Association between SLCO1B1 −521T>C and −388A>G polymorphisms and risk of statin-induced adverse drug reactions: A meta-analysis

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Abstract

An increasing number of studies have investigated the association between SLCO1B1 −521T>C and −388A>G polymorphisms and the risk of statin-induced adverse drug reactions (ADRs), but the results have been inconsistent. This meta-analysis was performed to gain more insight into the relationship. PubMed, Embase, Cochrane Library and Web of Science were searched for relevant articles published before March 5th, 2015. The quality of included studies was evaluated by the Newcastle-Ottawa Quality scale. Pooled effect estimates (odds ratios [ORs] or hazard ratios [HRs]) and corresponding 95% confidence intervals (CIs) were calculated to assess the association in overall and subgroup analyses for various genetic models. Begg’s rank correlation test and Egger’s linear regression test were used to examine the publication bias. A total of nine cohort and four case–control studies involving 11,246 statin users, of whom 2,355 developing ADRs were included in the analysis. Combined analysis revealed a significant association between the SLCO1B1 −521T>C polymorphism and increased risk for ADRs caused by various statins, but the synthesis heterogeneity was generally large (dominant model: pooled effect estimate = 1.85, 95% CI 1.20–2.85, P = 0.005; I² = 80.70%, Pheterogeneity < 0.001). Subgroup analysis by statin type showed that the ADRs risk was significantly elevated among simvastatin users (dominant model: pooled effect estimate = 3.43, 95% CI 1.80–6.52, P = 0.001; I² = 59.60%, Pheterogeneity = 0.060), but not among atorvastatin users. No significant relationship was found between the −388A>G polymorphism and ADRs caused by various statins (dominant model: pooled effect estimate = 0.94, 95% CI 0.79–1.13, P = 0.526; I² = 40.10%, Pheterogeneity = 0.196). The meta-analysis suggests that SLCO1B1 −521T>C polymorphism may be a risk factor for statin-induced ADRs, especially in simvastatin therapy. Conversely, there may be no significant association for −388A>G polymorphism.

Keywords: SLCO1B1, Polymorphism, Statin, Adverse drug reaction, Meta-analysis

Background

Statins or the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have become the most important pharmaceutical intervention for the primary and secondary prevention of cardiovascular diseases by lowering blood concentrations of low density lipoprotein cholesterol (LDL-C) (Baigent et al. 2005; Stewart 2013). In general, statins are safe and well tolerated, but there are still 25–50% of patients with coronary artery disease noncompliant after 1 year’s medication mainly because of adverse drug reactions (ADRs) (Ho et al. 2008). The musculoskeletal problem is the most common intolerance, symptoms of which range from mild clinical myalgias, “incipient” myopathy, “definite” myopathy to fatal rhabdomyolysis (Feng et al. 2012; Ghatak et al. 2010;
increased blood concentration of various statins, which may contribute to the risk of developing muscle toxicity in different studies (Niemi et al. 2011). In recent years, an association between the two SNPs, SLCO1B1 −521T>C or −388A>G polymorphisms and statin-induced various ADRs not only myopathy, under various genetic models. The finding of a significant correlation may become useful in prestatin treatment screening in order to predict the chance of the development of adverse effects.

Methods

Four databases were electronically searched to retrieve studies on association between statin-induced ADRs and polymorphisms of the SLCO1B1 gene until 5 March 2015, including PubMed, ISI web of knowledge, Embase, and the Cochrane Library. Searching terms were: “HMG-CoA reductase inhibitor” or “statin” or “simvastatin” or “lovastatin” or “fluvastatin” or “atorvastatin” or “pravastatin” or “rosuvastatin” or “cerivastatin” or “mevastatin”, combined with “SLCO1B1”. In addition, references of the retrieved publications were checked for relevant studies.

