td><td>-32.4%</td></tr>
</table>
</td>
<td>Author’s conclusion:<br>”Our conclusion suggests that the interaction between the SLCO1B1 388A>G and 521T>C polymorphisms could be an important genetic determinant of hepatic function and the therapeutic efficiency of simvastatin in Chinese patients with hyperlipidemia.”</td>
</tr>
</table>

<table>
<tr><td>ref. 6, continuation</td><td>388AG: AA</td><td>
<table>
<tr><td>LDL-cholesterol</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-39.5%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-36.4%</td></tr>
<tr><td>triglycerides</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-24.7%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>-25.9%</td></tr>
<tr><td>HDL-cholesterol</td><td>4 weeks</td><td>NS</td><td>NS</td><td>-10.2%</td></tr>
<tr><td></td><td>8 weeks</td><td>trend for a smaller change (p = 0.079) (NS)</td><td>trend for a smaller change (p < 0.074) (NS)</td><td>-18.1%</td></tr>
<tr><td>creatine kinase</td><td>4 weeks</td><td>NS</td><td>NS</td><td>+17.0%</td></tr>
<tr><td></td><td>8 weeks</td><td>NS</td><td>NS</td><td>+77.2%</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 7<br>Kitzmiller JP et al.<br>Candidate-gene study of functional polymorphisms in SLCO1B1 and CYP3A4/5 and the cholesterol-lowering response to simvastatin.<br>Clin Transl Sci 2017;10:172-7.<br>PubMed PMID: 28482130.</td><td>4<br><br>521CC: AA<br><br>521TC: AA</td><td>
883 patients, 592 White and 291 Black, were treated with simvastatin 40 mg/day for 6 weeks.<br>
Co-medication known to alter cholesterol levels or simvastatin pharmacokinetics was excluded. Compliance was determined by pill counts.<br>
Regression analyses, adjusting for age, smoking status, genetic ancestry and self-reported race (when applicable), were used to detect associations. Adjustments for multiple comparisons were made using the Benjamini and Hochberg’s linear step-up method, limiting the false discovery rate to 5%.<br>
The authors estimated 80% power to detect an 8% difference by SLCO1B1 genotype in unadjusted models.<br><br>
Genotyping:<br>
White:<br>- 441x 521TT<br>- 137x 521TC<br>- 14x 521CC<br>
Black:<br>- 277x 521TT<br>- 14x 521TC<br><br>
Results:
<table>
<tr><td colspan="5">Changes in lipid levels compared to 521TT:</td></tr>
<tr><td></td><td></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td rowspan="3">total cholesterol</td><td>all</td><td>x 0.74</td><td>x 1.00</td><td rowspan="2">-58 mg/dL</td></tr>
<tr><td colspan="2">S for 521CC versus 521CT versus 521TT, but NS after correction for multiple comparisons</td></tr>
<tr><td>White</td><td>x 0.72</td><td>x 0.95</td><td rowspan="2">-60 mg/dL</td></tr>
<tr><td colspan="2">S for 521CC versus 521CT versus 521TT, but only a trend after correction for multiple comparisons (p = 0.107) (NS)</td></tr>
<tr><td></td><td>Black</td><td>-</td><td>NS</td><td>-54 mg/dL</td></tr>
<tr><td rowspan="4">LDL-cholesterol</td><td>all</td><td colspan="2">trend for a smaller change with increasing number of 521C variants (p = 0.103) (NS), but NS after correction for multiple comparisons</td><td>-55 mg/dL</td></tr>
<tr><td>White</td><td>x 0.77</td><td>x 0.96</td><td rowspan="2">-57 mg/dL</td></tr>
<tr><td colspan="2">S for 521CC versus 521CT versus 521TT, but NS after correction for multiple comparisons</td></tr>
<tr><td>Black</td><td>-</td><td>NS</td><td>-51 mg/dL</td></tr>
<tr><td colspan="5">Race-gene interactions were not statistically significant.</td></tr>
</table>
</td><td>Author’s conclusion:<br>”SLCO1B1 521C resulted in a diminished cholesterol-lowering response, but a marginal effect size limits utility for predicting simvastatin response.”</td></tr>
<tr><td>ref. 8<br>Jiang J et al.<br>Association between</td><td>4</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 2520 patients (597 with and 1923 without myopathy) were included in the meta-analysis. 3 of the included studies</td><td>Author’s conclusion:<br>”The meta-analysis suggests that</td></tr>
</table>

