SLCO1B1 T521C가 스타틴에 의한 근육독성 발생에 미치는 영향: 체계적 문헌고찰 및 메타분석

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Effect of SLCO1B1 T521C on Statin-induced Myotoxicity: A Systematic Review and Meta-analysis

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ABSTRACT

Background: This study was performed to clarify the effect of SLCO1B1 T521C on statin-induced myotoxicity. **Methods:** The PubMed, Embase, Ovid, and Cochrane Library databases were searched for all published studies between database inception and April 2018. Using Review Manager 5, the pooled odds ratio (OR) and corresponding 95% confidence interval (CI) were determined to assess the effect of SLCO1B1 T521C on statin-induced myotoxicity by using different genetic models. **Results:** Eleven observational studies and one randomized controlled trial were included in the meta-analysis. The pooled analysis showed that the incidence of statin-induced myotoxicity was significantly associated with the SLCO1B1 521C variant allele. Among patients using statins, the incidence of myotoxicity was higher in those carrying the 521TC or 521CC variant than in those carrying the 521TT variant in the dominant model (TC + CC vs TT, OR: 1.57; 95% CI: 1.20, 2.05; $p = 0.001$). The 521TC genotype was associated with a higher risk of myotoxicity than the 521TT genotype (OR: 1.42; 95% CI: 1.09, 1.86; $p = 0.009$). Furthermore, the incidence of myotoxicity was higher in 521CC carriers than in 521TC carriers (OR: 1.40; 95% CI: 1.06, 1.83; $p = 0.02$) and noticeably higher in 521CC carriers than in 521TT carriers (OR: 2.26; 95% CI: 1.23, 4.17; $p = 0.009$). **Conclusion:** The identification of individuals with the SLCO1B1 521C variant allele prior to the initiation of statin therapy might be useful to predict the risk of toxicity development, determine the individual dose, and prevent myotoxicity.

KEY WORDS: SLCO1B1 T521C polymorphism, statin, myotoxicity

Statins, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, are among the most commonly used drugs for preventing and treating cardiovascular diseases. It is widely known that statins markedly reduce low-density lipoprotein cholesterol (LDL-C) levels and prevent stroke and coronary artery diseases, leading to remarkable decrease in cardiovascular morbidity and mortality.¹⁾ Thus far, seven statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin,

rosuvastatin, and simvastatin) have been approved by the United States Food and Drug Administration (U.S. FDA) as lipid-lowering agents, and are frequently prescribed for patients with hyperlipidemia, including high level of LDL-C, total cholesterol (TC), and/or triglyceride (TG) in blood.^{2,3)} The lipid-lowering effects of statins are attributed to the competitive inhibition of HMG-CoA reductase that catalyzes the conversion of HMG-CoA to mevalonate, an early rate-

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limiting step in cholesterol synthesis.⁴⁾ By inhibiting the mevalonate pathway, statins also suppress the production of proinflammatory cytokines and consequently increase the production of endothelial nitric oxide synthase (eNOS), stabilize atherosclerotic plaque, and inhibit inflammation and thrombosis. This allows statins to significantly reduce cardiovascular events and mortality.⁵⁻⁷⁾ Despite the beneficial cardioprotective effect, the adverse effects of statins are the major reasons for non-adherence and/or discontinuation. Myotoxicity is one of the major reasons for discontinuation, presenting as myalgia, myositis, and rhabdomyolysis, with an incidence rate of 7~29%.^{8,9)} The underlying mechanisms have not been clearly elucidated and multiple mechanisms are considered to be involved in pathogenesis of statin-induced myotoxicity. Firstly, the depletion of coenzyme Q10 (CoQ10, ubiquinone) caused by statin-induced reduction in mevalonate, a precursor of both cholesterol and CoQ10, has been shown to be involved in myotoxicity. The depletion of CoQ10 in myocyte mitochondria may impede ATP production and subsequently cause myotoxicity. However, the effect of CoQ10 supplementation on myotoxicity is inconsistent.^{10,11)} In addition, statins enhance skeletal muscle apoptosis in a dose-dependent manner secondary to the inhibition of geranylgeranyl prenylation and activation of small GTPases with subsequent RhoA/AKT inhibition and activation of caspase 3 and caspase 9.⁹⁾ Furthermore, statins increase cytosolic Ca^{2+} increasing mitochondrial Ca^{2+} permeability and Ca^{2+} release from the sarcoplasmic reticulum (SR), leading to mitochondrial membrane depolarization.¹²⁾ Moreover, statins reduce the resting chloride channel conductance in the sarcoplasm, causing fatigue, cramps, and myalgia.⁹⁾ There are many risk factors for statin-induced myotoxicity, including use of high-doses, advanced age (>80 years), female sex, Asian descent, low body mass index, impaired renal or hepatic function, hypothyroidism, and vitamin D deficiency.¹³⁾ Co-administered drugs can also increase the incidence of myotoxicity, such as organic anion transporting polypeptide (OATP) inhibitors (e.g., cyclosporine), CYP3A4 inhibitors (e.g. amiodarone), CYP3A4 substrates (e.g. protease inhibitors), macrolide antibiotics, azole antifungal agents, and fibrates.¹⁴⁻¹⁶⁾ Many studies have reported the effects of genetic polymorphisms of drug transporters on the incidence of statin-associated adverse effects. Solute carrier organic anion transporter family member 1B1 (SLCO1B1), also known as organic anion-transporting polypeptide 1B1 (OATP1B1), OATP2, organic anion-transporting polypeptide-C (OATPC), or liver-specific transporter 1 (LST1),

