SLCO1B1: pravastatin 7742/7743

AUC = area under the concentration-time curve, BMI = body mass index, HDL-cholesterol = high-density lipoprotein cholesterol, LDL-cholesterol = low-density lipoprotein cholesterol, 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.

Brief summary and justification of choices:
The organic anion transporter 1B1 (SLCO1B1) plays a role in pravastatin transport from the portal vein to liver cells, where pravastatin inhibits cholesterol production. Genetic variations in SLCO1B1 may reduce pravastatin transport to the liver and therefore increase pravastatin plasma concentrations. Higher pravastatin plasma concentrations may increase the risk of myopathy and lower intrahepatocellular concentrations may decrease the effectiveness of pravastatin.
Gene variant 521T>C:
None of the 2 studies investigating myopathy and/or pravastatin intolerance found an effect of the 521T>C gene variant (Akao 2012 (including 702x 521TC and 67x 521CC) and Voora 2009 (including 37x 521TC+521CC)). In addition, three case reports did not provide strong evidence for a role of gene variants leading to reduced SLCO1B1 transporter activity in development of myopathy either. Jessop 2023 showed a 521TC patient with left lower extremity pain and generalised weakness on atorvastatin 20 mg/day to have only minor left lower extremity pain primarily occurring at night after change to pravastatin 40 mg/day. This patient had five non-genetic risk factors for statin-associated muscular symptoms, i.e. female gender, age greater than 65 years, hypothyroidism, diabetes, and trauma (from a motor vehicle accident that occurred years ago). Khine 2016 showed a 521TC male patient with a history of rhabdomyolysis on simvastatin to also develop muscle symptoms on pravastatin. However, rhabdomyolysis was not mentioned and the patient also developed muscle symptoms on ezetimibe, so the symptoms were not restricted to statins. Finally, Morimoto 2004 showed one out of two patients with pravastatin-induced myopathy and without the 521C-allele to be heterozygous for a rare allele leading to reduced SLCO1B1 transporter activity (1628TG). So, the risk of pravastatin-induced myopathy seems low, even in patients with risk factors. This is confirmed by the SmPC Pravastatine Na STADA 21-7-2019, stating that there was no difference in the rates of myalgia, muscle weakness, and the incidence of creatine kinase level > 3x and > 10x the upper limit of normal compared to placebo in three pravastatin trials, including the one from which the data in Akao 2012 were derived.
Of the 3 studies with more than 40 patients investigating effectiveness, the largest study, performed in patients aged 72-80 years, found LDL-cholesterol lowering in the first 6 or 12 months to decrease with increasing number of the 521C-allele (Akao 2012 (including 702x 521TC and 67x 521CC)). However, the difference with 521TT was small (4.1-5.2% of baseline LDL-cholesterol for 521CC and 1.0-1.3% of baseline LDL-cholesterol for 521TC) and thus not very likely to be clinically significant. During the mean follow-up of 3.2 years, there was no effect of 521T>C on the percentage of patients with coronary heart disease death or non-fatal myocardial infarction. The middle study found no effect of 521T>C on lowering of LDL-cholesterol, total cholesterol, triglycerides, and C-reactive protein, and on increasing HDL-cholesterol (Martin 2012 (including 164x 521TC and 13x 521CC)). The smallest study found a decrease in total cholesterol lowering, but not in LDL-cholesterol lowering for 9x 521TC (Zhang). There was no effect of the 521TC genotype on increase in HDL-cholesterol and lowering of triglycerides.
Of the 5 studies with more than 2 521CC and/or more than 20 521CT investigating pravastatin exposure, the only study with daily dosing in patients did not find an effect of 521T>C on median pravastatin acid and lactone plasma concentrations, neither at a dose of 10 mg/day nor at a dose of 40 mg/day (Voora 2009 (including 24-27x 521TC and 0-1x 521CC)). Results in the 4 single dose studies in healthy volunteers varied. One study found an increase in AUC with increasing number of 521C-alleles (Yee 2019 (including 8x 521TC and 3x 521CC)) and one study an increase in 5x 521CC (Deng 2008). One study found an increase in 521CC, but not in 521TC (Niemi 2006 (including 12x 521TC (7 men and 5 women) and 4x 521CC (3 men and 1 women)). In this study, the increase was found in all volun-teers and in men, but not in women. The fourth study did not find an effect of 521T>C on AUC of pravastatin, but found the AUC of the isomer 3'α-isopravastatin to be higher in 521CC (Suwannakul 2008 (including 2x 521TC and 4x 521CC)). The 3 studies showing an increase in pravastatin AUC for 521CC, found this increase to be considerable (increase with 91-256%).
Because the majority of single dosing studies in healthy volunteers showed an effect of 521T>C on pravastatin