<table>
<tr>
<td>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.<br><br>ref. 8, continuation</td>
<td>521TC: AA<br><br>521CC: D<br><br>521TC +CC: D</td>
<td>were cohort studies and the other three were case-control studies. All studies included mainly White patients. For TC versus TT and CC versus TT 5 studies with a total of 2362 patients were included, for TC+CC versus TT 4 studies with a total of 665 patients, and for CC versus TC versus TT and for the C- versus the T-allele 3 studies with a total of 507 patients were included. The included studies scored 7-9 of the maximum of 9 points on the Newcastle-Ottawa Quality scale. Except for Voora 2009, follow-up in the included studies was at least 1 year.<br>Of the 5 publications included in the meta-analysis, 3 were also included in the meta-analysis of Turongkaravee 2021 (Carr 2013, Brunham 2012, and SEARCH Collaborative Group 2008) and 1 was also included in the meta-analysis of Xiang 2018 (SEARCH Collaborative Group 2008).<br>Of the 5 publications included in the meta-analysis, 4 were also included in our risk analysis separately (De Keyser 2014, Brunham 2012, Voora 2009, and SEARCH Collaborative Group 2008). Of the 5th publication (Carr 2013), we only included the meta-analysis data.<br>The effect estimates (OR or HR) of the studies were pooled. If available, adjusted effect estimates were used.<br>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.<br>Publication bias was assessed by Begg’s and Egger’s test.<br><br>Results:
<table>
<tr><td colspan="3">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC</td><td>NS</td><td rowspan="3">OR = 3.43 (95% CI: 1.80-6.52) (S) for TC+CC versus TT.<br>OR = 2.87 per C-allele (95% CI: 1.67-4.94) (S) for CC versus CT versus TT.</td></tr>
<tr><td rowspan="2">521CC</td><td>pooled effect estimate (OR or HR) = 3.62 (95% CI: 1.33-9.83) (S)</td></tr>
<tr><td>Significance was lost when Carr 2013 was excluded from the meta-analysis (trend for an increase in the pooled effect estimate, p = 0.059, NS).</td></tr>
<tr><td colspan="3">There was an increased risk for the 521C-allele compared to the 521T-allele (OR = 3.00 (95% CI: 1.39-6.48) (S)).</td></tr>
<tr><td colspan="3">For all comparisons, there was significant heterogeneity between the studies.</td></tr>
<tr><td colspan="3">For all comparisons, there were no indications of publication bias.</td></tr>
</table></td>
<td>SLCO1B1 − 521T>C polymorphism may be a risk factor for statin-induced ADRs, especially in simvastatin therapy. Conversely, there may be no significant association for − 388A>G polymorphism.”</td>
</tr>
<tr>
<td>ref. 9<br>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 699 patients (190 cases and 509 controls) were included in the meta-analysis. For the comparison of the C- with the T-allele 3 studies with a total of 507 patients (156 cases and 351 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.<br>All 4 studies included in the meta-analysis, were also included in the meta-analysis of Jiang 2016, 3 in the meta-analysis of Turongkaravee 2021 (Carr 2013, Brunham 2012, and SEARCH Collaborative Group 2008), and 1 in the meta-analysis of Xiang 2018 (SEARCH Collaborative Group 2008).<br>Of the 4 studies included in the meta-analysis, 3 were also included in our risk analysis separately (Brunham 2012, Voora 2009, and SEARCH Collaborative Group 2008). Of the 4th publication (Carr 2013), we only included the meta-analysis data.</td>
<td>Author’s conclusion:<br>”The available evidence suggests that SLCO1B1 gene T521C polymorphism is associated with an increased risk of statin-related myopathy, especially in individuals receiving simvastatin. Thus, a genetic test before initiation of statins</td>
</tr>
</table>

<table>
<tr><td>ref. 9, continuation</td><td>521TC +CC: D</td><td>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.<br>Analysis of publication bias was not performed for simvastatin. Neither was sensitivity analysis.<br><br>Results:<table><tr><td colspan="2">Myopathy risk compared to 521TT:</td></tr><tr><td>521TC+CC</td><td>OR = 3.09 (95% CI: 1.64-5.85) (S)</td></tr><tr><td colspan="2">There was an increased risk for the 521C-allele compared to the 521T-allele (OR = 3.00 (95% CI: 1.38-6.49) (S)).</td></tr><tr><td colspan="2">For both comparisons, there was significant heterogeneity between the studies.</td></tr></table></td><td>may be meaningful for personalizing the treatment.”</td></tr>
<tr><td>ref. 10<br>Luzum JA et al. Individual and combined associations of genetic variants in CYP3A4, CYP3A5, and SLCO1B1 with simvastatin and simvastatin acid plasma concentrations. J Cardiovasc Pharmacol 2015;66:80-5. PubMed PMID: 26164721.</td><td>4<br><br>521CC: A<br><br>521TC: A</td><td>646 patients, 447 White and 199 Black, were treated with simvastatin 40 mg/day for 6 weeks. For the comparison for all patients, only 562 patients, approximately 447 White and 115 Black, were analysed. The 646 patients in this study were a subgroup of the patients in Kitzmiller 2017. Not included patients (missing data or plasma concentrations below or above the quantitative ranges) did not significantly differ from included patients.<br>Co-medication known to alter cholesterol levels or simvastatin pharmacokinetics was excluded. Compliance was determined by pill counts.<br>Results were adjusted for age, gender, self-reported race, smoking status, body mass index (kg/m$^2$), compliance (percentage of doses taken during the two weeks leading up to when the blood sample was drawn), genetic ancestry, and CYP3A4 and CYP3A5 genotype combinations. The level of statistical significance was adjusted for multiple comparisons (5 comparisons) with Bonferroni correction, yielding a p-value for significance of ≤ 0.1/5 = 0.02.<br>The authors estimated ≥ 80% power to detect a 25% difference in simvastatin and simvastatin acid for all comparisons after Bonferroni correction.<br><br>Genotyping:<br>- 437x 521TT<br>- 115x 521TC<br>- 10x 521CC (all White)<br><br>Results:<table><tr><td colspan="5">Plasma concentration 12 hours after dosing compared to 521TT:</td></tr><tr><td></td><td></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr><tr><td rowspan="3">simvastatin acid</td><td>all</td><td>x 3.48 (S)</td><td>x 1.71 (S)</td><td>appr. 1.3 ng/ml</td></tr><tr><td>White</td><td>x 3.51 (S)</td><td>x 1.67 (S)</td><td></td></tr><tr><td>Black</td><td>-</td><td>NS</td><td></td></tr><tr><td rowspan="3">simvastatin</td><td>all</td><td>NS</td><td>NS</td><td></td></tr><tr><td>White</td><td>NS</td><td>NS</td><td></td></tr><tr><td>Black</td><td>-</td><td>NS</td><td></td></tr><tr><td colspan="5">Race-gene interactions were not statistically significant, although a trend for difference between White and Black patients was observed for simvastatin acid for 521TC compared to 521TT (p = 0.086; NS).</td></tr></table></td><td>Author’s conclusion:<br>”CYP3A4*22 and SLCO1B1 521C were significantly associated with increased plasma 12-hour concentrations of simvastatin and simvastatin acid, respectively.”</td></tr>
<tr><td>ref. 11<br>Dou Y et al. Meta-analysis</td><td>3</td><td>Meta-analysis of studies investigating the effect of gene variant 521T>C on LDL-cholesterol lowering. 3 studies with a total number of 681 patients (475x 521TT, 187x 521TC, and 19x 521CC) were inclu-</td><td>Author’s conclusion:<br>”No significant</td></tr>
</table>

