SLCO1B1: fluvastatin 4059/4060

AUC = area under the concentration-time curve, CI = confidence interval, HDL-cholesterol = high-density lipoprotein cholesterol, LDL-cholesterol = low-density lipoprotein cholesterol, NS = non-significant, S = significant, $t_{1/2}$ = 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.

Brief summary and justification of choices:
The organic anion transporter 1B1 (SLCO1B1) plays a role in fluvastatin transport from the portal vein to liver cells, where fluvastatin inhibits cholesterol production. However, this role seems to be limited, because SLCO1B1 polymorphisms have less effect on plasma concentrations of fluvastatin than on plasma concentrations of other statins.
Gene variant 521T>C:
Although two small studies showed no effect of gene variant 521T>C on fluvastatin AUC after single dosing (Mori 2019 (volunteers, 7x 521TC and 2x 521CC) and Niemi 2006 (volunteers, 12x 521TC and 4x 521CC)), one large study did (Hirvensalo 2019 (volunteers, 68x 521TC, 10x 521CC)). Hirvensalo 2019 showed an increase in fluvastatin AUC with every additional 521C-allele. In addition, Xiang 2020 showed an increase of $AUC_{0\text{-}24h}$ on day 7 of administration of fluvastatin 80 mg/day as extended release formulation, but not as immediate release formulation for 7 521TC. Although the AUC-increase was relatively high (69%), the resulting AUC remained lower than that for the (clinically slightly less efficient) immediate release formulation (which was still 139% higher). Because of the observed pharmacokinetic effect, the KNMP Pharmacogenetics Working Group concludes that there is a SLCO1B1-fluvastatin interaction.
Four studies did not show an effect of gene variant 521T>C on LDL-cholesterol lowering (Meyer zu Schwabedissen 2015 (22 patients, 8x 521TC+521CC), Couvert 2008 (428 patients, 110x 521TC, 5x 521CC) and Singer 2007 (707 patients, number of 521TC and 521CC not mentioned)) or effect on cholesterol synthesis or absorption in fluvastatin users (Pasanen 2008 (32 volunteers, 12x 521TC, 4x 521CC)). One meta-analysis of two studies revealed a-decrease in LDL-cholesterol lowering for carriers of the 521C-allele (Xiang 2018). However, the authors probably strongly overestimated the weight of the study showing the largest effect in this meta-analysis. One study found a lower fluvastatin dose in 521C-allele carriers (Meyer zu Schwabedissen 2015 (22 patients, 8x 521TC+521CC).. However, this study did not correct for confounders like the baseline cholesterol plasma concentration and coronary heart disease risk. One study showed a lower increase in HDL-cholesterol in carriers of the 521C-allele (Thompson 2005 (278 patients, number of 521TC and 521CC not mentioned)). Based on the data above, the KNMP Pharmacogenetics Working Group concludes that there is insufficient evidence for a clinical effect that makes therapy adjustment useful (yes/no-interactions).
You can find a detailed overview of the observed kinetic and clinical effects per genotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy of physician electronic decision support system.
Other gene variants:
For gene variant 388A>G, four studies and a meta-analysis of two studies found no effect on LDL-cholesterol lowering in fluvastatin users (Xiang 2018, Meyer zu Schwabedissen 2015, Couvert 2008, Singer 2007 and Thompson 2005). In addition, Xiang 2020 and Hirvensalo 2019 found no effect on fluvastatin AUC. Therefore, the KNMP Pharmacogenetics Working Group decided that there is not enough evidence for an effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
For gene variant 463C>A, there is one study that shows an effect on LDL-cholesterol lowering in fluvastatin users (Couvert 2008 (420 patients)). However, it concerns a stronger decrease in carriers of the allele variant, which means that a therapeutic recommendation is not useful. Another study does not show an effect of 463C>A on cholesterol lowering (Thompson 2005 (278 patients)). Hirvensalo 2019 found an effect of 463C>A on the AUC ratio of 3R,5S-fluvastatin/3S,5R-fluvastatin, but not on fluvastatin AUC. Therefore, it was decided that there was not enough evidence for a clinically important effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
For gene variant 1929A>C, Hirvensalo 2019 found an effect on the AUC ratio of 3R,5S-fluvastatin/3S,5R-fluvastatin, but not on fluvastatin AUC. Therefore, it was decided that there was not enough evidence for an effect of this gene

variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
For gene variant 1332-1091C>T, Hirvensalo 2019 found an effect on the AUC of 3R,5S-fluvastatin, but not on the AUC of total fluvastatin. In addition, 1332-1091C>T was in strong linkage disequilibrium with 521T>C, so it is not known whether the effect on the AUC of 3R,5S-fluvastatin is independent from the effect of 521C>T. Therefore, it was decided that there was not enough evidence for an effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.
For gene variant 728-2859G>A, Hirvensalo 2019 found an effect on the AUC ratio of 3R,5S-fluvastatin/3S,5R-fluvastatin, but not on fluvastatin AUC. Therefore, it was decided that there was not enough evidence for an effect of this gene variant on SLCO1B1 transporter activity and thus, no cause for inclusion of this gene variant in the SLCO1B1 pharmacogenetic interactions.

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
Xiang Q et al. The influence of genetic polymorphisms in drug metabolism enzymes and transporters on the pharmacokinetics of different fluvastatin formulations. Asian J Pharm Sci 2020;15:264-72.
PMID: 32373204.</td><td>4

388AG: AA
388GG: AA

521TC: A</td><td>In a crossover study, 24 healthy volunteers received fluvastatin immediate release 40 mg twice daily or fluvastatin extended release 80 mg once daily for 7 days.
Co-medication was excluded.

Genotyping:
521T>C
- 17x 521TT
- 7x 521TC

388A>G
- 3x 388AA
- 9x 388AG
- 12x 388GG

Results:
<table>
<tr><td colspan="6">Results for 521TC versus 521TT or for 388GG versus 388AG versus 388AA:</td></tr>
<tr><td></td><td></td><td>521T>C</td><td>388A>G</td><td>value for 521 TT</td><td>value for 388 AA</td></tr>
<tr><td colspan="6">Immediate release</td></tr>
<tr><td rowspan="2">AUC0-24h fluvastatin (ng.h/ml)</td><td>day 1</td><td>x 1.29 (NS)</td><td>NS</td><td>742.1</td><td>875.1</td></tr>
<tr><td>day 7</td><td>x 1.34 (NS)</td><td>NS</td><td>1087</td><td>1371</td></tr>
<tr><td rowspan="2">t1/2 fluvastatin (h)</td><td>day 1</td><td>x 1.26 (trend, p = 0.059) (NS)</td><td></td><td>2.15</td><td></td></tr>
<tr><td>day 7</td><td>x 1.04 (NS)</td><td></td><td>1.72</td><td></td></tr>
<tr><td colspan="6">Extended release</td></tr>
<tr><td rowspan="2">AUC0-24h fluvastatin (ng.h/ml)</td><td>day 1</td><td>x 1.29 (trend, p = 0.092) (NS)</td><td>NS</td><td>319.9</td><td>332.4</td></tr>
<tr><td>day 7</td><td>x 1.69 (S)</td><td>NS</td><td>360.0</td><td>393.3</td></tr>
<tr><td rowspan="2">t1/2 fluvastatin (h)</td><td>day 1</td><td>x 0.49 (NS)</td><td></td><td>10.1</td><td></td></tr>
<tr><td>day 7</td><td>x 1.40 (NS)</td><td></td><td>10.3</td><td></td></tr>
</table></td><td>Authors' conclusion:
'The lower exposure following ER was observed. For ER tablets, SLCO1B1 T521C genotype correlated with AUC0-24 of repeat doses. SLCO1B1 T521C genotype had no statistically significant effect on AUC0-24 of IR capsule of fluvastatin after single or repeated doses.''</td></tr>
<tr><td>ref. 2
Hirvensalo P et al. Enantiospecific pharmacogenomics of fluvastatin.
Clin Pharmacol Ther 2019;106:668-80.
PubMed PMID: 30989645.</td><td>3</td><td>200 healthy volunteers received a single dose of 40 mg fluvastatin.
The authors indicate that 3R,5S-fluvastatin is 30 times more active than 3S,5R-fluvastatin.
Co-medication and tobacco smoking were excluded.
Associations for 379 sequenced genes were investigated with stepwise forward linear regression analysis. In addition, analysis was performed after genotyping for selected gene variants. Bonferroni correction was used to adjust for multiple testing.

