

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), 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. <u>Gene variant 521T>C</u>:

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_{0-24h} 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 <u>gene variant 1929A>C</u>, 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 on SLCO1B1 transporter activity and thus, no cause for inclusion 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.

Source	Code	Effect						Comments	
ref. 1	4			healthy volunte				Authors' conclu-	
Xiang Q et al.		diate release	40 mg twic	e daily or fluva	statin extende	ed release	e 80 mg	sion:	
The influence		once daily for	7 days.					'The lower expo-	
of genetic poly-		Co-medicatio	n was exclu	uded.				sure following ER	
morphisms in								was observed.	
drug metabo-		Genotyping:						For ER tablets,	
lism enzymes		521T>C		38	8A>G			SLCO1B1 T521C	
and transpor-		- 17x 521TT		- 3	x 388AA			genotype correla-	
ters on the		- 7x 521TC		- 9	x 388AG			ted with AUC ₀₋₂₄	
pharmacokine-				- 1	2x 388GG			of repeat doses.	
tics of different								SLCO1B1 T521C	
fluvastatin		Results:						genotype had no	
formulations.			521TC vers	us 521TT or fo	r 388GG vers	us 388A0	3	statistically signi-	
Asian J Pharm		versus 388A						ficant effect on	
Sci				521T>C	388A>G	value	value	AUC ₀₋₂₄ of IR	
2020;15:264-						for	for	capsule of fluva-	
72.						521	388	statin after single	
PMID:						TT	AA	or repeated	
32373204.	388AG:	Immediate r	elease					doses."	
	AA	AUC _{0-24h}	day 1	x 1.29 (NS)	NS	742.1	875.1		
	388GG:	fluvastatin	day 7	x 1.34 (NS)	NS	1087	1371		
	AA	(ng.h/ml)	uay i						
		t _{1/2} fluva-	day 1	x 1.26		2.15			
		statin (h)		(trend, p =					
				0.059) (NS)					
			day 7	x 1.04 (NS)		1.72			
		Extended re			1				
		AUC _{0-24h}	day 1	x 1.29	NS	319.9	332.4		
		fluvastatin		(trend, p =					
	521TC:	(ng.h/ml)		0.092) (NS)					
	A		day 7	x 1.69 (S)	NS	360.0	393.3		
		t _{1/2} fluva-	day 1	x 0.49 (NS)		10.1			
		statin (h)	day 7	x 1.40 (NS)		10.3			
ref. 2	3			eceived a singl	e dose of 40 i		tatin	Authors' conclu-	
Hirvensalo P et	Ũ			t 3R,5S-fluvast				sion:	
al.		than 3S,5R-fl						"Thus, SLCO	
Enantiospecific		Co-medicatio		transporters have					
pharmacogeno-		Associations	enantiospecific						
mics of fluva-		wise forward	effects on fluva-						
statin.		performed aft	statin pharmaco-						
Clin Pharmacol			kinetics in hu-						
Ther			correction was used to adjust for multiple testing.						
2019;106:668-		Genotypina fo	or 521T>C	(based on the	observed 521	C allele fr	equen-	mans. Genoty- ping of both	
80.		cy):					• • • • •	CYP2C9 and	
PubMed PMID:		- 122x TT						SLCO1B1 may	
30989645.		- 68x TC						be useful in	
		- 10x CC						predicting fluva-	