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<tr>
<td>of the SLCO1B1 c.521T>C variant reveals slight influence on the lipid-lowering efficacy of statins. Ann Lab Med 2015;35:329-35.<br>PubMed PMID: 25932441.<br><br>ref. 11, continuation</td>
<td>521TC +CC: A</td>
<td>ded in the meta-analysis. Studies were performed in either the United Kingdom, Brazil or China. After exclusion of Bailey 2010, the total number of patients in the meta-analysis was 390 (275x 521TT, 105x 521TC, and 10x 521CC).<br>Of the 3 publications included in the meta-analysis, 2 were also included in our risk analysis separately (Sortica 2012 and Bailey 2010).<br>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 or absent heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent. The data extraction was standardised, but data extracted from Bailey 2010 were wrong. Instead of a decrease in LDL-cholesterol with 79.52% for 521TT and 77.77% for 521TC+CC as reported by Dou 2015, the decrease was 27.11% for 521TT and 23.90% for 521TC+CC according to the data in Bailey 2010. This raises the question whether the data used for the meta-analysis were right.<br>Quality of the included studies was assessed with the Newcastle-Ottawa Scale, but was not reported.<br>Publication bias analysis was not performed for simvastatin.<br><br>Results:
<table>
<tr><td colspan="3">Standard mean difference in the decrease in LDL-cholesterol compared to 521TT:</td></tr>
<tr><td rowspan="2">521TC+CC</td><td>all 3 studies</td><td>NS</td></tr>
<tr><td>Bailey 2010 excluded</td><td>-0.26 (95% CI: -0.47 - -0.05) (S)</td></tr>
<tr><td colspan="3">Bailey 2010 was excluded from the meta-analysis due to a difference in evaluation standards.</td></tr>
<tr><td colspan="3">For both comparisons, there was no significant heterogeneity between the studies, with heterogeneity being absent after exclusion of Bailey 2010.</td></tr>
</table>
</td>
<td>association was detected between the lipid-lowering efficacy of statins and the SLCO1B1 c.521 T>C polymorphism, with the exception of simvastatin.”</td>
</tr>
<tr>
<td>ref. 12<br>de Keyser CE et al.<br>The SLCO1B1 c.521T>C polymorphism is associated with dose decrease or switching during statin therapy in the Rotterdam Study.<br>Pharmacogenet Genomics 2014;24:43-51.<br>PubMed PMID: 24263182.</td>
<td>3</td>
<td>1462 patients from a population-based cohort, aged 55 years or older (mean 70.6 years), and 393 patients with hypercholesterolemia and/or hypertension from a myocardial infarction case-control study were treated with simvastatin. Follow-up started at the date of first simvastatin 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 of both groups.<br>In the largest group, the dose was decreased in 13% of patients, and a switch to another cholesterol-lowering drug was performed for 9% of patients. In the smallest group, this was 16% and 6%, respectively.<br>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.<br>Relevant co-medication was not excluded.<br>Hazard ratios were adjusted for age, sex, and starting dose.<br>The authors estimated a power of 100.0% to find an HR of 2.0 and a power of 87.8% to find an HR of 1.5 in the largest group, and a power of 83.3% and 44.5%, respectively, in the smallest group.<br><br>Genotyping:<br>Largest group:<br>- 1058x 521TT<br>- 361x 521TC<br>- 43x 521CC<br><br>Smallest group:<br>- 286x 521TT<br>- 99x 521TC<br>- 8x 521CC<br><br>Results:</td>
<td>Author’s conclusion:<br>”In simvastatin users in the Rotterdam Study, we demonstrated an association between the c.521T >C polymorphism and dose decrease or switching, as indicators of adverse drug reactions.”</td>
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<tr>
<td>ref. 12, continuation</td>
<td>521CC: C<br><br>521TC: AA#</td>
<td>
Risk of dose decrease of switch to another cholesterol-lowering drug compared to 521TT:
<table>
<tr><td colspan="2"></td><td>521CC</td><td>521TC</td></tr>
<tr><td rowspan="7">largest group</td><td>all</td><td>HR = 1.74 (95% CI: 1.05-2.88) (S)</td><td>trend for a decrease (p = 0.065) (NS)</td></tr>
<tr><td>men</td><td>NS</td><td></td></tr>
<tr><td>women</td><td>HR = 2.18 (95% CI: 1.20-3.96) (S)</td><td></td></tr>
<tr><td>starting dose ≤ 20 mg/day</td><td>HR = 1.83 (95% CI: 1.06-3.16) (S)</td><td></td></tr>
<tr><td>starting dose > 20 mg/day</td><td>NS</td><td></td></tr>
<tr><td>< 70 years</td><td>HR = 2.14 (95% CI: 1.18-3.88) (S)</td><td></td></tr>
<tr><td>≥ 70 years</td><td>NS</td><td></td></tr>
<tr><td colspan="2">smallest group</td><td>NS</td><td>NS</td></tr>
<tr><td colspan="2">meta-analysis of both groups</td><td>HR = 1.69 (95% CI: 1.05-2.73) (S)</td><td>HR = 0.76 (95% CI: 0.60-0.98) (S)</td></tr>
</table>
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<td></td>
</tr>
<tr>
<td>ref. 13<br>Carr DF et al.<br>SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the Clinical Practice Research Datalink.<br>Clin Pharmacol Ther 2013;94:695-701.<br>PubMed PMID: 23942138.</td>
<td>3<br><br>521TC +CC: D</td>
<td>
59 patients with myopathy (simvastatin discontinuation due to serum creatine kinase > 4x upper limit of normal) were compared to 222 patients receiving simvastatin for at least 3 months without above normal serum creatine kinase measurements.<br>
A meta-analysis was performed of the study above and 3 other studies investigating the effect of gene variant 521T>C on myopathy. All 4 studies included in the meta-analysis, were also included in the meta-analyses of Jiang 2016 and Hou 2015, 3 in the meta-analysis of Turongkaravee 2021 (Carr 2013, Brunham 2012, and SEARCH Collaborative Group 2008), and 1 in the meta-analysis of Xiang 2018 (SEARCH Collaborative Group 2008).<br>
All 3 other studies in the meta-analysis were also included in our risk analysis separately (Brunham 2012, Voora 2009, and SEARCH Collaborative Group 2008).<br>
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.<br>
Analysis of study quality and publication bias was not performed.<br><br>
Results:
<table>
<tr><td colspan="2">Myopathy risk compared to 521TT:</td></tr>
<tr><td>521TC+CC</td><td>OR = 3.25 (95% CI: 1.72-6.12) (S)</td></tr>
</table>
</td>
<td>Author's conclusion:<br>"Meta-analysis showed an association between c.521C>T and simvastatin-induced myopathy, although power for other statins was limited. Our data replicate the association of SLCO1B1 variants with statin-induced myopathy."</td>
</tr>
<tr>
<td>ref. 14<br>Hopewell JC et al.<br>Impact of common genetic variation on response to simvastatin therapy among 18 705 participants in the Heart Protection Study.<br>Eur Heart J 2013;34:982-92.<br>PubMed PMID: 23100282.</td>
<td>3</td>
<td>
18,357 patients with non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L and either a previous diagnosis of coronary disease, ischaemic stroke, other occlusive disease of non-coronary arteries, diabetes mellitus, or (if men 65 years or older) treated hypertension, were treated with simvastatin 40 mg/day for 4-6 weeks, followed by randomisation to simvastatin 40 mg/day (n = 6021) or placebo (n = 6046) for 5 years. Non-compliant patients were excluded. This is the same patient group as that in the replication study in SEARCH Collaborative Group 2008.<br>
The number of patients with genotyping data was 16,867 for 521T>C, 16,369 for 388A>G, 14,338 for 463C>A, and 18,357 for rs12372157 T>G.<br>
Treatment for 4-6 weeks resulted in a 42.4% reduction in LDL-cholesterol and a 32.8% reduction in apolipoprotein B, corresponding to an absolute reduction in LDL-cholesterol of 1.39 mmol/L and in apolipoprotein B of 0.37 g/L (baseline levels 3.37 mmol/L and 1.14 g/L, respectively). Random allocation to simvastatin 40 mg/day reduced the proportional 5-year risk of major vascular events by 23.3% and the absolute risk by 5.2%. 20% of patients in the simvastatin group had a
</td>