exposure, the KNMP Pharmacogenetics Working Group concludes that there is a SLCO1B1-pravastatin interaction. However, the KNMP Pharmacogenetics Working Group considers the evidence for a clinically significant effect of 521T>C (i.e. an increase in adverse events like myopathy or a clinically significant decrease in cholesterol lowering) to be insufficient to recommend therapy adjustment (yes/no-interactions).
An overview of the clinical and kinetic effects per genotype is provided in the background information text of the gene-drug interactions in the KNMP Kennisbank. You may also have access to this background text via your pharmacy or physician electronic decision support system.
<u>Gene variant 388A>G</u>:
Akao 2012 (including 1214x 388AG and 379x 388GG) did not find an effect of gene variant 388A>G on LDL-cholesterol reduction after 6 and 12 months and the percentage of patients with coronary heart disease death or non-fatal myocardial infarction during the mean follow-up of 3.2 years.
Because of the lack of evidence for a clinically relevant effect of this gene variant on SLCO1B1 transporter activity, the KNMP Pharmacogenetics Working Group decided that there is no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
<u>Gene variant 1628T>G</u>:
Morimoto 2004 showed one out of two patient with pravastatin-induced myopathy and without the 521C-allele to be 1628TG.
Based on the absence of articles confirming an effect of this gene variant and the low frequency of this gene variant (< 1% in Japanese, < 0.18% in Whites), 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.

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

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr><td>ref. 1
Jessop JP et al. Pharmacogenetic testing in a 70-year-old woman with polypharmacy and multiple comorbidities: a case report.
Am J Case Rep 2023;24: e938850.
PMID: 36804920.</td><td>2

521TC: B</td><td>A 70-year-old woman with comorbidities and polypharmacy, treated with atorvastatin 20 mg/day and ezetimibe 10 mg/day, presented with left lower extremity pain and generalised weakness. Ezetimibe was discontinued to reduce pill burden and atorvastatin 20 mg/day was changed to pravastatin 40 mg/day to minimise potential interactions with diltiazem and warfarin at CYP3A4 and to reduce the risk of continued left lower extremity pain and generalised weakness.
After the change to pravastatin 40 mg/day, the patient had minor left lower extremity pain primarily occurring at night. In addition, 7 months after the change, HDL, LDL and total cholesterol had changed from 1.2 to 1.3 mmol/L, 2.5 to 1.8 mmol/L, and 4.6 to 3.5 mmol/L, respectively, i.e. a 28% LDL-cholesterol reduction and 24% total cholesterol reduction.
The left lower extremity pain of the patient was attributed to trauma from a motor vehicle accident that occurred years ago. Statin therapy is known to reduce the threshold of experiencing muscle pain. Risk factors for statin-associated muscular symptoms include female gender, age greater than 65 years, hypothyroidism, diabetes, and trauma. This patient presented with all 5 risk factors.
Genotyping showed the patient to have the 521TC genotype.
The authors indicate that the recommendation to remove ezetimibe was made prior to pharmacogenomic testing and that this recommendation would have likely not been made if the pharmacogenomic test results would have been available at that time.</td><td>Author's conclusion:
"Pharmacogenomic testing can help identify drug-gene interactions, choose optimal therapies in medically complex older adults and minimize adverse drug event risk."</td></tr>
<tr><td>ref. 2
Yee SW et al. Organic anion transporter polypeptide 1B1 polymorphism modulates the extent of drug-drug interaction and associated biomarker levels in healthy volun-</td><td>3</td><td>20 healthy volunteers, selected for their 521T>C genotype, received a single dose of 40 mg pravastatin.
Comedication other than oral contraceptives was excluded.