Genotyping for 521T>C (based on the observed 521C allele frequency):
- 122x TT
- 68x TC
- 10x CC</td><td>Authors' conclusion:
''Thus, SLCO transporters have enantiospecific effects on fluvastatin pharmacokinetics in humans. Genotyping of both CYP2C9 and SLCO1B1 may be useful in predicting fluva-</td></tr>
</table>

<table>
<tr>
<td>ref. 2, continuation</td>
<td>1332-1091 CT+TT: A

728-2859 GA+AA: A

521TC +CC: A

388AG +GG: AA

463CA +AA: A

1929A C+CC: A</td>
<td>Results:
Stepwise forward regression analysis:
<table>
<tr><td colspan="4">Effect per variant allele:</td></tr>
<tr><td></td><td>521T>C</td><td>1332-1091C>T</td><td>728-2859G>A</td></tr>
<tr><td>AUC 3R,5S-fluvastatin</td><td>NS</td><td>x 1.34 (90% CI: 1.25-1.45) (S)</td><td>NS</td></tr>
<tr><td>AUC 3S,5S-fluvastatin</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC total fluvastatin</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC ratio 3R,5S-fluvastatin/3S,5R-fluvastatin</td><td>x 1.23 (90% CI: 1.20-1.27) (S)</td><td>NS</td><td>x 0.88 (90% CI: 0.85-0.92) (S)</td></tr>
<tr><td colspan="4">Note: 1332-1091C>T was in strong linkage disequilibrium with 521T>C and 388A>G. Moreover, 728-2859G>A was in relatively strong linkage disequilibrium with 463C>A, 1929A>C, and 388 A>G).</td></tr>
</table>
Genotyping for selected gene variants:
<table>
<tr><td colspan="5">Effect per variant allele:</td></tr>
<tr><td></td><td>521T>C</td><td>388A>G</td><td>463C>A</td><td>1929A>C</td></tr>
<tr><td>AUC 3R,5S-fluvastatin</td><td>x 1.34 (90% CI: 1.23-1.46) (S)</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC 3S,5S-fluvastatin</td><td>NS</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC total fluvastatin</td><td>x 1.20 (90% CI: 1.10-1.32) (S)</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>AUC ratio 3R,5S/3S,5R-fluvastatin</td><td>x 1.28 (90% CI: 1.24-1.33) (S)</td><td>NS</td><td>x 0.90 (90% CI: 0.86-0.93) (S)</td><td>x 0.84 (90% CI: 0.80-0.89) (S)</td></tr>
</table></td>
<td>statin efficacy and myotoxicity.''</td>
</tr>
<tr>
<td>ref. 3
Mori D et al. Effect of OATP-1B1 genotypes on plasma concentrations of endogenous OATP1B1 substrates and drugs, and their association in healthy volunteers. Drug Metab Pharmacokinet 2019;34:78-86. PubMed PMID: 30528195.</td>
<td>3

521TC: AA
521CC: AA</td>
<td>19 healthy volunteers, selected based on their genotypes, received a single dose of 2 mg fluvastatin (combined with very low dosed rosuvastatin, pitavastatin, and atorvastatin). All patients were homozygous for 388G.
Because the plasma concentration of fluvastatin was below the lower limit of quantification at 5 h post dose, the AUC was calculated from time zero to 4 h.
Other co-medication and grapefruit juice were excluded from at least 1 week before the study.

Genotyping for 521T>C:
- 10x 521TT
- 7x 521TC
- 2x 521CC

Results:
<table>
<tr><td colspan="2">AUC_{0-4h} of fluvastatin compared to 521TT (21.1 nM.h):</td></tr>
<tr><td>521TC</td><td>x 1.25 (NS)</td></tr>
<tr><td>521CC</td><td>x 1.31 (NS)</td></tr>
</table></td>
<td>Authors' conclusion:
''Mean area under the plasma concentration of atorvastatin, pitavastatin, and rosuvastatin in OATP1B1 *15/ *15 were 2.2, 1.7 and 1.58-times greater than the corresponding values in OATP 1B1 *1b/*1b, respectively, whereas that of fluvastatin was identical to those in other OATP1B1 genotypes.''</td>
</tr>
<tr>
<td>ref. 4
Xiang Q et al. The association</td>
<td>3</td>
<td>Meta-analysis of studies investigating the association between SLCO-1B1 gene variants and lipid response to fluvastatin. Two studies were included (Meyer zu Schwabedissen 2015 and Couvert 2008). The</td>
<td>Authors' conclusion:
''The findings of</td>
</tr>
</table>

<table>
<tr>
<td>between the SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid response to fluvastatin: a meta-analysis. Pharmacogenet Genomics 2018;28:261-7. PubMed PMID: 30363031.