<td>Author's conclusion:<br>"Common genetic variants do not appear to alter the lipid response to statin therapy by more than a few per cent, and there were similar large reductions in vascular risk with simvastatin irrespective of genotypes associated with the lipid response to simvastatin.</td>
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<tr>
<td>ref. 14, continuation</td>
<td>521CT +CC: A<br><br>388GA +GG: AA<br><br>463CA +AA: AA#<br><br>rs12372157 TG+GG : AA</td>
<td>major vascular event.<br>Major vascular event was defined as either non-fatal myocardial infarction or coronary death, coronary or non-coronary revascularisations, or any stroke.<br>Relevant co-medication was not excluded.<br>None of the gene variants had an effect on baseline levels of LDL-cholesterol and apolipoprotein B.<br>The authors estimated a power of 90% power to detect differences of 1% in LDL-C response (e.g. 41 vs. 40% reduction) at P < 0.001 in gene variants with at least a 15% minor allele frequency.<br><br>Genotyping (estimated based on gene variant frequencies):<br>521T>C: - 12186x TT - 4301x TC - 380x CC<br>388A>G: - 6091x AA - 7788x AG - 2490x GG<br>463C>A: - 10117x CC - 3854x CA - 367x AA<br>rs12372157 T>G: - 6390x TT - 8881x TG - 3086 GG<br><br>Results:
<table>
<tr><td colspan="3">Results per variant allele:</td></tr>
<tr><td rowspan="4">additional % reduction in LDL-cholesterol</td><td>521C</td><td>-1.15 (95% CI: -1.57 - -0.74) (S)</td></tr>
<tr><td>388G</td><td>NS</td></tr>
<tr><td>463A</td><td>0.92 (95% CI: 0.49-1.34) (S)</td></tr>
<tr><td>rs12372157G</td><td>NS</td></tr>
<tr><td rowspan="4">additional absolute reduction in LDL-cholesterol (in mmol/L)</td><td>521C</td><td>-0.028 (S)</td></tr>
<tr><td>388G</td><td>NS</td></tr>
<tr><td>463A</td><td>0.041 (S)</td></tr>
<tr><td>rs12372157G</td><td>NS</td></tr>
<tr><td rowspan="4">additional % reduction in apolipoprotein B</td><td>521C</td><td>-0.96 (95% CI: -1.31 - -0.60) (S)</td></tr>
<tr><td>388G</td><td>NS</td></tr>
<tr><td>463A</td><td>0.66 (95% CI: 0.29-1.02) (S)</td></tr>
<tr><td>rs12372157G</td><td>NS</td></tr>
<tr><td rowspan="4">additional absolute reduction in apolipoprotein B (in g/L)</td><td>521C</td><td>-0.009 (S)</td></tr>
<tr><td>388G</td><td>NS</td></tr>
<tr><td>463A</td><td>0.009 (S)</td></tr>
<tr><td>rs12372157G</td><td>NS</td></tr>
<tr><td>% risk reduction in major vascular events</td><td>combination of all 4 gene variations</td><td>NS</td></tr>
<tr><td>absolute risk reduction in major vascular events (in %)</td><td>combination of all 4 gene variations</td><td>NS</td></tr>
<tr><td colspan="3">The authors indicated that all four gene variants contributed independent information.</td></tr>
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</td>
<td>Consequently, their value for informing clinical decisions related to maximizing statin efficacy appears to be limited.”</td>
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<tr>
<td>ref. 15<br>Hu M et al. Intronic variants in SLCO1B1 related to statin-induced myopathy are associated with the low-density lipoprotein cholesterol response to statins in Chinese patients with hyperlipidaemia.</td>
<td>3<br><br>521TC: AA<br>521CC: AA<br><br>388AG: AA</td>
<td>247 Chinese patients with coronary heart disease or a high risk of coronary heart disease used simvastatin 40 mg/day for at least 4 weeks. 140 patients had heterozygous familial hypercholesterolaemia.<br>Relevant co-medication was not excluded.<br><br>Genotyping:<br>521T>C: 183x TT, 57x TC, 5x CC.<br>388A>G: 11x AA, 80x AG, 137x GG<br>rs4149081G>A: 56x GG, 132x GA, 59x AA<br><br>521TT versus 521TC versus 521CC:<br>- No significant difference in lowering of LDL-cholesterol (48.3% versus 46.3% versus 41.9%)<br><br>388AA versus 388AG versus 388GG:<br>- No significant difference in lowering of LDL-cholesterol (45.9% versus 48.2% versus 47.6%)</td>
<td>Authors’ conclusion:<br>“This study showed that the common intronic SNPs represented by rs4149081 in SLCO1B1 were associated with a greater LDL-C response to simvastatin and rosuvastatin in Chinese patients with hyperlipidaemia. The 388A>G and</td>
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| Pharmacogenet Genomics 2012;22:803-6. PubMed PMID: 22668755.<br><br>**ref. 15, continuation** | 388GG: AA<br><br><br><br><br><br>rs4149081 GA+AA : AA[#] | rs4149081GG versus rs4149081GA versus rs4149081AA:<br>- Greater decrease in LDL-cholesterol lowering in patients with an A-allele (44.6% versus 49.0% versus 47.7%) (S for the trend)<br>The association remained significant after correction for age, gender, familial hypercholesterolaemia, LDL-cholesterol before initiation of therapy and 512T>C genotype<br><br>(rs4149081GA + rs4149081AA) versus rs4149081GG:<br>- LDL-cholesterol lowering increased by 4.0 percentage points (from 44.6% to 48.6%) (S; 95% CI: 0.8-7.2 percentage points)<br>The association remained significant after correction for age, gender, familial hypercholesterolaemia, LDL-cholesterol before initiation of therapy and 512T>C genotype<br><br>NOTE: In White patients, there is strong linkage disequilibrium between 521T>C and rs4149081 contrary to in Chinese patients. This means that these two polymorphisms are linked in White patients, but not in Chinese patients. | 521T >C polymorphisms were not associated with the LDL-C response to either statin.” |
| **ref. 16**<br>Brunham LR et al.<br>Differential effect of the rs4149056 variant in SLCO1B1 on myopathy associated with simvastatin and atorvastatin.<br>Pharmacogenomics J 2012;12:233-7.<br>PubMed PMID: 21243006. | 3<br><br><br><br><br><br>521TC +CC: D | 12 Dutch cases with severe simvastatin-associated myopathy and 39 age and gender-matched controls using the same simvastatin dose. The mean simvastatin 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). Corrections were made for relevant co-medication.<br><br>Cases versus controls:<br>- The frequency of the 521C allele increased by 83% (from 0.18 to 0.33) (S)<br>The association remained significant after exclusion of patients using relevant co-medication.<br>- There was a 3-fold increased risk of myopathy for 521TC+CC compared to 521TT (S) (OR = 3.2; 95% CI 0.83-11.96)<br>The association remained significant after exclusion of patients using relevant co-medication (S) (OR = 4.5; 95% CI 0.73-27.59). | Authors’ conclusion:<br>“When subjects were stratified by statin type, the SLCO1B1 rs4149056 genotype was significantly associated with myopathy in patients who received simvastatin, but not in patients who received atorvastatin.” |
| **ref. 17**<br>Sortica VA et al. SLCO1B1 gene variability influences lipid-lowering efficacy on simvastatin therapy in Southern Brazilians.<br>Clin Chem Lab Med 2012;50:441-8.<br>PubMed PMID: 22505549. | 4<br><br><br><br><br><br>521TC: AA<br>521CC: AA<br><br><br><br>388AG: AA<br>388GG: AA | 216 Brazilian patients of European descent used simvastatin 20 mg/day for 6 months. Corrections were made for co-medication and CYP3A4 and CYP3A5 genotypes.<br><br>Genotyping:<br>521T>C: 152x TT, 59x TC, 5x CC.<br>388 A>G: 56x AA, 111x AG, 49x GG<br>463 C>A: 155x CC, 56x CA, 5x AA<br><br>521TT versus 521TC versus 521CC:<br>- No significant difference in LDL-cholesterol lowering (38.6% versus 39.3% versus 42.1%)<br>- No significant differences in lowering of total cholesterol and triglycerides and increase of HDL-cholesterol<br><br>388AA versus 388AG versus 388GG:<br>- LDL-cholesterol lowering increased with the number of G-alleles (30.5% versus 38.4% versus 40.2%) (S).<br>The difference was no longer significant after correction for multiple tests (NS).<br>- Total cholesterol lowering increased with the number of G-alleles (15.3% versus 20.7% versus 22.4%) (S)<br>- No significant differences in lowering of triglycerides and increase of HDL-cholesterol<br><br>(388AG + 388GG) versus 388AA: | Authors’ conclusion:<br>“The present study suggests that the SLCO1B1 c.388A>G polymorphism could play a role in the inter-individual variation of clinical response to simvastatin in Brazilians.” |