ref. 2, continu-		Results:						statin efficacy and myotoxicity."				
ation		Results: Stepwise forward	regression an	alvsis.								
		Effect per varia		aryolo.								
			521T>C	1332-10	091C>T	728	-2859G>A					
	1332-											
	1091 CT+TT:	AUC 3R,5S-	NS	x 1.34 (NS						
	A	fluvastatin		CI: 1.25 (S)	5-1.45)							
		AUC 3S,5S-	NS	NS		NS						
		fluvastatin										
		AUC total	NS	NS		NS						
	728-	fluvastatin										
	2859	AUC ratio	x 1.23 (90%	NS			88 (90%					
	GA+AA : A	3R,5S-fluva-	CI: 1.20-1.27)				0.85-0.92)					
	. ^	statin/3S,5R- fluvastatin	(S)			(S)						
		Note: 1332-109	1C>T was in st	rong linkage	e diseaui	libriur	n with					
		521T>C and 38										
		strong linkage o	lisequilibrium w	ith 463C>A	, 1929A>	C, ar	nd 388					
		A>G).										
		Genotyping for s		ariants:								
		Effect per varia	521T>C	388A>G	463C>	Λ	1929A>C					
		AUC 3R,5S-	x 1.34	NS	403C/	A	NS					
	521TC	fluvastatin	(90% CI:				No					
	+CC: A		1.23-1.46)									
			(S)									
		AUC 3S,5S-	NS	NS	NS		NS					
	388AG	fluvastatin										
	+GG:	AUC total	x 1.20	NS	NS		NS					
	AA	fluvastatin	(90% CI:	NO	IN O		NO					
	463CA	navastatin	1.10-1.32)									
	+AA: A		(S)									
	10001	AUC ratio	x 1.28	NS	x 0.90		x 0.84					
	1929A C+CC:	3R,5S/3S,5R-	(90% CI:		(90% ((90% CI:					
	A	fluvastatin	1.24-1.33)		0.86-0	.93)	0.80-0.89)					
ref. 3	3	19 healthy volunt	(S)	haaad on th	(S)		(S)	Authors' conclu-				
Mori D et al.	3	single dose of 2						sion:				
Effect of OATP-		statin, pitavastati						"Mean area				
1B1 genotypes		for 388G.	,	, ,			,,,	under the plasma				
on plasma		Because the plas						concentration of				
concentrations		limit of quantifica	tion at 5 h post	dose, the A	UC was	calcu	lated from	atorvastatin,				
of endogenous OATP1B1 sub-		time zero to 4 h.	tion and grapped	ruit iuice we	ro ovolu	had fr	am at least 1	pitavastatin, and				
strates and		Other co-medica week before the		ruit juice we	ere exclud		om at least 1	rosuvastatin in OATP1B1 *15/				
drugs, and their		week belore the	study.					*15 were 2.2, 1.7				
association in		Genotyping for 5	21T>C:					and 1.58-times				
healthy volun-		- 10x 521TT						greater than the				
teers.		- 7x 521TC						corresponding				
Drug Metab		- 2x 521CC						values in OATP				
Pharmacokinet 2019;34:78-86.		Results:						1B1 *1b/*1b, res- pectively, where-				
PubMed PMID:	521TC:	AUC _{0-4h} of fluva	statin compare	d to 521TT	(21.1 nM	.h).		as that of fluva-				
30528195.	AA	521TC	x 1.25 (NS)		<u></u>			statin was identi-				
·	521CC:	521CC	x 1.31 (NS)					cal to those in				
	AA	· · · · · · · · · · · · · · · · · · ·	· · · · /					other OATP1B1				
					• ••		a	genotypes."				
ref. 4	3	Meta-analysis of					ween SLCO- studies were	Authors' conclu- sion:				
Xiang Q et al.						· · · · · · · · · · · · · · · · · · ·						