Genotyping:
- 9x 521TT
- 8x 521TC
- 3x 521CC

Results:
<table><tr><td colspan="4">Results compared to 521TT:</td></tr><tr><td></td><td>521CC</td><td>521TC</td><td>value</td></tr></table></td><td></td></tr>
</table>

<table>
<tr>
<td>teers.
Clin Transl Sci 2019;12:388-99.
PMID: 30982223.

ref. 2, continuation</td>
<td>521CC: A

521TC: A</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>for 521TT</td></tr>
<tr><td rowspan="2">AUC pravastatin (including 3’α-isopravastatin)</td><td>x 1.88 (NS)</td><td>x 0.81 (NS)</td><td rowspan="2">154 ng.h/ml</td></tr>
<tr><td colspan="2">NS for 521CC versus 521TC versus 521TT</td></tr>
<tr><td rowspan="2">AUC pravastatin only</td><td>x 3.56 (NS)</td><td>x 1.11 (NS)</td><td rowspan="2">43.3 ng.h/ml</td></tr>
<tr><td colspan="2">S for 521CC versus 521TC versus 521TT</td></tr>
<tr><td rowspan="2">AUC 3’α-isopravastatin</td><td>x 1.24 (NS)</td><td>x 0.68 (NS)</td><td rowspan="2">111 ng.h/ml</td></tr>
<tr><td colspan="2">NS for 521CC versus 521TC versus 521TT</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 3
Khine H et al. Statin-associated muscle symptoms and SLCO1B1 rs 4149056 genotype in patients with familial hypercholesterolemia.
Am Heart J 2016;179:1-9.
PMID: 27595674.</td>
<td>1

521TC: C</td>
<td>A patient with familial hypercholesterolemia reported a history of rhabdomyolysis while taking simvastatin. He also developed muscle symptoms on pravastatin as well as ezetimibe. Statin-associated muscle symptoms were defined as muscle symptoms such as muscle aches, weakness, cramps, stiffness, “heaviness,” flu-like symptoms, severe enough to stop therapy.
Genotyping showed the patient to have the 521TC genotype.</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Akao H et al. Genetic variation at the SLCO1B1 gene locus and low density lipoprotein cholesterol lowering response to pravastatin in the elderly.
Atherosclerosis 2012;220:413-7.
PMID: 22189199.</td>
<td>3

521CC: A

521TC: A

388GG: AA

388AG: AA</td>
<td>2681 patients aged 72-80 years were treated with pravastatin. Follow-up was for a mean of 3.2 years. Baseline total or LDL-cholesterol levels or vascular disease did not differ between genotypes.
Pravastatin decreased the risk of developing cardiovascular heart disease by 19% in the total patient group. No patient had creatine kinase levels > 10 times the upper limit of normal after 3 months of treatment. Myalgia occurred in 1.25% of patients.
Relevant comedication other than lipid-lowering agents and cyclosporine was not excluded.
All analyses were fully adjusted for age, gender, country, history of vascular disease, body mass index, history of diabetes, as well as history of hypertension, alcohol use, current smoking, and apoE phenotype.

Genotyping:
521T>C
- 1912x TT
- 702x TC
- 67x CC

388A>G
- 1084x AA
- 1214x AG
- 379x GG

Results:
<table>
<tr><td colspan="5">Results compared to homozygous wildtype (521TT or 388AA):</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="2">LDL-cholesterol reduction after 6 months</td><td rowspan="2">521T>C</td><td>x 0.86</td><td>x 0.97</td><td rowspan="2">37.0%</td></tr>
<tr><td colspan="2">S for 521CC versus 521TC versus 521TT</td></tr>
<tr><td>LDL-cholesterol reduction after 6 months</td><td>388A>G</td><td colspan="2">NS for 388GG versus 388AG versus 388AA</td><td>36.7%</td></tr>
<tr><td rowspan="2">LDL-cholesterol reduction after 12 months</td><td rowspan="2">521T>C</td><td>x 0.89</td><td>x 0.96</td><td rowspan="2">35.9%</td></tr>
<tr><td colspan="2">S for 521CC versus 521TC versus 521TT</td></tr>
<tr><td>LDL-cholesterol reduction after 12 months</td><td>388A>G</td><td colspan="2">NS for 388GG versus 388AG versus 388AA</td><td>35.9%</td></tr>
<tr><td>% of patients</td><td>521T>C</td><td colspan="2">NS for 521CC versus</td><td>10.2%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”Our data indicate that the presence of the rs4149056 nonsynonymous SNP at the SLCO1B1 gene locus can significantly decrease the pravastatin induced LDL cholesterol lowering response.”</td>
</tr>
</table>