ref. 4, continuation</td>
<td>521TC +CC: A

388AG +GG: AA</td>
<td>authors indicate that these studies involved a total of 634 individuals, however the number of fluvastatin users in these studies was only 442. The authors judged the quality of Meyer zu Schwabedissen 2015 and Couvert 2008 to be 8 and 7 of the maximum of 9 points on the Newcastle-Ottawa Scale.
Both studies in the meta-analysis are also included in this risk analysis separately.
Prospective registration of the meta-analysis protocol was not mentioned, but the meta-analyses were performed with a random-effects model. This indicates that the statistical method was chosen prospectively. The search and selection strategy was transparent and the data extraction was standardised. However, the authors used the results for fluvastatin only from Meyer zu Schwabedissen 2015, but mention the number of patients for all statins. Thus, the authors probably overestimated the weight of Meyer zu Schwabedissen 2015 in the meta-analysis.
Analysis of publication bias analyses was not performed. Neither was sensitivity analysis.

Results:
<table>
<tr><td colspan="2">Weighted mean difference in percentage decrease in lipid levels for (521TC+521CC) compared to 521TT:</td></tr>
<tr><td>LDL-cholesterol</td><td>- 5.58% (95% CI: -0.52 - -10.64) (S)</td></tr>
<tr><td>total cholesterol</td><td>- 2.98% (95% CI: -0.84 - -5.12) (S)</td></tr>
<tr><td colspan="2">Weighted mean difference in percentage decrease in lipid levels for (388AG+388GG) compared to 388AA:</td></tr>
<tr><td>LDL-cholesterol</td><td>NS</td></tr>
<tr><td>total cholesterol</td><td>NS</td></tr>
<tr><td colspan="2">There was significant heterogeneity between the studies for both LDL-cholesterol comparisons.
There was no heterogeneity between the studies for both total cholesterol comparisons.</td></tr>
</table></td>
<td>this study suggested that the SLCO1B1 and ApoE polymorphisms could influence the lipid-lowering effect of fluvastatin, whereas the CYP2C9 genotypes were not associated with the therapeutic effects of fluvastatin.’’</td>
</tr>
<tr>
<td>ref. 5
Meyer zu Schwabedissen HE et al. Function-impairing polymorphisms of the hepatic uptake transporter SLCO1B1 modify the therapeutic efficacy of statins in a population-based cohort. Pharmacogenet Genomics 2015;25:8-18. PubMed PMID: 25379722.</td>
<td>3

521TC +CC: AA

388AG</td>
<td>22 patients with dyslipoproteinaemia were treated with fluvastatin for 5 years.
Co-medication with glucocorticoids was excluded, but other relevant co-medication was not.
The association between gene variants and changes in lipid levels was investigated using linear regression models adjusted for statin dose and baseline values.

Genotyping:
521T>C:
- 14x 521TT
- 8x (521TC+521CC)

388 A>G:
- 5x 388AA
- 17x (388AG+388GG)

Results:
<table>
<tr><td colspan="3">Results compared to 521TT:</td></tr>
<tr><td></td><td>521TC+521CC</td><td>value for 521TT</td></tr>
<tr><td>change in LDL-cholesterol</td><td>NS</td><td>-26.7%</td></tr>
<tr><td>change in total cholesterol</td><td>NS</td><td>-18.3%</td></tr>
<tr><td>fluvastatin dose</td><td>x 0.63 (S)</td><td>65.1 mg</td></tr>
<tr><td colspan="3">Note: The data on fluvastatin dose were not adjusted for confounders. Baseline LDL-cholesterol levels were 4.9 mmol/L for 521TT and 4.5 mmol/L for 521TC+521CC. The coronary heart disease risk for patients in both groups was not stated. In addition, the authors indicate that associations between genotype and drug efficacy lost statistical significance after correction for multiple testing.</td></tr>
</table>
<table>
<tr><td colspan="3">Results compared to 388AA:</td></tr>
<tr><td></td><td>388AG+388GG</td><td>value for 388AA</td></tr>
<tr><td>change in LDL-cholesterol</td><td>NS</td><td>-27.7%</td></tr>
<tr><td>change in total cholesterol</td><td>NS</td><td>-16.0%</td></tr>
</table></td>
<td>Authors’ conclusion:
‘’There was no statistically significant effect of the SLCO1B1 c.521T>C genotype on LDL-lowering and TC-lowering efficacy of particular statins. Similar results were obtained on testing the influence of the SLCO1B1 c.388G>A genotype on LDL-lowering and TC-lowering efficacy.’’</td>
</tr>
</table>

