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Meta-Analysis of the *SLCO1B1* c.521T>C Variant Reveals Slight Influence on the Lipid-Lowering Efficacy of Statins

Ye Dou, M.S.[1], Xiaohai Zhu, M.B.[1], Qinglu Wang, Ph.D.[1], Xuewen Tian, M.S.[2], Jingjing Cheng, M.S.[2], and Enying Zhang, Ph.D.[3]

Key Laboratory of Biomedical Engineering & Technology of Shandong High School[1], Shandong Wanjie Medical College, Zibo; Sports Science Research Center of Shandong Province[2], Jinan; College of Agronomy and Plant Protection[3], Qingdao Agricultural University, Qingdao, Shandong, China

Background: Several studies have focused on the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism; however, the results are conflicting. The effects of statins show significant variability between individuals. This meta-analysis aimed to investigate the effects of the *SLCO1B1* c.521T>C polymorphism on the lipid-lowering effects of statins.

Methods: We systematically searched PubMed and Web of Science to screen relevant studies. Meta-analysis was performed to identify the association between *SLCO1B1* c.521 polymorphisms and the lipid-lowering effects of statinson the basis of the standard mean difference (SMD) and 95% confidence intervals (CIs). Additionally, we checked for heterogeneity (I^2) among studies and evidence of publication bias. We obtained eight studies including 2,012 wild genotype (T/T) and 526 variant genotype (T/C and C/C) cases.

Results: No significant difference was observed in the lipid-lowering efficacy of statins between the wildand variant genotypes of *SLCO1B1*, with a pooled SMD of 0.03 (95% CI: -0.07-0.13). Furthermore, there was no significant effect in the meta-analyses of the variant heterozygote, homozygote, and Chinese populations. Subgroup meta-analysis indicated that the timerequired for the statin to take effectdid notsignificantly affect the association between lipid-lowering efficacy of statins and *SLCO1B1* c.521T>C polymorphism. However, thewild genotype improved the lipid-lowering efficacy of simvastatin with a pooled SMD of -0.26 (95% CI: -0.47- -0.05).

Conclusions: No significant association was detected between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism, with the exception of simvastatin.

Key Words: *SLCO1B1* gene, Statins, Lipid-lowering effect, Meta-analysis

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Corresponding author: Qinglu Wang
Key Laboratory of Biomedical Engineering & Technology of Shandong High School, Shandong Wanjie Medical College, Boshan Economic Development Zone, Zibo, Shandong 255213, China
Tel: +86-533-4662146
Fax: +86-533-4619638
E-mail: wql_zcq@126.com

Co-corresponding author: Enying Zhang
College of Agronomy and Plant Protection, Qingdao Agricultural University, Qingdao, Shandong 266109, China
Tel: +86-533-4662146
Fax: +86-533-4619638
E-mail: eyzhang@sina.com

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. Both high LDL-cholesterol and low HDL-cholesterol concentrations are important risk factors for cardiovascular disease. Lowering cholesterol is the most common method to prevent cardiovascular disease, especially during the primary and secondary levels of cardiovascular disease. Furthermore, statins are the most conventional and widely used cardiovascular disease prevention drugs for the treatment of hyperlipemia [1, 2].

By principally inhibiting hepatic β-hydroxy-β-methyl glutaryl CoA reductase (HMG-CoA reductase), statins limit the rate of cholesterol synthesis. This reduces plasma concentrations of both total and LDL-cholesterols [3]. There are various forms of

statins, including pravastatin, fluvastatin, lovastatin, pitavastatin, rosuvastatin, cerivastatin, and simvastatin. However, the process of plasma reduction increases the risk of myopathy and rhabdomyolysis during statin therapy [4]. In spite of this, there is a great deal of variability between individuals with respect to the therapeutic reactions to these drugs; however, the origins of this variation are still only partially understood. Thus, to explain this variation better, recent studies have focused on hepatocytes, which are the primary sites of statin action. With a better understanding of hepatic influx and efflux transporters, researchers may be better able to explain the underlying genetic variations contributing to response to statin treatment [5].