Inclusion and exclusion criteria

Titles and abstracts of all retrieved publications were screened. Then the full-text screening was conducted by two researchers (Jiang and Tang) independently. Any discordance was subsequently resolved through discussion or a third party (Zhang). Studies were considered eligible if they met all of the following criteria: (1) It investigated the association between −521T>C or −388A>G polymorphisms in the SLCO1B1 gene and the risk of statin-induced ADRs; (2) It provided effect estimates (OR, RR, or HR) and their corresponding 95 % confidence intervals (95 % CIs) or allele or genotype frequencies for calculating the effect estimates; (3) The publication language was English. Studies consistent with any of the following
conditions were excluded: (1) Reviews, case reports, comments, letters, news, editorials; (2) In vitro or animal trials; (3) Studies lacking information necessary or usable data for the analysis; (4) For overlapping and republished studies, only the most recent or the largest population was included.

Data extraction
Data were extracted independently by two reviewers (Jiang and Tang). Disagreements were solved by discussion, and a third party (Zhang) was involved when necessary. The collected information included: first author; year of publication, country where study was conducted, ethnicity, study design, definition of ADRs, characteristics of participants, statin type, dose and regimen, sample size, polymorphism region, allele or genotype frequencies in patients with or without ADRs during the treatment of statins, crude and adjusted effect estimates (ORs, RRs, HRs) and their corresponding 95% CIs as reported, any multivariate analyses adjustment factors, genotyping method, and information about Hardy–Weinberg Equilibrium (HWE).

Quality assessment of included studies
Newcastle-Ottawa Quality scale (NOS) (Crowther et al. 2010; Cota et al. 2013) was developed for quality assessment. A “star system” (range 0–9 stars) was used for the present analysis to evaluate each included study on the following: selection of the study groups, between-group comparability, and the ascertainment of either the exposure for case–control studies or the outcome for cohort studies. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure or Outcome categories. A maximum of two stars can be assigned for Comparability. With respect to the follow-up period sufficient for outcomes to occur, the minimum follow-up of the exposed group was set at 1 year, given that the risk of an adverse drug reaction is greater during the first year of therapy, and decreases afterwards (de Keyser et al. 2014).

Statistical analysis
The effect estimates that were extracted, if available, or de novo calculated from available data, were crude and adjusted ORs and HRs. We pooled OR estimates and HR estimates for each study together. If both the crude and the adjusted effect estimates were available for the same outcome, we incorporated the adjusted one into the analysis. Pooled effect estimates were calculated for all of the following genetic models: the allele contrast, the homozygote comparison, the heterozygote comparison, the dominant model, the recessive model, and the additive model respectively. Heterogeneity among included studies was assessed by Chi square-based Q test and I² test (Higgins and Thompson 2002). If the data showed no heterogeneity (P > 0.10, I² < 50%), the Mantel–Haenszel fixed effect model was used (Mantel and Haenszel 1959), otherwise the DerSimonian-Laird random effect model was used (DerSimonian and Laird 1986). In addition, stratification analysis was conducted by the type of statin. If the original research did not provide information about HWE, we calculated it using an online HWE calculation tool (Rodriguez et al. 2009). Sensitivity analysis was carried out to investigate the influence of a single study on the overall risk by omitting one study each time and was conducted based on leave-one-out sensitivity procedure. Publication bias was assessed by the Begg’s rank correlation test and Egger’s linear regression test if the number of included studies in the meta-analysis was more than two (Begg and Mazumdar 1994; Egger et al. 1997). Data were analyzed using the STATA 12.0 (Stata Statistical Software, College Station, TX, USA, www.stata.com) software. A P value of 0.05 for any test or model was considered to be statistically significant.