is one of the most extensively studied drug transporters. The SLCO1B1 transporter is encoded by the *SLCO1B1* gene located in chromosome 12, and is exclusively expressed in the liver. On the sinusoidal membrane of human hepatocytes, SLCO1B1 plays a key role in hepatic uptake of various endogenous and exogenous organic anions, including statins.^{17,18)}

SLCO1B1 T521C (rs4149056, 174Va > Ala) is a non-synonymous single nucleotide polymorphism (SNP) and located on exon 5. In many pharmacokinetic studies, 521CC produced a higher area under the plasma concentration-time curve (AUC) of statins compared to that associated with 521TT or 521TC by reducing the activity and membrane expression of SLCO1B1.¹⁹⁾ However, the results from the studies that examined the association between SLCO1B1 T521C polymorphism and the incidence of statin-induced myotoxicity are inconsistent. In a meta-analysis conducted by Hou *et al.*, patients carrying a SLCO1B1 521C allele had a two-fold times higher risk for statin-induced myotoxicity than patients carrying the 521TT allele.²⁰⁾ In contrast, in the randomized controlled trial (RCT) in which 4,404 subjects were analyzed, no association was found between SLCO1B1 T521C polymorphism and statin-induced myotoxicity.²¹⁾ Since then, four more studies reporting the effect of the 521C allele on statin-induced myotoxicity have been published. Because statin-associated adverse effects occur in a dose-dependent manner and 5.2% of the events can be prevented, before initiating statin therapy, the importance of evaluating risk factors for myotoxicity and determining individualized doses cannot be emphasized enough.²²⁾

In this study, therefore, we investigated the association between SLCO1B1 T521C polymorphism and the incidence of statin-induced myotoxicity through a comprehensive systematic review and meta-analysis analyzing the results from 12 studies.

METHODS

Literature search

A systematic literature search was performed to identify publications reporting the effect of SLCO1B1 T521C polymorphism on the incidence of statin-induced myotoxicity. The PubMed, Embase, Ovid, and Cochrane Library databases were searched for all published studies from inception to April 2018. We also examined several review articles for additional pertinent publications. There was no limitation of publication

language. The terms of “solute carrier organic anion transporter 1b1,” “SLCO1B1,” and “OATP1B1” were combined with “statin,” “HMG-CoA reductase inhibitor,” or “3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor” and then the combined terms were used for keywords.