The organic anion transporting polypeptide (OATP) 1B1 (also known as OATP-C, OATP2, and LST-1), which is encoded by the solute carrier organic anion transporter family member 1B1 gene (*SLCO1B1*), is located on the basolateral (sinusoidal) membrane of hepatocytes. *OATP1B1* is a major determining factor for the transport (uptake) of several HMG-CoA reductase (statins) inhibitors from the portal circulation into hepatocytes. Previous single-dose studies have shown that plasma concentrations of pravastatin, rosuvastatin, and pitavastatin are considerably higher in subjects with certain *SLCO1B1* single-nucleotide polymorphisms (SNPs), especially c.521T>C (Val174Ala, *OATPC*5*, rs4149056) [3]. Some research groups also reported that the *SLCO1B1* c.521T>C SNP of *SLCO1B1* increased the concentration of atorvastatin and simvastatin in human plasma [6, 7]. Therefore, whether or not the *SLCO1B1* c.521T>C genetic variation can influence the lipid-lowering effect of statins is a crucial question. Zhang *et al*. [8] reported that the *SLCO1B1* c.521T/C genotype (variant heterozygote) attenuated total cholesterol levels comparedwith the 521T/T genotype (wild genotype). Tachibana-Iimori *et al*. [9] performed a retrospective study on elderly Japanese patients who received treatment with atorvastatin (N=11), simvastatin (N=33), or pravastatin (N=22). They demonstrated that subjects with the *SLCO1B1* c.521T>C genotype (N=20) showed a smaller mean percentage reduction in lipid-lowering effectsin patients with 521T/C genotype than in patients with the wild genotype 521T/T (N=44) after statin treatment. By contrast, some studies showed that *SLCO1B1* c.521T>C polymorphisms may not be associated with the lipid-lowering effects of statins [5, 10]. Accordingly, the influence of the *SLCO1B1* c.521T>C polymorphism on the lipid-lowering response to statins remains uncertain [5]. Thus, the objective of our meta-analysis was to determine the effect of *SLCO1B1* c.521T>C genetic variation on the lipid-lowering efficacy of statins.

METHODS

1. Literature search

We searched the PubMed database from 1990 to April 2014 as well as the Web of Science database, with an index ranging from 1985 to April 2014. We ran searches based on the following terms: "*SLCO1B1*," "*OATP1B1*," "cardiovascular disease," "LDL-cholesterol," "lipid-lowering," "polymorphism," and "statins," including all possible combinations therein. We also conducted manual searches following up on all of the studies' references. Lastly, we inspected several related articles from reviews and other pertinent sources such as research bibliographies.

2. Inclusion and exclusion criteria

The criteria that we used to determine whether a study was suitable for our meta-analysis included five factors: (1) the research must involve cases; (2) the relationships between *SLCO1B1* c.521T>C polymorphisms and the lipid-lowering efficacy of statins must be assessable; (3) the concentration change of LDL-cholesterol must be provided; (4) the article must be written in English; and (5) the research should provide sufficient information to estimate the standard mean difference (SMD) and corresponding 95% confidence intervals (CIs).

We excluded the following materials: (1) reviews, letters, conference abstracts, and case reports; (2) studies lacking information on the change in the LDL-cholesterol concentration; (3) articles that did not offer enough data to estimate the SMD related to the *SLCO1B1* c.521T>C variant and statins' lipid-lowering efficacy; (4) non-English articles; and (5) overlapping articles. Accordingly, these articles were not applied into the scope of our meta-analysis.

3. Data extraction and assessment

After careful review, we extracted the following data from each of the eligible articles: the name of the first author, publication year, nationality, number of patients (T/T, T/C, and C/C genotype), drug type, the cycle of drugs, daily dosage, change ratio (%) in LDL-cholesterol (T/T, T/C, and C/C genotype), and the genotyping method. The quality of each study was evaluated according to the Newcastle-Ottawa quality assessment scale [11].

4. Description of studies

A total of 550 studies were initially identified from a search of the two data bases, according to the aforementioned inclusion and exclusion criteria (Fig. 1). After a thorough survey of these identified studies, we found and selected eight eligible studies for

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closer analysis [1, 3-5, 8, 10, 12, 13].