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| **ref. 17, continuation** | 463CA: AA<br>463AA: AA | - LDL-cholesterol lowering increased by 8.4 percentage points (from 30.6% to 39.0%) (S)<br>The difference was no longer significant after correction for multiple tests (NS).<br>- Total cholesterol lowering increased by 13.0 percentage points (from 15.8% to 28.8%) (S)<br>- No significant differences in lowering of triglycerides and increase of HDL-cholesterol<br><br>463CC versus 463CA versus 463AA:<br>- No significant difference in LDL-cholesterol lowering (37.3% versus 41.3% versus 40.0%)<br>- No significant differences in lowering of total cholesterol and triglycerides and elevation of HDL-cholesterol | |
| **ref. 18**<br>Bailey KM et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study.<br>Circ Cardiovasc Genet 2010;3:276-85.<br>PubMed PMID: 20207952. | 3<br><br>521TC +CC: AA | 291 White patients with a recent myocardial infarction received simvastatin 40 mg/day for 3 months. Relevant co-medication was not excluded.<br><br>Genotyping: 521T>C: 200x TT, 82x TC, 9x CC.<br><br>(521TC + 521CC) versus 521TT:<br>- No significant difference in LDL-cholesterol at initiation of therapy (106.7 versus 104.5 mg/dL)<br>- No significant difference in LDL-cholesterol after 3 months (77.77 versus 79.52 mg/dL)<br>- Average age was 4.6% higher (from 61.23 to 64.07 years) (S). However, regression analysis did not find a significant effect of age on achieving LDL-cholesterol targets. | Authors' conclusion:<br>"There were no significant differences in mean 3-month LDL-C concentrations between wild-type (most common allele) and variant groups for the SLCO1B1 genotype." |
| **ref. 19**<br>Voora D et al. The SLCO1B1 *5 genetic variant is associated with statin-induced side effects.<br>J Am Coll Cardiol 2009;54:1609-16.<br>PubMed PMID: 19833260. | 3<br><br>521TC +CC: B | 158 American patients used simvastatin 20 mg/day for 8 weeks, followed by simvastatin 80 mg/day for 8 weeks. Relevant co-medication was not excluded.<br>Plasma concentrations were determined for 58 patients.<br><br>Genotyping:<br>521T>C: total population: 108x TT, 50x (TC + CC).<br>pharmacokinetics: 28x TT, 27x TC, 3x CC<br><br>(521TC + 521CC) versus 521TT:<br>- There was a 2.2-fold increase from 16% to 34% 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 (S).<br><br>521TT versus 521TC versus 521CC:<br>- The median plasma concentration of the metabolite simvastatin acid increased with the number of C-alleles for both dosages (S)<br>20 mg/day: 1.2 versus 1.4 versus 11.2 ng/mL<br>80 mg/day: 3.7 versus 3.7 versus 77.5 ng/mL<br>- No differences in median plasma concentration of the parent compound simvastatin lactone (NS)<br>- As the plasma concentration of the acid exceeds that of the lactone, the total simvastatin plasma concentration also increased for both doses (S). | Authors' conclusion:<br>"We defined a composite adverse event (CAE) as discontinuation for any side effect, myalgia, or CK >3x upper limit of normal during follow-up. SLCO1B1*5 was associated with CAE (percent with ≥1 allele in CAE vs. no CAE groups, 37% vs. 25%, p = 0.03) and those with CAE with no significant CK elevation (p ≤ 0.03). Finally, the CAE risk appeared to be greatest in those carriers assigned to simvastatin." |
| **ref. 20**<br>Pasanen MK et | 3 | 32 genotype-selected White volunteers were given a single dose of 40 mg simvastatin. Co-medication, CYP3A5 expressors and carriers of | Authors' conclusion: |