Study selection and data extraction

Myotoxicity was defined as follows: myalgia, myositis, myopathy, rhabdomyolysis, or acute elevation of creatine kinase (CK) greater than 10 times the upper limit of normal (ULN).^{20,23,24} To be included, original studies needed to fulfill the following criteria: (1) investigation of the effect of SLCO1B1 T521C on the incidence of statin-induced myotoxicity; and (2) reporting of sufficient data for odds ratio (OR) determination. Articles were excluded if they fulfilled the following criteria: (1) reviews, conference abstract or paper, editorial, letter, supplement, case report; (2) studies without genotype frequency for OR; (3) studies investigating the elevation of CK and reporting events of CK elevation greater than 3 times the ULN irrespective of muscle symptoms. We extracted the following information from the selected articles: age, body mass index (BMI), and ethnicity of statin users; generic names and doses of statins used in each study; frequency of SLCO1B1 T521C polymorphism; and incidence of statin-induced myotoxicity in each genotype. Two investigators (PC and YL) independently identified relevant studies and extracted detailed information from each study. Any discrepancies were resolved by consensus after discussion.

Quality assessment

The quality of the observational studies was assessed using the nine-star Newcastle-Ottawa Scale (NOS).²⁵ The NOS assigns up to a maximum of 9 points for the least risk of bias: 4 for selection, 2 for comparability, and 3 for assessment of outcome (for cohort study) or exposure (for case-control study). Studies with points 0-3, 4-6, and 7-9 were rated as “low quality,” “moderate quality,” and “high quality,” respectively.²⁶ For quality evaluation of RCT, Cochrane’s risk of bias (ROB) tool was used. Each study was evaluated for 6 domains of bias: risk of selection bias in relation to adequate or inadequate random sequence generation; risk of selection bias with regard to allocation concealment; risk of performance bias in terms of blinding of participants and personnel; risk of detection bias in relation to blinding of outcome assessment; risk of attrition bias due to incomplete outcome data; and

ROB from selective reporting of outcomes. The RCT was assessed for each domain and judged as “low risk,” “unclear risk,” or “high risk” based on the following definitions: ‘low’ risk, plausible bias unlikely to alter the results; ‘unclear’ risk, plausible bias that raises some doubt about the results; ‘high’ risk, plausible bias that seriously weakens confidence in the results.²⁷ The assessments were independently performed by two researchers (PC and YL) and any disagreements were resolved by a consensus.

Statistical analysis

Statistical analyses were performed using Review Manager version 5.1 (Cochrane Collaboration, Oxford, United Kingdom). To assess the association between the SLCO1B1 T521C polymorphism and statin-induced myotoxicity, the weighted pooled estimates of the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in different genetic models: dominant model (TC + CC vs TT), heterozygote contrast model (TC vs TT, CC vs TC), and homozygote contrast model (CC vs TT). If the incidences of myotoxicity were reported separately according to symptom presentation and the numbers of the subjects monitored for each symptom were different in one study, the incidences of each symptom were considered as independent outcomes from separate studies. Two-sided *p* values less than 0.05 were considered statistically significant. Study heterogeneity was estimated with the *I*² statistic, with values of 25, 50, and 75% representing “low,” “moderate,” and “high,” respectively.²⁸ When the studies with an *I*² statistic of >50% were considered to have substantial heterogeneity, a random-effects model analysis was used. Otherwise, a fixed-effect model was employed.²⁹ Publication bias was evaluated by visual inspection of a funnel plot. When asymmetry was found in funnel plots, a sensitivity analysis was performed by outlier elimination to assess the influence of the outliers on the overall results of this meta-analysis.³⁰

RESULTS

Literature search

The process of study selection is outlined in Fig. 1. Of the 419 records identified in the database search, 266 articles were considered potentially relevant. After further review of their full text, one RCT,²¹ three prospective cohort studies,³¹⁻³³ one retrospective cohort study,³⁴ and seven case-control studies³⁵⁻⁴¹ met the inclusion and exclusion criteria of the

Fig. 1. Flow of the study selection process for a systematic review and meta-analysis

present meta-analysis.

Study characteristics

The characteristics of the included studies are summarized in Table 1. A total of 14,277 subjects were analyzed and statin-induced myotoxicity was observed in 20.3% of these subjects. Of the total subjects, 40.7% had the 521C allele. Among the carriers of the 521C allele, 21.6% experienced myotoxicity, whereas 19.7% of the 521TT carriers developed the toxicity. More than 63.3% of the total subjects were Caucasian, whereas 2.8% of the total were Asian. Statins produced myotoxicity in 30.4% of the Caucasians and 30.8% of the events were observed in the subjects carrying the 521C allele. A variety of statins were taken and the daily doses varied from less than 10 to 160 mg. The range of the participants' mean age was 52-71 years. The subjects' BMI suggested that no study was conducted in subjects with a high risk for myotoxicity.