Table 1 shows a summary of the extracted data of the eight included studies item by item. In total, these studies included 2,538 cases comprising 2,012 wild genotype (T/T) cases and 526 variant genotypes cases (T/C and C/C). These cases were compared to determine the lipid-lowering efficacy of statins between the wild and variant genotypes. Five studies included multi-parallel data, owing to the specific drug type and genotype in the respective experiment groups. Sample sizes ranged from five to 305 cases. Four studies recruited less than 100 cases and the other four studies involved more than 100 cases. Three of the eight studies were conducted in China, and the remaining five studies were conducted in Finland, Germany, France, the United Kingdom, and Brazil, respectively.

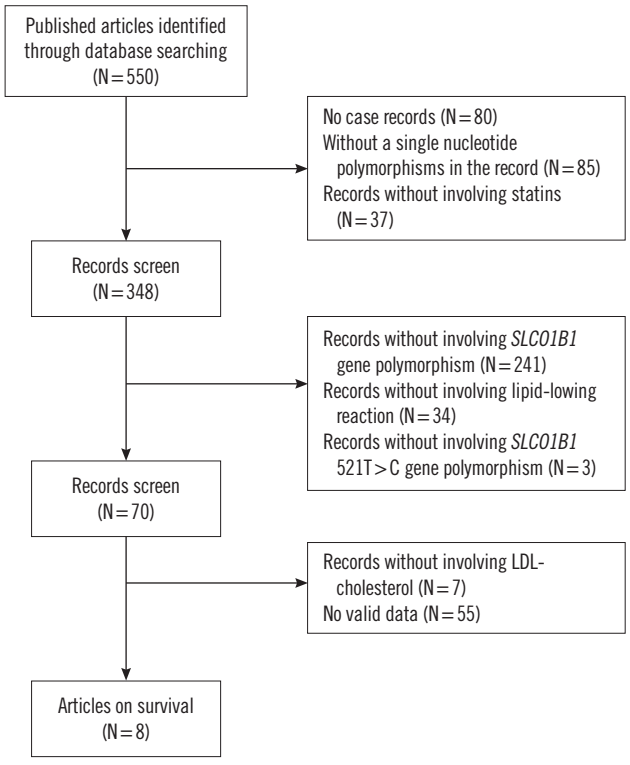

Fig. 1. Flow diagram of the study selection process.

5. Statistical analysis

The SMDs and corresponding 95% CIs were combined to determine the overall effect size of the continuous variables. We then used this result to assess the association between the *SLCO1B1* c.521T>C variant and the statins' lipid-lowering efficacy (based on LDL-cholesterol) in relation to several variables, including the type of statin, the medication dose, the length of time taken for the medicine to be effective, and the genotype (only *SLCO1B1* c.521T>C). For the pooled analysis of the difference in the effect of the *SLCO1B1* c.521T>C variant on the lipid-lowering (LDL-cholesterol) ability of statins, the SMD and 95% CI served as the summary statistics for our meta-analysis using the fixed-effects (FE) model. In some cases, we were able to pool statistical variables directly; this occurred whenever the statistical infor-

Table 1. Summary of the data used in the meta-analysis

First author	Year	Country	Drug	N of patient			Duration of treatment	Medication dose	Percentage change (%) of LDL-cholesterol level			Genotyping method
				TT	TC	CC			TT	TC	CC	
Igel M	2006	Germany	Pravastatin	8	8		3 weeks	40 mg/day	-19.10±8.30	-13.10±9.10		PHASE program
Hedman M	2006	Finland	Pravastatin	14	6	-	2 months	10 mg/day	-20.10±10.20	-23.20±11.60	-	TaqMan
Zhang W	2007	China	Pravastatin	36	9	-	30 days	20 mg/day	-22.40±10.30	-14.50±6.60	-	PCR
Couvert P	2008	France	Fluvastatin	305	110	5	2 months	80 mg/day	-34.00±15.90	-30.70±17.40	-31.30±5.20	TaqMan
Bailey KM	2010	United	Simvastatin	200	82	9	3 months	-	-79.52±25.36	-77.77±25.25		TaqMan
		Kingdom	Rosuvastatin	231	72	7			-73.24±23.41	-76.34±20.85		
Yang GP	2010	China	Pitavastatin	64	21		4 weeks	2 mg/day	-31.00±21.00	-30.00±26.00		PCR-RFLP ARMS-PCR
Yang GP	2010	China	Pitavastatin	64	21		8 weeks	2 mg/day	-29.00±26.00	-27.00±29.00		PCR-RFLP ARMS-PCR
Sortica VA	2012	Brazil	Simvastatin	152	59	5	6 months	20 mg/day	-38.60±8.00	-39.90±8.60	-42.10±15.80	TaqMan
Fu Q	2013	China	Atorvastatin	133	49	7	4 weeks	20 mg/day	-27.80±5.30	-26.50±6.00	-26.80±3.50	AS-PCR
			Simvastatin	123	46	5			-27.20±5.40	-28.90±5.90	-30.80±5.40	RFLP

