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

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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 statins on the basis of the standard mean difference (SMD) and 95% confidence intervals (CIs). Additionally, we checked for heterogeneity (I²) 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 wild and 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 time required for the statin to take effect did not significantly affect the association between lipid-lowering efficacy of statins and SLCO1B1 c.521T>C polymorphism. However, the wild 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

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

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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 compared with the 521T/T genotype (wild genotype). Tachibana-limori 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 effect in 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, “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.

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

550
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.

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 information

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 |
|--------------|------|---------|------|--------------|----------------------|----------------|---------------------------------------------|------------------|
| Igel M       | 2006 | Germany | Pravastatin | 8 | 8 | 3 weeks | 40 mg/day | -19.10 ± 8.30 | TT | -13.10 ± 9.10 | PHASE program |
| Hedman M     | 2006 | Finland | Pravastatin | 14 | 6 | 2 months | 10 mg/day | -20.10 ± 10.20 | TC | -23.20 ± 11.60 | TagMan |
| Zhang W      | 2007 | China   | Pravastatin | 36 | 9 | 30 days | 20 mg/day | -22.40 ± 10.30 | CC | -14.50 ± 6.60 | PCR |
| Couvert P    | 2008 | France  | Fluvastatin | 305 | 110 | 2 months | 80 mg/day | -34.00 ± 15.90 | TT | -30.70 ± 17.40 | TaqMan |
| Bailey KM    | 2010 | United Kingdom | Simvastatin | 200 | 82 | 3 months | - | -79.52 ± 25.36 | TC | -77.77 ± 25.25 | TaqMan |
| Yang GP      | 2010 | China   | Pitavastatin | 64 | 21 | 4 weeks | 2 mg/day | -31.00 ± 21.00 | CC | -30.00 ± 26.00 | PCR-RFLP |
| Yang GP      | 2010 | China   | Pitavastatin | 64 | 21 | 8 weeks | 2 mg/day | -29.00 ± 26.00 | TT | -27.00 ± 29.00 | PCR-RFLP |
| Sortica VA   | 2012 | Brazil  | Simvastatin | 152 | 59 | 6 months | 20 mg/day | -38.60 ± 8.00 | TC | -39.90 ± 8.60 | TaqMan |
| Fu Q         | 2013 | China   | Atorvastatin | 133 | 49 | 7 | 4 weeks | 20 mg/day | -27.80 ± 5.30 | CC | -26.50 ± 6.00 | AS-PCR |

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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 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 no statistically 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; $P=0.59$).

| 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 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.
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 the variant heterozygote (T/C) and homozygote (C/C) genotypes of the \textit{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 the variant 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 \textit{SLCO1B1} c.521T>C polymorphism was not influenced by the length of time that the medicine required to take effect (patients were treated with statins for $>$1 or $\leq$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-

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www.annlabmed.org 333
provement in patients with the \textit{SLCO1B1} c.521T>C wild genotype relative to patients with the variant genotype. This became apparent when the data from Bailey \textit{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 significant association between the lipid-lowering efficacy of statins and the \textit{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).

\section*{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 \textit{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 provide 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 \textit{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 \textit{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 the lipid-lowering efficacy of statins, because their SMD were 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 \textit{SLCO1B1} c.521T>C polymorphism. However, the \textit{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 \textit{SLCO1B1} c.521T>C polymorphism altered the pharmacokinetics of statins [6, 7]. For example, Tachibana-Iimori \textit{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 \textit{SLCO1B1} c.521T>C polymorphism may not be associated with the lipid-lowering effects of statins [5, 10]. Considering the non-parallel effects of \textit{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 \textit{SLCO1B1} c.521T>C polymorphism. Specifically, there appears to be a 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 \textit{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 \textit{SLCO1B1} c.521T>C polymorphism might alter the pharmacokinetics of statins but does not appear to influence the lipid-lowering efficacy of statins.

\section*{Authors’ Disclosures of Potential Conflicts of Interest}
No potential conflicts of interest relevant to this article were reported.

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