Quality assessment

The assessment of the quality of 11 observational studies indicated that two studies met the criteria of moderate quality while nine were assessed as having high quality: five stars for two studies^{32,36}; seven stars for three studies^{31,34,38}; eight stars for three studies^{33,35,40}; and nine stars for three studies^{37,39,41} (Supplementary Table S1). The ROB of one RCT was evaluated and the study was rated as "low risk" for all domains.²¹

Effect of SLCO1B1 T521C on the incidence of statin-induced myotoxicity

A total of 11 observational studies and one RCT were included in the present meta-analysis. The SLCO1B1 521C allele was significantly associated with statin-induced myotoxicity. A significantly higher incidence rate of statin-induced myotoxicity was observed in the 521TC- or 521CC-carrying users than in the 521TT-carrying users under the dominant genetic model

Table 1. Characteristics of the included studies and genotype frequencies of SLCO1B1 T521C polymorphism in statin users

Study	Study design	Ethnicity	Age (years) (mean $\pm$ SD)	BMI (kg/m ²) (mean $\pm$ SD)	Statins; dose (mg/day)	Genotypes (n)					
						case			control		
						TT	TC	CC	TT	TC	CC
Link <i>et al.</i> , 2008	case-control	Caucasian	<65 (35%); ≥ 65 (65%)	NR	S; 80	12	15	14	70	17	3
Voora <i>et al.</i> , 2009*	cohort	Caucasian (86%); African American (5%)	56 $\pm$ 10	29.1 $\pm$ 5.2	A, P, S; 10~80	62	31	4	263	84	4
Linde <i>et al.</i> , 2010	cohort	NR	case: 59.5 $\pm$ 10; control: 59.3 $\pm$ 13.8	case: 27.9 $\pm$ 5.7; control: 27.5 $\pm$ 5.5	A, F, L, P, R, S; 10~80	14	12	1	15	4	0
Donnelly <i>et al.</i> , 2011	cohort	NR	63 $\pm$ 10.6	30.6 $\pm$ 5.6	A, C, F, P, R, S (69% of all); ≥ 40 mg for 65% of all	565	227	24	905	348	22
Marcianti <i>et al.</i> , 2011	case-control	Caucasian (88%)	case: 63.5 $\pm$ 10.6; control: 69.1 $\pm$ 6.7	NR	C; case: 33.2 $\pm$ 15.7; control: 30.6 $\pm$ 15.7	141		44	630		102
Brunham <i>et al.</i> , 2012	case-control	Caucasian	case: 53 $\pm$ 13; control: 57 $\pm$ 12	NR	A (42% of all), P, R, S (47% of all); 10~80 for all; case: 31 $\pm$ 23; control: 36 $\pm$ 25	15	8	2	57	20	6
Santos <i>et al.</i> , 2012	cohort	Caucasian (87%); Mulatto (10%); African (3%)	case: 54.3 $\pm$ 13.2; control: 52.5 $\pm$ 14.9	case: 28.3 $\pm$ 4.7; control: 26.9 $\pm$ 5.2	A; 20~80; case: 33.2 $\pm$ 15.7; control: 30.6 $\pm$ 15.7	10		4	70		59
Carr <i>et al.</i> , 2013	case-control	Caucasian	case: 69.9 $\pm$ 10.4; control: 71.2 $\pm$ 8.7	case: 29.3 $\pm$ 5.4; control: 28.5 $\pm$ 4.9	A, C, F, P, R, S (63% of all); case: 33.2 $\pm$ 15.7; control: 30.6 $\pm$ 15.7	40	29	6	260	100	11
Danik <i>et al.</i> , 2013a Danik <i>et al.</i> , 2013b	RCT	Caucasian (71.4%); others (28.6%)	65.7 $\pm$ 8.1	28.5 $\pm$ 5.0	R; 20	300 628	104 211	13 23	2792 2465	1077 974	108 98
Mirošević <i>et al.</i> , 2015 [†]	case-control	Caucasian	case: 56(median); control: 60(median)	NR	A; 10~80; 20 (median)	34	22	4	69	21	0
Liu <i>et al.</i> , 2017	case-control	Asian	case: 60.56 $\pm$ 10.81; control: 63.3 $\pm$ 10.7	case: 24.9 $\pm$ 3.3; control: 24.1 $\pm$ 3.2	A (57%), F, L, P, R, S; NR	101		47	200		55
Bakar <i>et al.</i> , 2018	case-control	Caucasian	case: 60.3; control: 60.9	28.5 (median)	A (33%), S(67%); 10~80	78	45	2	353	112	11