<table>
<tr><td>ref. 4, continuation</td><td></td><td>
<table>
<tr><td rowspan="2">with coronary heart disease death or non-fatal myocardial infarction</td><td></td><td>521TC versus 521TT</td><td></td></tr>
<tr><td>388A>G</td><td>NS for 388GG versus 388AG versus 388AA</td><td>9.4%</td></tr>
<tr><td>% of patients with myalgia</td><td>521T>C</td><td>NS for 521CC versus 521TC versus 521TT</td><td></td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 5
Martin NG et al. The effects of a single nucleotide polymorphism in SLCO1B1 on the pharmacodynamics of pravastatin. Br J Clin Pharmacol. 2012;73:303-6. PMID: 21851379.</td><td>3

521CC: AA

521TC: AA</td><td>626 patients were treated with pravastatin 40 mg/day for 12 months. Relevant comedication other than valsartan was not excluded. However, serious illness was excluded and results were adjusted for history of diabetes and hypertension.
Results were adjusted for baseline value, BMI, systolic blood pressure, diastolic blood pressure, HDL, LDL, log triglycerides, nitrate use, history of angina, history of hypertension and history of diabetes.
A retrospective power calculation showed a power of 80% to detect a 13.1% difference in LDL response between 521CC and 521TT+ 521TC.

Genotyping:
- 449x 521TT
- 164x 521TC
- 13x 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>% decrease in LDL-cholesterol</td><td>NS</td><td>NS</td><td rowspan="2">22.2%</td></tr>
<tr><td colspan="2">NS
Results were also NS for 521CC versus 521TC versus 521TT.</td></tr>
<tr><td>% decrease in total cholesterol</td><td>NS</td><td>NS</td><td rowspan="2">16.6%</td></tr>
<tr><td colspan="2">NS
Results were also NS for 521CC versus 521TC versus 521TT.</td></tr>
<tr><td>% increase in HDL-cholesterol</td><td colspan="2">NS
Results were also NS for 521CC versus 521TC versus 521TT.</td><td>7.2%</td></tr>
<tr><td>% decrease in triglycerides (geometric mean)</td><td colspan="2">NS
Results were also NS for 521CC versus 521TC versus 521TT.</td><td>6%</td></tr>
<tr><td>% decrease in C-reactive protein (geometric mean)</td><td colspan="2">NS
Results were also NS for 521CC versus 521TC versus 521TT.</td><td>8%</td></tr>
</table>
</td><td>Author’s conclusion:
”The rs4149056 SNP did not significantly affect the pharmacodynamics of pravastatin.”</td></tr>
<tr><td>ref. 6
Voora D et al. The SLCO1B1*5 genetic variant is associated with statin-induced side effects. J Am Coll Cardiol 2009;54:1609-16. PubMed PMID: 19833260.</td><td>3</td><td>143 patients were treated with pravastatin 10 mg/day for 8 weeks, followed by pravastatin 40 mg/day for 8 weeks. Plasma concentrations were determined in 48-53 patients.
Pravastatin discontinuation and/or muscle symptoms was defined as premature discontinuation of pravastatin due to any side effect and/or myalgia/muscle cramps (irrespective of creatine kinase values) and/or creatine kinase elevation > 3x the upper limit of normal (irrespective of symptoms). 22% of patients (n = 31) discontinued pravastatin and/or developed muscle symptoms.
Trough plasma concentrations were determined at the end of each 8-week period.
Relevant comedication was not excluded.
To account for multiple comparisons (7 alleles of 5 genes were analysed), the false discovery rate was calculated as described by Benjamini and Hochberg.
A power calculation showed a 3.2 higher sample size to be required for a power of 82-85% to detect a relative risk of 2.0 associated with 521T>C.</td><td>Authors’ conclusion:
“We observed that carriers of SLCO1B1*5 had no excess risk of adverse events if assigned to pravastatin, even though the composite adverse event rates were the same for all 3 statins.”</td></tr>
</table>