Results

Literature search
A total of 676 records were yielded by the search strategy from four electronic databases. Among these, 35 publications met the inclusion criteria after title and abstract screening. Based on full-text inspection, we excluded another 25 publications because 11 of them lacked information necessary or usable data for the analysis (Dlouha et al. 2013; Dmitri et al. 2013; Mafalda et al. 2013; Pranulis and Kucinskas 2013; Hopewell et al. 2012; Khan et al. 2011; Johansen et al. 2010; Tamraz et al. 2013; Tom et al. 2010; Kamatani and Mushiroda 2011; Kroemer 2010); seven articles were reviews (three articles) (Patel et al. 2014; de Keyser et al. 2012a, b; Dendramis 2011), comments (two articles) (Wright et al. 2011; Nakamura 2008), news (one article) (Dolgin 2013) or letters (one article) (Puccetti et al. 2010); four articles reported overlapping data for the same study (de Keyser et al. 2012a, b; Tom et al. 2009; Danik et al. 2012; Voora et al. 2008); two studies were published in Russian (Sychev et al. 2013; Petrov et al. 2013) and one study was an in vitro study (Furihata et al. 2009). Among the 10 publications included, one (de Keyser et al. 2014) described four independent studies. Of these, two investigated simvastatin-related ADRs and the remaining two investigated atorvastatin-related ADRs. Thus, 13 studies from 10 publications (Link et al. 2008; de Keyser et al. 2014; Marcianete et al. 2011; Voora et al. 2009; Danik et al. 2013; Donnelly et al. 2011; Carr et al. 2013; Santos et al. 2012; Brunham et al. 2012; Linde et al. 2010) were included in the meta-analysis. Details of the study selection process are presented in Fig. 1.
Study characteristics
Characteristics of the eligible studies are summarized in Table 1. All studies were published between 2008 and 2014, with a total number of 11, 246 subjects, of whom 2, 355 developing ADRs. Five studies were conducted in the Netherlands, three in the UK, two in the US, one in Brazil, one in the US and Canada and one in 26 countries. There were 11 studies entirely or predominantly involving Caucasian participants and two not reporting the ethnicity. Nine were cohort studies and four were case–control studies. Definitions of statin-induced ADRs, doses and treatment periods were heterogeneous among these studies. There were four hospital-based and nine population-based studies. Among the included 13 studies, three focused on simvastatin, three on atorvastatin, one on rosuvastatin, one on cerivastatin, two on mixed statins and three on both mixed statins and specific statin. Seven studies provided genotype frequencies which helped us to calculate the crude ORs under various genetic models. Nine studies reported adjusted effect estimates in some genetic models.

Quality of included studies
Rating of the quality of the included studies according to the NOS is presented in Table 2. The quality scores ranged from 5 to 9. The case definition was adequate in all of the included case–control studies, but the non-response rate between the case and control groups was equal in only one study (Brunham et al. 2012). For all cohort studies, 4 stars were assigned to Selection category. The follow-up time for exposed participants was not reported in the study by Linde et al. (2010) and not long enough (<1 year) for the outcome to occur in the study by Voora et al. (2008). Nearly all included cohort studies did not mention the loss to follow-up.

Meta-analysis results
All of the 13 included studies explored the association between −521T>C polymorphism of the SLCO1B1 gene and statin-induced ADRs. The results of meta-analysis are presented in Table 3. A significant increased risk of ADRs induced by different types of statins was found for the C vs. T: pooled effect estimate = 1.99, 95 % CI 1.20–3.29, \( P = 0.007 \); the homozygote comparison (CC vs. TT: pooled effect estimate = 2.21, 95 % CI: 1.41–3.47, \( P = 0.001 \)); the dominant model (TC/CC vs. TT: pooled effect estimate = 1.85, 95 % CI 1.20–2.85, \( P = 0.005 \)); the recessive model (CC vs. TT/TC: pooled effect estimate = 2.76, 95 % CI 1.73–4.39, \( P < 0.001 \)) and the additive model (per C allele: pooled effect estimate = 1.76, 95 % CI 1.25–2.50, \( P = 0.001 \)), but not for the homozygote comparison (TC vs. TT: pooled effect estimate = 1.26, 95 % CI 0.96–1.65, \( P = 0.091 \)). Figure 2 shows the pooled effect estimate and 95 % CI for any statin induced ADRs in the dominant model.