SLCO1B1, apolipoprotein E, and CYP2C9 genes and lipid. however the number of fluxastatin users in these studies was only and Couvert 2008 to be 8 and 7 of the maximum of 9 points on the Newcastle-Ottawa Scale. SLCO1B1 and Account 2008 to be 8 and 7 of the maximum of 9 points on the successful the meta-analysis are also included in this risk analysis interaction of the meta-analysis are obtained was not mer- pharmacogenet Genomics Oth studies in the meta-analysis are obtained was not mer- pharmacogenet Genomics Prospective registration of the meta-analysis protocol was not mer- pharmacogenet Genomics O18/28/281-7. Trop obtained for and selection strategy was transparent and the data genotypes were extraction was standardiaed. However, the authors used the results of fluxastatin on from Meyer zu Schwabedissen 2015 bit meta- analysis. Schwabedissen analysis. ref. 4, continu- ation S21TC For (15/17-t521CC) compared to 328/AC to (25/17C-t521CC) Schwabedissen to (25/17C-t521CC) Statin, Weighted mean difference in percentage decrease in lipid levels for (388/AC+388GG) compared to 388/AC. Authors' conclu- there statin, " Tef. 5 Mayer zu Schwabedissen Planta organic 3 22 patients with dysipoproteinaemia were treated with fluxastatin for statin drobesteriol marking linear regression models adjusted for statin to emedication was not. Authors' conclu- sitent effection to emedication was not. Schwabedissen Planta dropket Ing polymor- phamacogenet Results: 3 22 patients with dysipoproteinaemia were not adjusted for confoun- ders association betwere not adjusted for confoun- ders fassibili		1				
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Cenomics 2018;28:261-7. model. This indicates that the statistical method was chosen prospen tref. 4, continu- ation the CYP2C9 was transparent and the data extraction was standardised. However, the authors used the results for fluxastatin only from Meyer zu Schwabedissen 2015. In the meta- analysis. the CYP2C9 enotypes were not associated in the threa- analysis. 8 521TC Fesults: Weighted mean difference in percentage decrease in lipid levels for (388AG+386G) compared to 521TT: LDL-cholesterol the CYP2C9 enotypes were estimuty analysis. 8 888AG + GG: The was gainfoan theterogeneity between the studies for both LDL-cholesterol total cholesterol total cholesterol Status in for (388AG+386G) compared to 388A2: LDL-cholesterol Authors' conclu- sion: "There was no statistically significant heterogeneity between the studies for both LDL-cholesterol comparisons. Co-medication with glucocorticoids was excluded, but other relevant co-medication was not. Function-impai- ring polymor- phase of cohore population- pheatic uptake transporter SLCO1B1 mo- glify the thera- population- phase of cohore statis in a population- population- population- the sasciation betwen gene variants and changes in lipid levels for attsuitar. Sintastically significant heterogeneity between the studies for both LDL-cholesterol comparisons. Co-medication with glucocorticoids was excluded, but other relevant does and baseline values. Authors' conclu- sion: "There was no statistically significant heterogeneity between the studies for both LDL-cholesterol NS Authors' conclu- sion: "There was no statistically significant heterogeneity between co-medication with glucocorticoids was excluded, but other relevant does and baseline values.						
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			cacy lost statistical significan	ce after correction for multi	value for	
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ref. 5, continu-	+GG:	fluvastatin dose	trend for a decrease (p	72.1 mg	
ation	AA	แนงสรเสเทา นบระ	= 0.087) (NS)	12.1 mg	
		Note: The data on fluvastatin ders. Baseline LDL-cholester and 4.8 mmol/L for 388AG+3 risk for patients in both group			
ref. 6	3	32 White volunteers were give			Authors' conclu-
Pasanen MK et al. Polymorphism of the hepatic influx transpor-		Co-medication, CYP3A5 expre 1446G and CYP2C9*3 polymo concerns the same patient gro Genotyping: 521T>C: 16x TT,	orphisms were excluded. Tl oup as Niemi 2006.		sion: "The short-term effects of statins on cholesterol homeostasis
ter organic anion transpor-		521TT versus 521TC versus 5	2100		were not asso- ciated with the
ting polypeptide 1B1 is associa- ted with increa- sed cholesterol	521TC: AA 521CC: AA	 No differences in the mean a cholesterol precursor/choles statin The cholesterol precursors in 	nd maximum percentage d terol ratio after administrati	on of fluva-	SLCO1B1 poly- morphism."
synthesis rate. Pharmacogenet Genomics 2008;18:921-6. PubMed PMID:		sterol. - No differences in the mean a cholesterol absorption marke fluvastatin The cholesterol absorption n avenasterol.	er/cholesterol ratio after adr	ministration of	
18794729.		 No difference in total cholest (NS) The authors stated that the sa 	mple size was too small to		
		rences in statin response sma			
ref. 7 Couvert P et al. Association between a fre- quent allele of	3	420 European patients aged 7 statin 80 mg/day for 2 months ded. Genotyping: 521T>C: 305x TT	. Relevant co-medication w		Authors' conclu- sion: "These results reveal that OATP1B1 is
the gene enco- ding OATP1B1 and enhanced LDL-lowering		463C>A: 294x 521TT versus 521TC versus 5			implicated in the pharmacological action and effica- cy of fluvastatin.
response to fluvastatin the- rapy. Pharmacoge- nomics	521TC: AA 521CC: AA	 No difference in LDL-cholest versus 200 versus 206 mg/d No significant difference in flucholesterol (34.0% versus 30 	L) (NS) uvastatin-induced lowering).7% versus 31.3%) (NS)		Indeed, the com- mon *14 allele, which is distin- guished by the presence of the
2008;9:1217- 27. PubMed PMID: 18781850.	388AG: AA 388GG:	 388AA versus 388GA versus No significant difference in L py (204 versus 203 versus 1 No significant difference in flucholesterol (31.3% versus 33) 	DL-cholesterol before initia 95 mg/dL) (NS) uvastatin-induced lowering		c.463C>A poly- morphism, was associated with enhanced lipid- lowering efficacy
	AA 463CA:	 463CC versus 463CA versus No difference in LDL-cholest versus 200 versus 197 mg/d Fluvastatin-induced LDL-cho 	erol before initiation of ther L) (NS) lesterol lowering increased	with the	in this study."
ref 0	AA# 463AA: AA [#]	number of A-alleles (31.5%) Multiple regression analysis pendent predictor of LDL-che	confirmed that the A-allele plesterol lowering.	was an inde-	Authors:
ref. 8 Singer JB et al. Genetic analy- sis of fluvasta- tin response and dyslipide-	3 388AG +GG: AA	707 North European and Cana fluvastatin 40-80 mg/day for 5 not excluded. All patients used Possible associations were de - There was no association be	-6 years. Relevant co-medi d the SLCO1B1 inhibitor cy termined for 42 SNPs in 18	cation was closporine. 3 genes.	Authors' conclu- sion: "We found no evidence for genetic factors affecting fluva-
mia in renal transplant reci- pients.	521TC +CC:	rs4149069 and rs4149087 S cholesterol			statin response."