<table>
<tr>
<td>ref. 6, continuation</td>
<td>521TC: AA

521CC: AA</td>
<td>
Genotyping:
Adverse event study:
- 106x 521TT
- 37x 521TC+CC

Pharmacokinetic study:
- 23-26x 521TT
- 24-27x 521TC
- 0-1x 521CC

Results:
<table>
<tr><td colspan="5">Results compared to 521TT:</td></tr>
<tr><td colspan="2"></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td colspan="2">% of patients with pravastatin discontinuation and/or muscle symptoms</td><td colspan="2">NS
Note: the observed RR was 1.000 (95% CI not mentioned, p = 0.97), making it unlikely that the absence of significance is due to the small sample size.</td><td>22%</td></tr>
<tr><td rowspan="3">median pravastatin acid concentration (ng/ml)</td><td rowspan="2">10 mg/day</td><td>x 1.0
NS for 521CC versus 521TC versus 521TT</td><td>x 1.0</td><td rowspan="2">0.2</td></tr>
<tr><td>40 mg/day</td><td></td><td>x 1.0 (NS)</td></tr>
<tr><td rowspan="3">median pravastatin lactone concentration (ng/ml)</td><td rowspan="2">10 mg/day</td><td>x 0.1
NS for 521CC versus 521TC versus 521TT</td><td>x 0.5</td><td rowspan="2">0.02</td></tr>
<tr><td>40 mg/day</td><td></td><td>x 0.7 (NS)</td></tr>
</table>
Note: This study did not show a difference in pravastatin plasma concentrations between the sexes.
</td>
<td></td>
</tr>
<tr>
<td>ref. 7
Deng JW et al. The effect of SLCO1B1*15 on the disposition of pravastatin and pitavastatin is substrate dependent: the contribution of transporting activity changes by SLCO1B1*15. Pharmacogenet Genomics 2008;18:424-33.
PMID: 18408565.</td>
<td>3

521CC: A</td>
<td>
11 healthy male volunteers, selected for their 521T>C genotype, received a single dose of 40 mg pravastatin.
Comedication, alcohol, caffeine and fruit juice were excluded.
On the basis of results on the pharmacokinetics of pravastatin, a sample size of five volunteers in each genotype group was calculated to have a power of at least 80%.to detect a 100% larger AUC of pravastatin in 521CC than in 521TT.

Genotyping:
- 6x 521TT
- 5x 521CC

Results:
<table>
<tr><td colspan="2">Pravastatin AUC compared to 521TT (value for 521TT is 275.21 ng.h/ml):</td></tr>
<tr><td>521CC</td><td>x 1.99 (S)</td></tr>
</table>
</td>
<td>Authors' conclusion:
"This study suggests that substrate dependency in the consequences of the SLCO1B1*15 variant could modulate the effect of SLCO1B1 polymorphism on the disposition of pitavastatin and pravastatin."</td>
</tr>
<tr>
<td>ref. 8
Suwannakul S et al. Pharmacokinetic interaction between pravastatin and olmesartan in relation to SLCO1B1 polymorphism. J Hum Genet</td>
<td>3</td>
<td>
10 healthy male volunteers, selected for their 521T>C genotype, received a single dose of 10 mg pravastatin.
Comedication, alcohol, caffeine and grapefruit and orange juice were excluded.

Genotyping:
- 4x 521TT
- 2x 521TC
- 4x 521CC

Results:
<table>
<tr><td>Results compared to 521TT:</td></tr>
</table>
</td>
<td>Authors' conclusion:
"There were no significant differences in any pharmacokinetic parameters of pravastatin among SLCO-1B1 genotypes for both dosing phases."</td>
</tr>
</table>

<table>
<tr><td>2008;53:899-904.
PMID: 18641915.

ref. 8, continuation</td><td>521TC: AA

521CC: A</td><td>
<table>
<tr><td></td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td>AUC_{0-24h} pravastatin</td><td>x 1.17 (NS)</td><td>x 0.79 (NS)</td><td>48 ng.h/ml</td></tr>
<tr><td>AUC_{0-24h} 3’α-isoprava-statin</td><td>x 4.38 (S)</td><td>x 3.75 (NS)</td><td>16 ng.h/ml</td></tr>
<tr><td>AUC_{0-24h} pravastatin+ 3’α-isopravastatin</td><td>x 2.03 (S)</td><td>x 1.53 (NS)</td><td>64 ng.h/ml</td></tr>
</table>
</td><td></td></tr>
<tr><td>ref. 9
Zhang W et al. SLCO1B1 521T-->C functional genetic polymorphism and lipid-lowering efficacy of multiple-dose pravastatin in Chinese coronary heart disease patients. Br J Clin Pharmacol. 2007;64:346-52.
PMID: 17439540.</td><td>4

521TC: A</td><td>45 patients were treated with pravastatin 20 mg/day for 30 days.
No patient showed any elevation of aminotransferase or creatine phosphokinase after treatment, and no patient reported skeletal muscle abnormalities or other notable safety concerns.
There was no difference in baseline lipid levels between the genotypes.
Relevant comedication (other lipid-lowering drugs, cyclosporine, rifampicin, methotrexate, fexofenadine, caspofungin, irinotecan or flavonoids) in the previous 2 months and during pravastatin treatment was excluded, as were smoking, alcohol and caffeine during pravastatin treatment.
The power of the study was calculated afterwards to be 80%.