BMI: body mass index, *: 51% of all cases were myotoxicity, [†]: 62% of all cases were myotoxicity, A: atorvastatin, C: cerivastatin, F: fluvastatin, L: lovastatin, P: pravastatin, R: rosuvastatin, S: simvastatin, RCT: randomized controlled trial, Danik *et al.*, 2013a for myalgia; Danik *et al.* 2013b for muscle weakness, stiffness, or pain, NR: not reported

Fig. 2. Forest plots of the association between SLCO1B1 T521C polymorphism and statin-induced myotoxicity under the dominant genetic model. Squares represent study-specific OR; horizontal lines represent 95% CIs; diamond represents a summary odds ratio estimate with corresponding 95% CI

Fig. 3. Forest plots of the association between SLCO1B1 T521C polymorphism and statin-induced myotoxicity under the heterozygote contrast model (TC vs TT). Squares represent study-specific OR; horizontal lines represent 95% CIs; diamond represents a summary odds ratio estimate with corresponding 95% CI

(TC + CC vs TT, OR: 1.57; 95% CI: 1.20, 2.05; $p = 0.001$; I^2 : 82%) (Fig. 2). Compared to the 521TT carriers, the 521TC carriers had a higher incidence rate of myotoxicity under the heterozygote contrast model (TC vs TT, OR: 1.42; 95% CI: 1.09, 1.86; $p = 0.009$; I^2 : 77%) (Fig. 3). Similarly, a higher incidence rate was associated with the 521CC genotype than with the 521TC genotype (CC vs TC, OR: 1.40; 95% CI: 1.06, 1.83; $p = 0.02$; I^2 : 8%) (Fig. 4). A markedly higher incidence rate of myotoxicity was observed in the 521CC-carrying users than in the 521TT-carrying users under homozygote contrast model (CC vs TT, OR: 2.26; 95% CI: 1.23, 4.17; $p = 0.009$; I^2 : 70%) (Fig. 5). High levels of

heterogeneity were found in the dominant, heterozygote contrast (TC vs TT), and homozygote contrast models, whereas low level of heterogeneity was found in the heterozygote contrast model (CC vs TC).

Publication bias and sensitivity analysis

Some asymmetry was found in the funnel plots of the analysis for the dominant, heterozygote contrast (TC vs TT), and homozygote contrast models (Fig. 6). Because the study by Link *et al.*³⁵⁾ was one of the factors that contributed to the asymmetry as an outlier, a sensitivity analysis was performed by outlier elimination. Although the asymmetry improved

Fig. 4. Forest plots of the association between SLCO1B1 T521C polymorphism and statin-induced myotoxicity under the heterozygote contrast model (CC vs TC). Squares represent study-specific OR; horizontal lines represent 95% CIs; diamond represents a summary odds ratio estimate with corresponding 95% CI

Fig. 5. Forest plots of the association between SLCO1B1 T521C polymorphism and statin-induced myotoxicity under the homozygote contrast model. Squares represent study-specific OR; horizontal lines represent 95% CIs; diamond represents a summary odds ratio estimate with corresponding 95% CI

after the exclusion of the study by Link *et al.*, a publication bias was still detected. In the analyses for the dominant and homozygote contrast models, few studies resided in the bottom part, indicating that some smaller studies might have been missed. In the analysis for the heterozygote contrast (TC vs TT) model, no studies resided in the bottom-left part, implying that some smaller studies reporting negative results might have been missed (Fig. 7). On the other hand, the funnel plot of the analysis for the heterozygote contrast model (CC vs TC) had no outlier. However, in the analysis, few studies resided in the bottom part, suggesting that some smaller studies might have been missed (Fig. 8). In the sensitivity analysis performed after excluding the study by Link *et al.*, which reported a remarkably high incidence, a

significant association between the SLCO1B1 521C allele and statin-induced myotoxicity was still found (TC + CC vs TT, OR: 1.40; 95% CI: 1.11, 1.76; $p = 0.005$; $I^2 = 76\%$; TC vs TT, OR: 1.28; 95% CI: 1.01, 1.63; $p = 0.04$; $I^2 = 71\%$; CC vs TT, OR: 1.35; 95% CI: 1.03, 1.76; $p = 0.009$; $I^2 = 39\%$) (Supplementary Fig. S1, S2, S3).