r			
-	AA		
2007;48:2072-			
8.			
PubMed PMID:			
17563401.			
	3	32 White volunteers were given a single dose of 40 mg fluvasta-tin.	Authors' conclu-
Niemi M et al.		Co-medication and carriers of the ABCC2 1446G and CYP2C9*3	sion:
SLCO1B1 poly-		polymorphisms were excluded.	"SLCO1B1 poly-
morphism and			morphism has a
sex affect the		Genotyping: 521T>C: 16x TT, 12x TC, 4x CC.	large effect on
pharmacokine-			the pharmaco-
tics of prava-		521TC versus 521TT:	kinetics of prava-
statin but not	521TC:	- The fluvastatin AUC increased non-significantly by 13% from 422.7	statin but not
fluvastatin.	AA	to 479.5 ng.hour/mL (NS)	fluvastatin."
Clin Pharmacol			
Ther		521CC versus 521TT:	
2006;80:356-	521CC:	- The fluvastatin AUC increased non-significantly by 19% from 422.7	
66.	AA	to 503.4 ng.hour/mL (NS)	
PubMed PMID:			
17015053.			
ref. 10	3	278 White patients used fluvastatin 20 mg/day for 6 weeks. Relevant	Authors' conclu-
Thompson JF		co-medication was not excluded. Possible associations were	sion:
et al.		determined for 43 SNPs in 16 genes.	"None of the as-
An association	521TC:		sociations found
	Α	- Lower increase in HDL-cholesterol in carriers of the 521C allele	here predict ator-
SNPs in 16	521CC:	(increase by 0.5% for CC, 0.65% for CT and 5.45% for TT) (S with-	vastatin LDL-C
candidate	A	out correction for multiple tests; $p = 0.0061$)	lowering in a
genes with		- The 388A>G, 463C>A, -540C>T, Phe73Leu, rs2291073, rs4149036,	manner sufficient
atorvastatin	388AG	rs4149080, Gly488Ala and Leu643Phe SNPs were not associated	to impact deci-
response.	+GG:	with reductions in cholesterol and triglyceride concentrations	sions on treat-
Pharmacoge-	AA		ment. As with
nomics J			atorvastatin,
2005;5:352-8.	463CA		SNPs in OATP-C
PubMed PMID:	+AA:		showed associa-
16103896.	AA		tion with HDL-C
			and triglyceride
			effects with fluva- statin."

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:

 resonninendation per genetype group.										
Genotype	Implications	Recommendation ^a	Classifi-	Considerations						
group			cation of							
			recom-							
			menda-							

			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 guide- lines. Prescriber should be aware of possible increased risk for myopa- thy 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 evalua- ted prior to initiating a sta- tin. The effects of drug- drug interactions may be more pronounced, resulting in a higher risk of myopa- thy.
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-spe- cific guidelines. If patient is tolera- ting 40 mg per day but higher potency is needed, a higher dose (>40 mg) or an alternative statin or combination therapy (i.e., fluvasta- tin plus nonstatin guideline-direc- ted 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 evalua- ted prior to initiating a sta- tin. The effects of drug- drug interactions may be more pronounced, resulting in a higher risk of myopa- thy.
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).

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	521TC	4 A	yes	no	16 May 2023
Working Group decision	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.

^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.