Genotyping:
- 36x 521TT
- 9x 521TC

Results:
<table>
<tr><td colspan="3">Results for 521TC compared to 521TT:</td></tr>
<tr><td></td><td></td><td>value for 521TT</td></tr>
<tr><td>% decrease in LDL-cholesterol</td><td>NS</td><td>27.5%</td></tr>
<tr><td>% decrease in total cholesterol</td><td>x 0.65 (S)</td><td>22.4%</td></tr>
<tr><td>% increase in HDL-cholesterol</td><td>NS</td><td>5.3%</td></tr>
<tr><td>% decrease in triglycerides</td><td>NS</td><td>20.7%</td></tr>
</table>
</td><td>Author’s conclusion:
”The 521T→C polymorphism of SLCO1B1 appears to modulate significantly the total cholesterol-lowering efficacy of pravastatin in Chinese patients with coronary heart disease.”</td></tr>
<tr><td>ref. 10
Niemi M et al. SLCO1B1 polymorphism and sex affect the pharmacokinetics of pravastatin but not fluvastatin. Clin Pharmacol Ther 2006;80:356-66.
PubMed PMID: 17015053.</td><td>3

521CC: A

521TC: AA</td><td>32 healthy volunteers, selected for their 521T>C genotype, received a single dose of 40 mg pravastatin.
Comedication, grapefruit products and carriers of the ABCC2 1446G and CYP2C9*3 gene variants were excluded.
On the basis of previous data on the pharmacokinetics of pravastatin, the sample size of each genotype group was calculated to provide a power of at least 80% to detect a 50% and 100% greater AUC of pravastatin in 521TC and 521CC, respectively, than in 521TT.

Genotyping:
- 16x 521TT (8 men and 8 women)
- 12x 521TC (7 men and 5 women)
- 4x 521CC (3 men and 1 women)

Results:
<table>
<tr><td colspan="5">Results compared to 521TT:</td></tr>
<tr><td></td><td>sex</td><td>521CC</td><td>521TC</td><td>value for 521TT</td></tr>
<tr><td rowspan="3">AUC pravastatin (ng.h/ml)</td><td>all</td><td>x 1.91 (S)</td><td>x 1.10 (NS)</td><td>150,3</td></tr>
<tr><td>men</td><td>x 3.32 (S)</td><td>x 1.65 (NS)</td><td>92.7</td></tr>
<tr><td>women</td><td>x 1.08 (NS)</td><td>x 0.87 (NS)</td><td>207.9</td></tr>
<tr><td colspan="4">Adjusting the AUC of pravastatin by body weight or lean body weight only slightly changed the results.</td></tr>
<tr><td colspan="4">The authors indicate that the finding of the difference between the sexes should be cautiously interpreted, because of the smaller number of women than men with variant genotypes and the post hoc nature of the analysis,</td></tr>
</table>
</td><td>Authors’ conclusion:
“SLCO1B1 polymorphism has a large effect on the pharmacokinetics of pravastatin but not fluvastatin. Moreover, the results suggest that sex may affect the pharmacokinetics of pravastatin and possibly the functional consequences of SLCO1B1 polymorphism.”</td></tr>
</table>