In the stratified analysis by statin type (Table 3), the synthesis of studies investigating simvastatin pointed to a statistically significant increased risk for the allele contrast model (C vs. T: pooled effect estimate = 3.00, 95 % CI 1.39–6.48, \( P = 0.005 \)), the homozygote comparison (CC vs. TT: pooled effect estimate = 3.62, 95 % CI 1.33–9.83, \( P = 0.012 \)), the dominant model (TC/CC vs. TT: pooled effect estimate = 3.43, 95 % CI 1.80–6.52, \( P < 0.001 \)) (Fig. 3), the recessive model (CC vs. TT/TC: pooled effect estimate = 5.98, 95 % CI 2.53–14.13, \( P < 0.001 \)) and the additive model (per C allele: pooled effect estimate = 2.87, 95 % CI 1.67–4.94, \( P < 0.001 \)). Whereas in contrast, the combined effect estimates for atorvastatin-induced ADRs were far from being statistically significant in any of the six genetic models. The association between the −521T>C polymorphism and atorvastatin-induced ADRs in the dominant model is shown in Fig. 4.

Three of the included studies explored the relationship between the −388A>G polymorphism of the SLCO1B1 gene and statin-induced ADRs. Due to the limited available data from the original studies, we only performed meta-analysis under the dominant model and the additive model based on two studies respectively. Both of the results yielded a decreased risk for statin-related ADRs among −388G allele carriers, although the pooled effect estimates did not reach statistical significance (AG/GG vs. AA: pooled effect estimate = 0.94, 95 % CI 0.79–1.13, \( P = 0.526 \); the additive model: pooled effect estimate = 0.91, 95 % CI 0.81–1.02, \( P = 0.114 \)) (Table 3).

Sensitivity analysis
For −521T>C polymorphism and risk of ADRs induced by any statin, the conclusion of insignificant association for the homozygote comparison was materially altered by removing the study by de Keyser et al. (2014) with the overall effect estimates changing to 1.36 (95 % CI 1.02–1.84, \( P = 0.038 \)) and 1.34 (95 % CI: 1.01–1.79, \( P = 0.044 \)) respectively. In addition, the result changed and became insignificant when we excluded the study by Carr et al. (2013) in the homozygote comparison for −521T>C polymorphism and simvastatin-related ADRs (pooled effect estimate = 3.17, 95 % CI 0.96–10.53, \( P = 0.059 \)). The results were not materially altered for other analysis except for the above situations.

Publication bias
The Begg’s rank correlation test and Egger’s linear regression test indicated no evidence of publication bias among studies testing −521T>C and −388A>G polymorphisms of the SLCO1B1 gene and the risk of ADRs induced by
various statins or specific statin ($P > 0.05$ for all of the genetic models) except in the analysis of $-521T>C$ polymorphism and ADRs induced by any statin in the heterozygote comparison (Begg’s, $P = 0.049$; Egger’s, $P = 0.025$) and the additive model (Begg’s, $P = 0.386$; Egger’s, $P = 0.025$) (Table 3).

**Discussion**

ADRs give rise to the discontinuation of statin treatment (Simons et al. 1996). Recent studies showed that genetic variants in the SLCO1B1 gene modified the risk of statin-induced myopathy, but the results were controversial. The meta-analysis aimed to retrieve all published relative articles to identify the associations between the two functional variants $-521T>C$ and $-388A>G$ of the SLCO1B1 gene and the risk of ADRs during statin therapy. We included articles about any ADR and the dose decrease, discontinuation or switches to other cholesterol-lowering drugs related to statin toxicity as indicators of ADRs.

The results of the meta-analysis demonstrated that the minor allele of the $-521C$ significantly increased the risk of ADRs.
Table 1  Characteristics of included studies