DISCUSSION

The results of the present meta-analysis demonstrated that the incidence of statin-induced myotoxicity was 1.57 times higher in the carriers of SLCO1B1 521C allele than in the carriers of the 521TT allele. This result is consistent with the result from a previous study by Hou *et al.*²⁰⁾, in which the

Fig. 6. Funnel plots for publication bias of the included studies for the effects of SLCO1B1 T521C on statin-induced myotoxicity under the different genetic models: (A) dominant genetic model, (B) heterozygote contrast (TC vs TT) model, (C) homozygote contrast model

521C allele increased the incidence 2.09 times to that associated with the 521TT allele.

This meta-analysis analyzed the results of three case-control studies and one RCT that had been published after the meta-analysis by Hou *et al.* However, the study by Ferrari *et al.*⁴²⁾ was excluded in this meta-analysis. The reason is that most clinical trials used CK elevation of greater than 10 times the ULN to define statin-associated myopathy,^{43,44)} but Ferrari *et al.*, in contrast, reported the events of CK elevation greater than 3 times the ULN irrespective of muscle symptoms. Despite the differences in the studies included in each meta-analysis, the results of this study coincide with the results of the previous meta-analysis by Hoe *et al.* Similarly, Jiang *et al.* reported 1.85 times higher risk for statin associated adverse drug reactions in the carriers of the 521C allele than in the 521TT carriers.⁴⁵⁾ These results are supported those of the pharmacokinetic studies in which the 521C allele was associated with a significantly increased statin AUC.^{19,43)}

There are some limitations in this meta-analysis. First, we did not consider the effects of OATP2B1 and OATP1B3 on the hepatic uptake of statins, although SLCO1B1 plays a key role in the transport of hydrophilic statins such as pravastatin and rosuvastatin. In addition, atorvastatin is a substrate for OATP2B1 as well as SLCO1B1, while fluvastatin and pitavastatin are substrates for OATP1B3 and OATP2B1 in addition to SLCO1B1.⁴⁶⁻⁴⁸⁾

Furthermore, although statin-associated myotoxicity occurs in a dose-dependent manner and the use of high doses is one of the risk factors,⁴⁹⁾ in this meta-analysis, we could not conduct a subgroup analysis stratified by statin doses because the daily doses were varied and most of studies did not report the doses according to the SLCO1B1 T521C polymorphism. In addition, the incidence of myotoxicity is also affected by medical conditions, concurrent medications, and food,^{15,16,50)} and it is difficult to believe that all these factors were controlled because most of the studies included in the meta-

Fig. 8. Funnel plot for publication bias of the included studies for the effects of SLCO1B1 T521C on statin-induced myotoxicity under heterozygote contrast (CC vs TC) model

analysis were retrospective studies. Lastly, this study failed to examine the effect of ethnicity on the incidence of myotoxicity because more than 63% of the participants were Caucasian and only 2.8% were Asian.

Fig. 7. Funnel plots for publication bias of the studies included in the sensitivity analysis for the effects of SLCO1B1 T521C on statin-induced myotoxicity under the different genetic models: (A) dominant genetic model, (B) heterozygote contrast (TC vs TT) model, (C) homozygote contrast model

In the present meta-analysis, a significantly higher incidence rate of statin-induced myotoxicity was observed in the carriers of the SLCO1B1 521C allele. Based on the results of this study, 41% of the total users were 521C carriers and 20% of them experienced myotoxicity.

CONCLUSION

Taking these factors into consideration, before the initiation of statin therapy, identification of individuals with the SLCO1B1 521C allele might be useful in predicting the risk for toxicity development, determining individualized doses, and preventing myotoxicity.

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