ref. 10, continuation		$t_{1/2}$ pravastatin (h)	all, men and women	The 521T>C genotype was not associated with differences in the $t_{1/2}$ of pravastatin.	1.5-1.8	
ref. 11 Morimoto K et al. A novel variant allele of OATP-C (SLCO1B1) found in a Japanese patient with pravastatin-induced myopathy. Drug Metab Pharmacokinet 2004;19:453-5. PMID: 15681900. Furihata T et al. Functional analysis of a mutation in the SLCO1B1 gene (c.1628T>G) identified in a Japanese patient with pravastatin-induced myopathy. Pharmacogenomics J 2009;9:185-93. PMID: 19238167.	1 1628TG: C	Sequencing of all exons and exon-intron junctions of SLCO1B1 in two patients with pravastatin-induced myopathy without the 521C allele, showed a novel variant (1628T>G, Leu543Trp) in one of them. No variants were found in the other. The severity of myopathy in the patients was not mentioned, neither was indicated whether relevant comedication was present. The 1628T>G variant was shown to result in reduced SLCO1B1 transport activity in transiently and stably transfected cells. The variant is rare and was not detected in 50 healthy Japanese volunteers and 285 Whites.				Author's conclusion: "There were two patients who experienced pravastatin-induced myopathy despite the fact that they did not possess OATP-C*15 or other known mutations of OATP-C that have been reported to decrease the function of OARP-C. In this study, we sequenced all of the exons and exon-intron junctions of OATP-C of the two patients and found a novel mutation in exon 12 of OATP-C in one of the patients."

Risk group	-

Comments:

- For effectiveness, only studies with more than 40 patients were included. For the kinetic outcomes, only studies reporting AUC or plasma concentration per genotype and with more than 2 521CC and/or more than 20 521CT were included. Other studies did not add enough to the evidence to be included.
- Existing guidelines:
  Cooper-DeHoff RM et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022;111:1007-21. PMID: 35152405.
  CPIC distinguishes the following SLCO1B1 genotype groups: poor function (521CC), decreased function (521TC), normal function (521TT, excluding homozygotes for the *14-allele (which has both gene variants 388A>G and 463C>A)), and increased function (homozygotes for the *14-allele). However, CPIC does not recommend therapy adjustment for SLCO1B1 increased function.
  CPIC indicates that, although the association of gene variant 521T>C with myopathy varies by statin, there is evidence supporting the role of SLCO1B1 variants in the systemic clearance of all statins. CPIC mentions that in the single-dose studies, the plasma AUC of pravastatin has been 57-130% higher in 521CC than in 521TT, but refers for this to a figure showing a 82-99% higher AUC (Deng 2008, Niemi 2006; and Ho RH et al. Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. Pharmacogenet Genomics 2007;17: 647-56). In single-dose studies, the effect of 521T>C on statin pharmacokinetics is fourth strongest for pravastatin (after simvastatin, atorvastatin and rosuvastatin).
  Recommendation per genotype group:

Genotype group	Implications	Recommendation[a]	Classification of recommendation[b]	Considerations
521TC	Typical myopathy risk with doses ≤40 mg. Increased pravastatin exposure as compared with normal function.	Prescribe desired starting dose and adjust doses of pravastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy with pravastatin especially with doses >40 mg per day.	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug-drug interactions may be more pronounced, resulting in a higher risk of myopathy.
521CC	Typical myopathy risk with doses ≤40 mg. Increased pravastatin exposure as compared with normal function and 521TC.	Prescribe ≤40 mg as a starting dose and adjust doses of pravastatin based on disease-specific guidelines. If patient is tolerating 40-mg dose but higher potency is needed, a higher dose (>40 mg) or an alternative statin or combination therapy (i.e., pravastatin plus non-statin guideline-directed medical therapy) could be considered. Prescriber should be aware of possible increased risk for myopathy especially with pravastatin doses >40 mg.	Moderate	The potential for drug–drug interactions and dose limits based on renal and hepatic function should be evaluated prior to initiating a statin. The effects of drug-drug interactions may be more pronounced, resulting in a higher risk of myopathy.
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: 28 March 2023.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetic Working Group decision	521TC	4 C	yes	no	16 May 2023
	521CC	3 A	yes	no	

Mechanism:
The organic anion transporter 1B1 (SLCO1B1) plays an important role in pravastatin transport from the portal vein to liver cells, where pravastatin inhibits cholesterol production, although transport of pravastatin by other organic anion transporters (SLCO1B3) has been reported. Genetic variations in SLCO1B1 may reduce pravastatin transport to the

liver and therefore increase pravastatin plasma concentrations. Higher pravastatin plasma concentrations may increase the risk of myopathy.
Pravastatin is largely excreted in unchanged form. However, it is extensively converted to the isomer 3'α-isopravastatin, which has one-tenth to one-fortieth of the inhibitory activity of the parent compound on 3-hydroxy-3-methylglutaryl coenzyme A reductase.