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| al.<br>Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate.<br>Pharmacogenet Genomics 2008;18:921-6.<br>PubMed PMID: 18794729.<br><br>**ref. 20, continuation** | 521TC: AA<br>521CC: AA | the ABCC2 1446C>G and CYP2C9*3 polymorphisms were excluded.<br><br>Genotyping: 521T>C: 16x TT, 12x TC, 4x CC<br><br>521TT versus 521TC versus 521CC:<br>- No differences in the mean and maximum percentage decrease in cholesterol precursor/cholesterol ratio after administration of simvastatin<br>The cholesterol precursors investigated were lathosterol and desmosterol.<br>- No differences in the mean and maximum percentage decrease in cholesterol absorption marker/cholesterol ratio after administration of simvastatin<br>The cholesterol absorption marker investigated was the plant sterol avenasterol.<br>- No difference in total cholesterol before administration of simvastatin (NS)<br>The authors stated that the sample size was too small to exclude differences in statin response smaller than 40%. | "The short-term effects of statins on cholesterol homeostasis were not associated with the SLCO1B1 polymorphism." |
| **ref. 21**<br>SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy -- a genomewide study.<br>N Engl J Med 2008;359:789-99.<br>PubMed PMID: 18650507. | 3<br><br>521TC: D<br><br>521CC: D<br><br>388AG +GG: AA[#]<br><br>rs3567 1512 CC+CA : AA | Genome-wide association study in 85 White patients with proven or early myopathy and 90 control patients without myopathy using simvastatin 80 mg/day. Proven myopathy was defined as muscle symptoms and creatine kinase exceeding 10 times the upper limit of normal. Early myopathy was defined as creatine kinase exceeding 3 times the upper limit of normal and creatine kinase exceeding 5 times and alanine aminotransferase exceeding 1.7 times the baseline levels prior to initiation of simvastatin (independent of muscle symptoms). Controls were selected on the basis of gender, age, estimated glomerular filtration rate and amiodarone usage. Apart from for amiodarone, no corrections were made for co-medication.<br>Reproducibility was tested in a group of 16,664 White patients using simvastatin 40 mg/day.<br><br>Case-control study:<br>- There was a strong association between myopathy and rs4363657 in intron 1 of SLCO1B1<br>- rs4363657 was in almost complete linkage disequilibrium with 521T>C ($r^2 > 0.95$). This means that these two polymorphisms are linked.<br>- The OR for myopathy was 4.5 (95% CI: 2.6-7.7) per 521C allele (S)<br>- The OR for myopathy was 16.9 (95% CI: 4.7-61.1) for 521CC versus 521TT (S)<br>- Based on a prevalence of 0.15 for the 521C allele, cumulative myopathy risks for 521CC, 521CT and 521TT were calculated to be 18%, 3% and 0.6% respectively.<br>The mean in this population was 1.6%.<br>Myopathy mainly occurred in the first year.<br>- More than 60% of the myopathy cases could be explained by the 521C allele<br>- There was no significant difference between the OR values for proven myopathy and for early myopathy (OR for 521CC versus 521TT was 27.2 (95% CI: 6.8-109.2) for proven myopathy (S) and 9.6 (95% CI: 2.2-41.1) for early myopathy).<br>48% of the patients with myopathy had proven myopathy (41% of the 521TT with myopathy, 43% of the 521TC with myopathy and 67% of the 521CC with myopathy).<br>- The 388G allele and rs35671512C allele in 521C haplotypes appear to reduce the risk of myopathy (borderline significant and almost significant respectively)<br>- The 463 C>A polymorphism did not affect the risk<br><br>Replication study:<br>- The OR for myopathy was 2.6 (95% CI: 1.3-5.0) per 521C allele (S).<br>The incidence of myopathy was 0.23% in this study. | Authors' conclusion:<br>"The prevalence of the rs4149056 C allele in the population was 15%. The odds ratio for myopathy was 4.5 (95% confidence interval [CI], 2.6 to 7.7) per copy of the C allele, and 16.9 (95% CI, 4.7 to 61.1) in CC as compared with TT homozygotes. More than 60% of these myopathy cases could be attributed to the C variant." |