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Abbreviations: ARMS, amplification refractory mutation system; AS, allele-specific; RFLP, restriction fragment length polymorphism.

mation was adequately described in the literature. In other cases, however, these statistical variables were calculated from available numerical data provided in the articles using the Parmar methods [14]. According to the *SLCO1B1* c.521T>C genotype, the participants were divided into two different groups: (1) wild type genotype and (2) variant genotype. In the variant genotype group, patients were further divided into two subgroups: (1) variant heterozygote or (2) homozygote. While these subgroups were treated as two different studies in the literature, they were considered as parts of the same study during our meta-analysis.

Whenever observed, SMD=0 implied unfavorable parameters for the group, as it indicated a lack of association between the *SLCO1B1* c.521T>C polymorphism and the lipid-lowering efficacy of statins. We identified the differential impact of the *SLCO1B1* c.521T>C variant on the lipid-lowering effect of statins as statistically significant if the 95% CI did not overlap with 0. We assessed the heterogeneity of all studies by using the chi-square statistic, which is based on the Q statistical test. The quantification of the proportion of total heterogeneity across studies was based on the I^2 statistic, which is measured from 0% to 100%. Absence of heterogeneity was confirmed if $I^2<50\%$ or $P>0.10$ among the studies. The pooled SMD estimate of each study was then calculated by using the FE model (specifically, the inverse-variance method). The probability of publication bias was evaluated by using the funnel plot method. We carried out the statistical analyses using Review Manager 5.2 software (The Nordic Cochrane Center, The Cochrane Collaboration,Copenhagen, Denmark). All *P* values were for a two-sided test, and differences were considered statistically significant whenever $P<0.05$.

RESULTS

1. Meta-analysis

We observed no obvious heterogeneity ($I^2=31\%$) among the eight studies that evaluated the lipid-lowering efficacy of statins between the wild and variant genotypes, based on a change in-LDL-cholesterol concentration (Fig. 2). Accordingly, the FE model was used to calculate the pooled SMDs with corresponding 95% CIs. Overall, the meta-analysis results indicated that there was nostatistically significant association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism. The overall SMD was 0.03 (95% CI: -0.07-0.13; $P=0.59$). When stratifying among the Chinese population specifically, we obtained an SMD of 0.03 (95% CI: -0.15-0.21; *P*=

Table 2. Meta-analysis results of all studies and each subgroup studies

	Cases	Heterogeneity analysis		Pooled SMD	95% CI
		I^2 (%)	*P* value		
Variant genotype*	526	31	0.12	0.03	-0.07-0.13
China populations†	158	49	0.07	0.03	-0.15-0.21
Variant genotype (T/C)‡	284	63	0.02	0.06	-0.08-0.20
Variant genotype (C/C)§	22	0	0.41	-0.15	-0.57-0.28
Variant genotype (T/C & C/C)‖	220	0	0.55	0.01	-0.15-0.16

*Analysis of the association between the lipid-lowering efficacy of statins and *SLCO1B1* c.521T>C polymorphism; †Analysis of the association between the lipid-lowering efficacy of statins and *SLCO1B1* c.521T>C polymorphism in Chinese populations; ‡Analysis of the association between the lipid-lowering efficacy of statins and *SLCO1B1* variant heterozygotes (T/C); §Analysis of the association between the lipid-lowering efficacy of statins and *SLCO1B1* variant homozygotes (C/C); ‖These studies did not provide the cases of single heterozygote (T/C) or homozygote (C/C).
Abbreviations: SMD, standard mean difference; CI, confidence interval.