ref. 5, continuation	+GG: AA	fluvastatin dose	trend for a decrease (p = 0.087) (NS)	72.1 mg
		Note: The data on fluvastatin dose were not adjusted for confounders. Baseline LDL-cholesterol levels were 4.4 mmol/L for 388AA and 4.8 mmol/L for 388AG+388GG. The coronary heart disease risk for patients in both groups was not stated.		
ref. 6 Pasanen MK et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. Pharmacogenet Genomics 2008;18:921-6. PubMed PMID: 18794729.	3 521TC: AA 521CC: AA	32 White volunteers were given a single dose of 40 mg fluvasta-tin. Co-medication, CYP3A5 expressors and carriers of the ABCC2 1446G and CYP2C9*3 polymorphisms were excluded. This study concerns the same patient group as Niemi 2006. Genotyping: 521T>C: 16x TT, 12x TC, 4x CC 521TT versus 521TC versus 521CC: - No differences in the mean and maximum percentage decrease in cholesterol precursor/cholesterol ratio after administration of fluvastatin The cholesterol precursors investigated were lathosterol and desmosterol. - No differences in the mean and maximum percentage decrease in cholesterol absorption marker/cholesterol ratio after administration of fluvastatin The cholesterol absorption marker investigated was the plant sterol avenasterol. - No difference in total cholesterol before administration of fluvastatin (NS) The authors stated that the sample size was too small to exclude differences in statin response smaller than 40%.	Authors' conclusion: "The short-term effects of statins on cholesterol homeostasis were not associated with the SLCO1B1 polymorphism."
ref. 7 Couvert P et al. Association between a frequent allele of the gene encoding OATP1B1 and enhanced LDL-lowering response to fluvastatin therapy. Pharmacogenomics 2008;9:1217-27. PubMed PMID: 18781850.	3 521TC: AA 521CC: AA 388AG: AA 388GG: AA 463CA: AA[#] 463AA: AA[#]	420 European patients aged 70-85 years used modified-release fluvastatin 80 mg/day for 2 months. Relevant co-medication was not excluded. Genotyping: 521T>C: 305x TT, 110x TC, 5x CC 388A>G: 155x AA, 195x GA, 70x GG 463C>A: 294x CC, 111x CA, 15x AA 521TT versus 521TC versus 521CC: - No difference in LDL-cholesterol before initiation of therapy (203 versus 200 versus 206 mg/dL) (NS) - No significant difference in fluvastatin-induced lowering of LDL-cholesterol (34.0% versus 30.7% versus 31.3%) (NS) 388AA versus 388GA versus 388GG: - No significant difference in LDL-cholesterol before initiation of therapy (204 versus 203 versus 195 mg/dL) (NS) - No significant difference in fluvastatin-induced lowering of LDL-cholesterol (31.3% versus 33.9% versus 34.9%) (NS) 463CC versus 463CA versus 463AA: - No difference in LDL-cholesterol before initiation of therapy (203 versus 200 versus 197 mg/dL) (NS) - Fluvastatin-induced LDL-cholesterol lowering increased with the number of A-alleles (31.5% versus 36.2% versus 41.0%) (S). Multiple regression analysis confirmed that the A-allele was an independent predictor of LDL-cholesterol lowering.	Authors' conclusion: "These results reveal that OATP1B1 is implicated in the pharmacological action and efficacy of fluvastatin. Indeed, the common *14 allele, which is distinguished by the presence of the c.463C>A polymorphism, was associated with enhanced lipid-lowering efficacy in this study."
ref. 8 Singer JB et al. Genetic analysis of fluvastatin response and dyslipidemia in renal transplant recipients.	3 388AG +GG: AA 521TC +CC:	707 North European and Canadian kidney transplant patients received fluvastatin 40-80 mg/day for 5-6 years. Relevant co-medication was not excluded. All patients used the SLCO1B1 inhibitor cyclosporine. Possible associations were determined for 42 SNPs in 18 genes. - There was no association between 388A>G, 521T>C, rs2291075, rs4149069 and rs4149087 SNPs and change in LDL- and HDL-cholesterol	Authors' conclusion: "We found no evidence for genetic factors affecting fluvastatin response."