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| **ref. 21, continuation** | 463CA + AA: AA | - LDL-cholesterol lowering at 4-6 weeks decreased by 1.28 percentage points per 521C allele (mean decrease was 40.6%) (S)<br>- LDL-cholesterol lowering at 4-6 weeks decreased by 0.62 percentage points per 388G allele (mean decrease was 40.6%) (S)<br>- There were no differences in LDL cholesterol before initiation of simvastatin between the genotypes | |
| **ref. 22**<br>Pasanen MK et al.<br>SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid.<br>Pharmacogenet Genomics 2006;16:873-9.<br>PubMed PMID: 17108811. | 3<br><br>521CC: A<br><br>521TC: AA | The 32 White volunteers in Pasanen et al. were given a single dose of 40 mg simvastatin. One volunteer with the 521TC genotype was excluded from the analysis due to outlying plasma concentrations. Co-medication and CYP3A5 expressers were excluded.<br><br>Genotyping: 521T>C: 16x TT, 12x TC, 4x CC<br><br>521CC versus 521TT:<br>- The simvastatin acid AUC increased by 221% (from 16.4 to 52.7 ng.hour/mL (S)<br>- There was no difference in the simvastatin acid $t_{1/2}$ (from 3.3 to 3.4 hours) (NS)<br>- The simvastatin lactone AUC increased by 44% (from 26.4 to 37.9 ng.hour/mL) (NS)<br>- The simvastatin lactone $t_{1/2}$ increased by 37% (from 2.7 to 3.7 hours) (NS)<br><br>521TC versus 521TT:<br>- The simvastatin acid AUC increased by 23% (from 16.4 to 20.1 ng.hour/mL) (NS)<br>- There was no difference in the simvastatin acid $t_{1/2}$ (from 3.3 to 3.2 hours) (NS)<br>- The simvastatin lactone AUC increased by 21% (from 26.4 to 31.9 ng.hour/mL) (NS)<br>- The simvastatin lactone $t_{1/2}$ increased by 19% (from 2.7 to 3.2 hours) (NS)<br><br>Other polymorphisms:<br>- The SLCO1B1 haplotype did not have a significant effect on simvastatin acid AUC for 521TC. This haplotype is determined by 521T>C and also by the 388A>G, -1187 G>A and -10499A>C polymorphisms. | Authors' conclusion: "SLCO1B1 polymorphism markedly affects the pharmacokinetics of active simvastatin acid, but has no significant effect on parent simvastatin." |
| **ref. 23**<br>SmPC Zocor (simvastatin) 20-05-21. | 0<br><br>521CC: D<br><br>521TC: D | <u>Warning</u>:<br>Reduced function of OATP transporter proteins in the liver can elevate the systemic exposure to simvastatin acid and increase the risk of myopathy and rhabdomyolysis. Reduced function can occur due to inhibition by interacting medication (for example cyclosporine) or in carriers of the SLCO1B1 c.521T>C-genotype.<br>Carriers of the SLCO1B1 allele (c.521T>C), that codes for a less active OATP1B1 protein, have an increased systemic simvastatin acid exposure and a higher chance of myopathy. The myopathy risk related to high dose (80 mg) simvastatin is in general approximately 1%, without genetic testing. Based on the results of the SEARCH study, carriers of the homozygous C-allele (also called CC) treated with 80 mg have a 15% myopathy risk within one year, while carriers of the heterozygous C-allele (CT) have a 1.5% risk. The corresponding risk is 0.3% in patients with the most prevalent genotype (TT). If available, genotyping for the presence of the C-allele should be considered as part of the benefit/risk-evaluation preceding the prescription of 80 mg simvastatin to individual patients and high doses should be avoided in carriers of the CC-genotype. However, absence of this gene in the genotyping results does not exclude that myopathy can occur.<br><u>Pharmacokinetics</u>:<br>Special populations<br>SLCO1B1 polymorphism<br>Carriers of the SLCO1B1-allele (c.521T>C) have a lower OATP1B1 activity. The average exposure (AUC) to the most important active metabolite, simvastatin acid, is 120% in heterozygous carriers (CT) of | |