Table 3. Main results of meta-analysis for the drug type and treatment length subgroups

	N of cases	Heterogeneity analysis		Pooled SMD	95% CI
		I^2 (%)	*P* value		
Pravastatin	23	37	0.20	0.46	-0.05-0.97
Simvastatin	206	24	0.26	-0.12	-0.28-0.04
Simvastatin*	115	0	0.71	-0.26	-0.47- -0.05
Length of time required for medicine to be effective (≤1 month)	145	54	0.04	0.05	-0.14-0.24
Length of time required for medicine to be effective (>1 month)	381	1	0.42	0.02	-0.10-0.14

*The data by Bailey *et al*. [12] were excluded. If $P>1$, there is no heterogeneity in simvastin subgroup.
Abbreviations: SMD, standard mean difference; CI, confidence interval.

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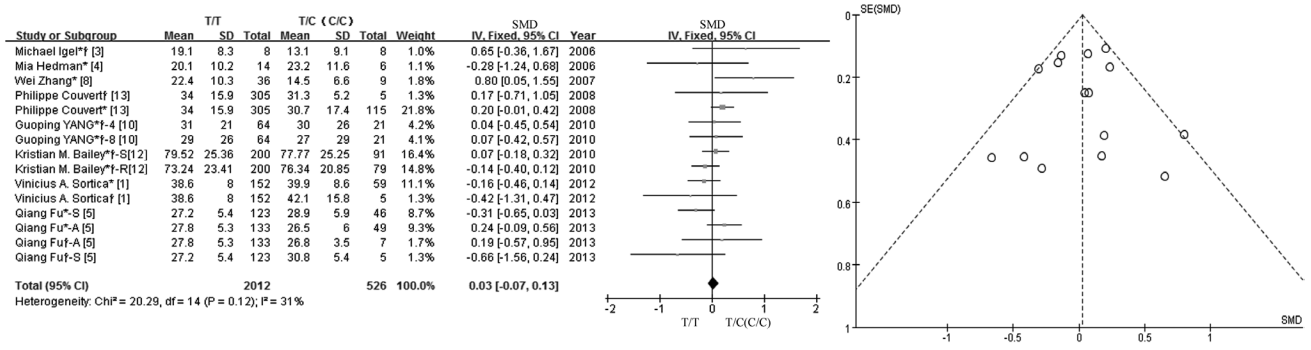

Fig. 2. Forest plot of SMD for the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism, and funnel plots for evaluating publication bias. *TC genotype; †CC genotype; *†TC and CC genotype.
Abbreviations: SMD, standard mean difference; CI, confidence interval; df, degrees of freedom; S, simvastatin; A, atorvastatin; R, rosuvastatin; 4, 4 weeks; 8, 8 weeks.