J Lipid Res 2007;48:2072-8. PubMed PMID: 17563401.	AA		
ref. 9 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.	3 521TC: AA 521CC: AA	32 White volunteers were given a single dose of 40 mg fluvasta-tin. Co-medication and carriers of the ABCC2 1446G and CYP2C9*3 polymorphisms were excluded. Genotyping: 521T>C: 16x TT, 12x TC, 4x CC. 521TC versus 521TT: - The fluvastatin AUC increased non-significantly by 13% from 422.7 to 479.5 ng.hour/mL (NS) 521CC versus 521TT: - The fluvastatin AUC increased non-significantly by 19% from 422.7 to 503.4 ng.hour/mL (NS)	Authors' conclusion: "SLCO1B1 polymorphism has a large effect on the pharmacokinetics of pravastatin but not fluvastatin."
ref. 10 Thompson JF et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352-8. PubMed PMID: 16103896.	3 521TC: A 521CC: A 388AG +GG: AA 463CA +AA: AA	278 White patients used fluvastatin 20 mg/day for 6 weeks. Relevant co-medication was not excluded. Possible associations were determined for 43 SNPs in 16 genes. - Lower increase in HDL-cholesterol in carriers of the 521C allele (increase by 0.5% for CC, 0.65% for CT and 5.45% for TT) (S without correction for multiple tests; p = 0.0061) - The 388A>G, 463C>A, -540C>T, Phe73Leu, rs2291073, rs4149036, rs4149080, Gly488Ala and Leu643Phe SNPs were not associated with reductions in cholesterol and triglyceride concentrations	Authors' conclusion: "None of the associations found here predict atorvastatin LDL-C lowering in a manner sufficient to impact decisions on treatment. As with atorvastatin, SNPs in OATP-C showed association with HDL-C and triglyceride effects with fluvastatin."

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

Risk group	High doses and factors that increase the fluvastatin plasma concentration (hepatic or renal impairment), female gender, advanced age, hypothyroidism

Comments:

- For the period after 2008, only studies with more than 15 patients or volunteers were included. Other studies did not add enough to the evidence.
- Existing guideline:
  Cooper-DeHoff RM et al. The Clinical Pharmacogenetics Implementation Consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. Clin Pharmacol Ther 2022;111:1007-21. PMID: 35152405.
  CPIC distinguishes the following SLCO1B1 genotype groups: poor function (521CC), decreased function (521TC), normal function (521TT, excluding homozygotes for the *14-allele (which has both gene variants 388A>G and 463C>A)), and increased function (homozygotes for the *14-allele). However, CPIC does not recommend therapy adjustment for SLCO1B1 increased function.
  CPIC indicates that, although the association of gene variant 521T>C with myopathy varies by statin, there is evidence supporting the role of SLCO1B1 variants in the systemic clearance of all statins. CPIC indicates in a supplementary figure that in the single-dose study Niemi 2006, the plasma AUC of fluvastatin has been 19% higher in 521CC than in 521TT. In single-dose studies, the effect of 521T>C on statin pharmacokinetics is weakest for fluvastatin.
  Recommendation per genotype group:

Genotype group	Implications	Recommendation[a]	Classification of recommenda-	Considerations

			tion[b]	
521TC	Typical myopathy risk with doses ≤40 mg. Increased fluvastatin exposure as compared with normal function.	Prescribe desired starting dose and adjust doses of fluvastatin based on disease-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for 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 fluvastatin exposure as compared with normal function and 521T>C.	Prescribe ≤40 mg per day as a starting dose and adjust doses of fluvastatin based on disease-specific guidelines. If patient is tolerating 40 mg per day but higher potency is needed, a higher dose (>40 mg) or an alternative statin or combination therapy (i.e., fluvastatin plus nonstatin guideline-directed medical therapy) could be considered. Prescriber should be aware of possible increased risk for myopathy with fluvastatin 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.
388GG+ 463AA	Typical myopathy risk and statin exposure.	Prescribe desired starting dose and adjust doses based on disease-specific guidelines.	Strong	The potential for drug–drug interactions and dose limits based on renal and hepatic function and ancestry should be evaluated prior to initiating a statin.

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

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

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

Date of literature search: 13 March 2023.

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

Mechanism:
The organic anion transporter 1B1 (SLCO1B1) plays a role in fluvastatin transport from the portal vein to liver cells, where fluvastatin inhibits cholesterol production. However, this role seems to be limited, because SLCO1B1 polymorphisms have less effect on plasma concentrations of fluvastatin than on plasma concentrations of other statins.