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| **ref. 23, continuation** | | the C-allele and 221% in homozygous (CC) carriers compared to patients with the most common genotype (TT). The C-allele has a frequency of 18% among European patients. Patients with the SLCO-1B1 polymorphism have a risk of increased exposure to simvastatin acid, which can result in an increased risk of rhabdomyolysis. | |

AA[#]: The allele has a significant effect, but this effect is favourable instead of unfavourable.

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| Risk group | High doses and factors that increase the simvastatin 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 2012, only studies and meta-analyses with more than 500 patients or more than 60 cases, and investigating either effectiveness for established indications, adverse events or simvastatin or cholesterol concentrations, were included. Other studies did not contribute enough to the evidence. A large study investigating the effect on incident type 2 diabetes mellitus risk was not included, because simvastatin did not significantly increase the risk of incident type 2 diabetes mellitus in this cohort (Fernandes Silva L et al. Effects of SLCO1B1 genetic variant on metabolite profile in participants on simvastatin treatment. Metabolites 2022;12:1159. PMID: 36557197).
- 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, for simvastatin, the evidence linking statin associated muscle symptoms to gene variant 521 T>C is of high quality, and that this association has been reproduced in retrospective studies of randomised trials and clinical practice-based cohorts. In addition, CPIC mentions that the single-dose study Pasanen 2006 determined 521CC to have substantiality greater exposure to the active simvastatin acid ($AUC_{0-12}$) (221% higher) than 521TT. In single-dose studies, the effect of 521T>C on statin pharmacokinetics is strongest for simvastatin.
  In addition, CPIC indicates that 521C-allele carriers experience lesser LDL-cholesterol reduction when taking simvastatin (Generaux GT et al. Impact of SLCO1B1 (OATP1B1) and ABCG2 (BCRP) genetic polymorphisms and inhibition on LDL-C lowering and myopathy of statins. Xenobiotica 2011;41;639-51; Kaddurah-Daouk R et al. Enteric microbiome metabolites correlate with response to simvastatin treatment. PLoS One 2011;6:e25482; Ho RH and Kim RB. Transporters and drug therapy: implications for drug disposition and disease. Clinical pharmacology and therapeutics 2005;78:260-77; Campana C et al. Efficacy and pharmacokinetics of simvastatin in heart transplant recipients. Ann Pharmacother 1995;29:235-9), but one report suggests this may be due to poor drug adherence (Donnelly LA et al. Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. Clin Pharmacol Ther 2011;9:210-6). However, even for simvastatin, the change in LDL-cholesterol level due to gene variant 521T>C is small (<0.26 mmol/L) (Generaux GT et al. Impact of SLCO1B1 (OATP1B1) and ABCG2 (BCRP) genetic polymorphisms and inhibition on LDL-C lowering and myopathy of statins. Xenobiotica 2011;41;639-51), and there is no evidence that this variant impacts vascular events (Postmus I et al. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. Nat Commun 2014;5:5068).
  Recommendation per genotype group:

| Genotype group | Implications | Recommendation[a] | Classification of recommendation[b] | Considerations |
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| 521TC | Increased risk of myopathy; increased simvastatin acid exposure as compared with normal function. | Prescribe an alternative statin depending on the desired potency. If simvastatin therapy is warranted, limit dose to <20 mg/day. | Strong | 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. |

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| 521CC | Highly increased myopathy risk; increased simvastatin acid exposure compared with normal function and 521TC; | Prescribe an alternative statin depending on the desired potency. | Strong | 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. |
| 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. However, 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 pharmacokinetics 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 pharmacokinetics. J Clin Pharmacol 2018;58:823-33).

[b]: Strong = the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

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

- Cost-effectiveness analysis:

Brunette CA et al. A cost-consequence analysis of preemptive SLCO1B1 testing for statin myopathy risk compared to usual care. J Pers Med 2021;11:1123. PMID: 34834475.

For US military Veteran patients, differences in mean per-patient costs for lipid therapy prescriptions, including statins, for SLCO1B1 genotype informed therapy (n = 193, 45 521C-allele carriers) compared to non-genotype informed therapy (n = 215, 75 521C-allele carriers) were not statistically significant (Integrating Pharmacogene-tics in Clinical Care (I-PICC) Study). Not all patients received a statin in this study and, of statin prescriptions, only 18% concerned simvastatin. Differences in per-patient costs attributable to the intervention, including SLCO1B1 testing, lipid-lowering prescriptions, statin-associated muscle symptoms, laboratory and imaging expenses, and primary care and cardiology services, were also non-significant. Only one incident of simvastatin-associated muscle symptoms was observed, which occurred in a 521TT patient on simvastatin 20 mg/day in the treatment arm.

In the hypothetical cohort (n = 10,000, simvastatin for all as non-genotype guided therapy and simvastatin in 521TT and either atorvastatin or rosuvastatin (both in half of patients) for 521C-allele carriers as genotype-guided therapy), SLCO1B1-informed simvastatin therapy averted 109 myalgias and 3 myopathies at 1-month follow up. Fewer statin discontinuations (78 vs. 109) were also observed, but the SLCO1B1 testing strategy was US $96 more costly per patient compared to no testing (US $124 vs. 28).

The implementation of SLCO1B1 testing resulted in small, non-significant increases in the proportion of patients receiving CPIC-concordant statin prescriptions within a real-world primary care context, diminished the incidence of statin-associated muscle symptoms, and reduced statin discontinuations in a hypothetical cohort of 10,000 patients. Despite these effects, SLCO1B1 testing administered as a standalone test did not result in lower per-patient health care costs at 1 month or over 1 year of treatment. The inclusion of SLCO1B1, among other well-validated pharmacogenes, into pre-emptive panel-based testing strategies may provide a better balance of clinical benefit and cost.

Costs were calculated from a health system perspective and for a period of 12 months. The calculation was based a price of simvastatin 20-40 mg of US $0.33/day, a price of atorvastatin 10-80 mg of US $0.62/day, a price of rosuvastatin 5-40 mg of US $0.69/day, a price of myopathy/myalgia treatment of US $440, and genotyping costs of US $99.

Date of literature search: 24 February 2023.

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

**Mechanism:**
Simvastatin is administered as a prodrug (lactone form). It is converted non-enzymatically and enzymatically in the body to the active metabolite simvastatin acid. The organic anion transporter 1B1 (SLCO1B1) plays an important role in simvastatin acid transport from the portal vein to liver cells, where simvastatin inhibits cholesterol production. Genetic variations in SLCO1B1 may reduce simvastatin acid transport to the liver and therefore increase simvastatin plasma concentrations. Higher simvastatin plasma concentrations increase the risk of myopathy.

**Clinical Implication Score:**

Table 1: Definitions of the available Clinical Implication Scores

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| **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** | |
|---|---|---|---|
| | | **≤40 mg/day** | **80 mg/day** |
| **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+ | 5+ | 7+ |
| **Corresponding Clinical Implication Score:** | | Beneficial | Essential |