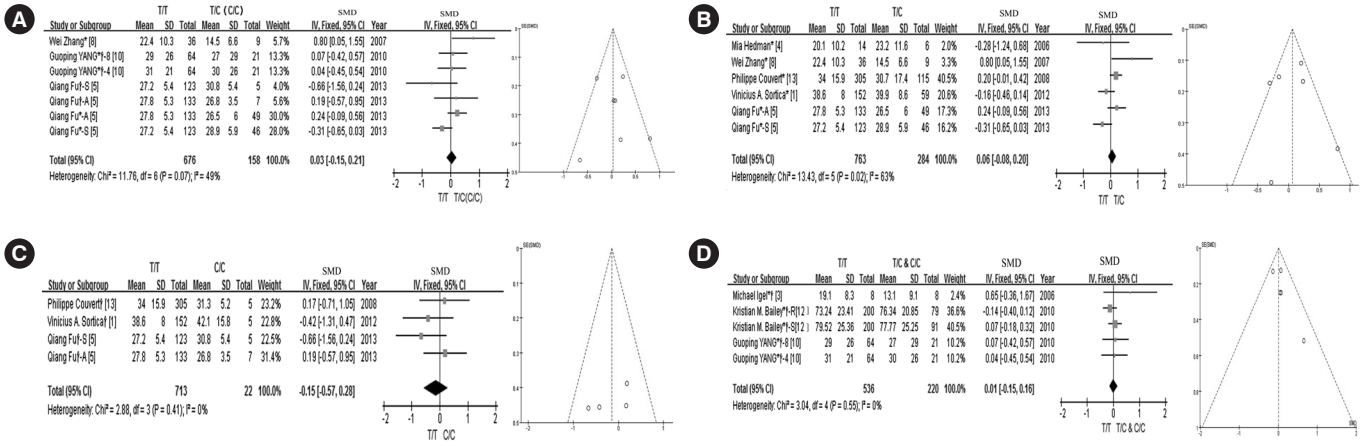

Fig. 3. Forest plots and funnel plots of each subgroup. (A) Forest plots of SMD for the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism of Chinese populations, and funnel plot for evaluating publication bias; (B) Forest plot of SMD for the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C heterozygous genotype, and funnel plot for evaluating publication bias; (C) Forest plot of SMD for the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C homozygote genotype, and funnel plotfor evaluating publication bias; (D) Forrest plot of SMD for the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C variant genotypes (T/C and C/C genotype), and funnel plot for evaluating publication bias. *TC genotype; †CC genotype; *†TC and CC genotype; S: simvastatin; A: atorvastatin; R: rosuvastatin; 4: 4 weeks; 8: 8 weeks.
Abbreviations: SMD, standard mean difference; CI, confidence interval; df, degrees of freedom.

0.74) and inconsistent coefficients, indicating moderate heterogeneity (I^2=49%; Fig. 3A). We found no significant association in the stratified analyses according to the Chinese population sample size.

Subsequently, we assessed the effect of thevariant heterozygote (T/C) and homozygote (C/C) genotypes of the *SLCO1B1* c.521T>C polymorphism on the lipid-lowering efficacy of statins, both independently and conjointly. As shown in Fig. 3B and C, the overall SMD of thevariant heterozygote (T/C) and the homozygote genotype (C/C) was 0.06 (95% CI: -0.08-0.20; P=0.38) and -0.15 (95% CI: -0.57-0.28; P=0.50), respectively. When assessed conjointly, the SMD of the variant genotype (T/C and C/C) was 0.01 (95% CI: -0.15-0.16; P=0.94) (Fig. 3D). The above results were summarized in the Table 2.

The association of the lipid-lowering efficacy of statins was also evaluated with respect to drug types and the length of time that the medicine required to be effective. The results (Table 3) showed that the statistically insignificant association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism was not influenced by the length of time thatthe medicine required to take effect (patients were treated with statins for >1 or ≤1 month), nor was it influenced when considering patients treated with pravastatin. Surprisingly, however, the lipid-lowering efficacy of simvastatin did in fact show an im-

provement in patients with the *SLCO1B1* c.521T>C wild genotype relative to patients with the variant genotype. This became apparent when the data from Bailey *et al*. [12] were removed owing to a difference in evaluation standards.

Except in the case of simvastatin, the above meta-analysis results consistently indicate that there is no statistically significantassociation between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism, regardless of whether the genotype is heterozygote (T/C) or homozygote (C/C). These results included studies of a variety of statins, including pravastatin, fluvastatin, simvastatin, rosuvastatin, pitavastatin, and atorvastatin.

2. Publication bias assessment

The data of the eight studies were included in a funnel plot, which was used to analyze the publication bias of the literature included in this meta-analysis. The funnel plot results did not suggest any evidence of publication bias (Figs. 2 and 3).

DISCUSSION

This is the most comprehensive meta-analysis conducted to date with respect to the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism. The main advantage of this study was due to the accumulation of published data on the PubMed and Web of Science databases. These resources providea great deal of information that proved useful in generating enough statistical power to detect significant differences between studies. Our meta-analysis involved eight studies including 2,012 wild genotype (T/T) cases and 526 variant genotype (T/C and C/C) cases. These cases were all used to analyze the effect of the *SLCO1B1* c.521T>C polymorphism. The main results of our meta-analysis are displayed in Table 1, and demonstrate that no significant association was detected between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism, which includes patients with both variant heterozygote (T/C) and homozygote (C/C) genotypes. Our results also show that there may be a difference between heterozygotes (T/C) and homozygotes (C/C) with respect to thelipid-lowering efficacy of statins, because their SMD swere 0.06 [95% CI: -0.08-0.20] and -0.15 [95% CI: -0.57-0.28], respectively.

In the subgroup analysis that focused on drug type and the length of time required for the medicine to take effect, we found that the latter did not alter the association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism. However, the *SLCO1B1* c.521T>C wild genotype could, in fact, improve the lipid-lowering efficacy of simvastatin, with an SMD of-0.26 (95% CI: -0.47--0.05).

Previous research found that the *SLCO1B1* c.521T>C polymorphism altered the pharmacokinetics of statins [6, 7]. For example, Tachibana-Iimori *et al*. [9] demonstrated that statins had stronger lipid-lowering efficacy in patients with wild genotypes (T/T) compared with variant heterozygotes (T/C). By contrast, some other studies showed that the *SLCO1B1* c.521T>C polymorphism may not be associated with the lipid-lowering effects of statins [5, 10]. Considering the non-parallel effects of *SLCO1B1* c.521T>C polymorphisms on pharmacokinetics and the drugs' lipid-lowering efficacies, it appears that other elements such as dosage, the duration of the treatment, the timing of cholesterol level measurement, and ethnic differences between samples from various studies may play a significant role. As a result, the lipid-lowering efficacies of statins vary considerably across different studies. Our meta-analysis results suggest that there is no significant association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism. Specifically, there appears to bea slight difference between heterozygotes (T/C) and homozygotes (C/C) with respect to the lipid-lowering efficacy of statins.

In summary, the results from our meta-analysis show that there is no significant association between the lipid-lowering efficacy of statins and the *SLCO1B1* c.521T>C polymorphism, with an exception of simvastatin, which showed a significant effect in the drug type subgroup meta-analysis. Future studies should be carried out to analyze why the *SLCO1B1* c.521T>C polymorphism might alter the pharmacokinetics of statins but does not appear to influence the lipid-lowering efficacy of statins.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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REFERENCES

1. Sortica VA, Fiegenbaum M, Lima LO, Van der Sand CR, Van der Sand LC, Ferreira ME, et al. *SLCO1B1* gene variability influences lipid-lowering efficacy on simvastatin therapy in Southern Brazilians. Clin Chem Lab Med 2012;50:441-8.
2. Zhang P, Wang M, Zhang H, Wang Q. Effects of statins on rat liver microsomal aspirin esterase activities in vitro. Lat Am JPharm 2013;32:1501-7.
3. Igel M, Arnold KA, Niemi M, Hofmann U, Schwab M, Lütjohann D, et al. Impact of the *SLCO1B1* polymorphism on the pharmacokinetics and lipid-lowering efficacy of multiple-dose pravastatin. Clin Pharmacol Ther 2006;79:419-26.
4. Hedman M, Antikainen M, Holmberg C, Neuvonen M, Eichelbaum M, Kivistö KT, et al. Pharmacokinetics and response to pravastatin in paediatric patients with familial hypercholesterolaemia and in paediatric cardiac transplant recipients in relation to polymorphisms of the *SLCO1B1* and *ABCB1* genes. Br J Clin Pharmacol 2006;61:706-15.
5. Fu Q, Li YP, Gao Y, Yang SH, Lu PQ, Jia M, et al. Lack of association between *SLCO1B1* polymorphism and the lipid-lowering effects of atorvastatin and simvastatin in Chinese individuals. Eur J Clin Pharmacol 2013;69:1269-74.
6. Pasanen MK, Fredrikson H, Neuvonen PJ, Niemi M. Different effects of *SLCO1B1* polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. Clin Pharmacol Ther 2007;82:726-33.
7. Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M. *SLCO1B1* polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 2006;16:873-9.
8. Zhang W, Chen BL, Ozdemir V, He YJ, Zhou G, Peng DD, 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.
9. Tachibana-Iimori R, Tabara Y, Kusuhara H, Kohara K, Kawamoto R, Nakura J, et al. Effect of genetic polymorphism of OATP-C (*SLCO1B1*) on lipid-lowering response to HMG-CoA reductase inhibitors. Drug Metab Pharmacokinet 2004;19:375-80.
10. Yang GP, Yuan H, Tang B, Zhang W, Wang LS, Huang ZJ, et al. Lack of effect of genetic polymorphisms of *SLCO1B1* on the lipid-lowering response to pitavastatin in Chinese patients. Acta Pharmacol Sin 2010;31:382-6.
11. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, Eur J Epidemiol 2010;25:603-5.
12. Bailey KM, Romaine SP, Jackson BM, Farrin AJ, Efthymiou M, Barth JH, et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. Circ Cardiovasc Genet 2010;3:276-85.
13. Couvert P, Giral P, Dejager S, Gu J, Huby T, Chapman MJ, 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.
14. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998;17:2815-34.