| Study (first author, year) | Country       | Ethnicity                     | Study design | Definition of adverse drug reactions                                                                 | Population disease          | Source of participants |
|---------------------------|---------------|-------------------------------|--------------|------------------------------------------------------------------------------------------------------|----------------------------|------------------------|
| Voora et al. (2009)       | USA           | Caucasian 86%; African American 5%; other | Cohort       | A composite adverse event (CAB) of premature discontinuation for any side effect or myalgia/muscle cramps (irrespective of CK values) or CK > 3×ULN (irrespective of symptoms) | Hypercholesterolemia        | Hospital               |
| Dank et al. (2013)        | 26 countries  | Caucasian 100%                | Cohort       | Clinical myalgia or the broader categories of muscle weakness, stiffness, or pain and clinically severe myopathy (frank myopathy and rhabdomyolysis) | No disease                 | Population             |
| Donnelly et al. (2011)    | UK (Scotland) | NA                            | Cohort       | Intolerance defined as composite of abnormal CK measure 1–3 × ULN, with no abnormal recorded before statin commencement; or an abnormal ALT measure, with no abnormal before statin commencement (≥50% increase in ALT from baseline also considered abnormal) and a relevant change in prescribing (switching statin to equivalent or lower dose, dose reduction of same statin, or discontinuation of statin prescribing) | Type 2 diabetes             | Population             |
| Link et al. (2008)        | UK            | Caucasian 100%                | Case–control | "Definite" myopathy: muscle symptoms, with CK > 10 × ULN; "incipient" myopathy: CK > 3 × ULN and 5 × baseline level, plus AAT > 1.7 × the baseline value without an elevated AAT level alone at any other visit irrespective of muscle symptoms | Myocardial infarction       | Population             |
| de Keyser et al. (2014)   | Netherlands   | Caucasian 100%                | Cohort       | The occurrence of either a dose decrease or a switch to another cholesterol-lowering drug or a too strong reduction in cholesterol level | NA                         | Population             |
| de Keyser et al. (2014)   | Netherlands   | Caucasian 100%                | Cohort       | The occurrence of either a dose decrease or a switch to another cholesterol-lowering drug or a too strong reduction in cholesterol level | NA                         | Population             |
| de Keyser et al. (2014)   | Netherlands   | Caucasian 98%                 | Cohort       | The occurrence of either a dose decrease or a switch to another cholesterol-lowering drug or a too strong reduction in cholesterol level | Hypercholesterolemia and/or hypertension | Population             |
| de Keyser et al. (2014)   | Netherlands   | Caucasian 98%                 | Cohort       | The occurrence of either a dose decrease or a switch to another cholesterol-lowering drug or a too strong reduction in cholesterol level | Hypercholesterolemia and/or hypertension | Population             |
| Carr et al. (2013)        | UK            | Caucasians 100%               | Case–control | Myopathy: CK > 4 × ULN; severe phenotype denoted by CPK > 10 × ULN or rhabdomyolysis | Type 2 diabetes, Alcohol dependence, Asthma, hypertension et al. | Population             |
| Santos et al. (2012)      | Brazil        | Caucasian 87%; Mulatto 10%; African 3% | Cohort       | Myalgia defined as muscle pain irrespective of CK values or CK > 3×ULN irrespective of symptoms | Familial hypercholesterolemia | Hospital               |
| Linde et al. (2010)       | USA           | NA                            | Cohort       | Myalgia: defined as muscular pain or weakness as reported by the patients, who graded their symptoms as mild, moderate or severe | Endocrine disorders         | Hospital               |
| Study (first author, year) | Statin type | Dose/ regimen (mean [SD]) (mg/d) | SNP | Case (control or cohort size) | Control |
|---------------------------|-------------|---------------------------------|-----|-------------------------------|---------|
| Voora et al. (2009)       | Mixed       | Multiple doses                  | rs4149056 | 97/351                         | 263/84 |
|                          | Simvastatin | 20.0 for 8 weeks + 80.0 for 8 weeks | rs4149056 | 34/124                         | 91/33 b |
|                          | Atorvastatin| 10.0 for 8 weeks + 80.0 for 8 weeks | rs4149056 | 31/115                         | 88/27 b |
|                          | Pravastatin | 10.0 for 8 weeks + 40.0 for 8 weeks | rs4149056 | 31/111                         | 83/28 b |
| Donnelly et al. (2011)    | Mixed (simvastatin major) | Multiple doses                  | rs4149056 | 816/1275                       | 905/348 |
| Link et al. (2008)        | Simvastatin | 80.0                            | rs2306283 | 816/1275                       | 471/606 |
| de Keyser et al. (2014)   | Simvastatin | Starting dose:200 (11.4)         | rs4149056 | 85/90                          | 70/17  |
| de Keyser et al. (2014)   | Atorvastatin| Starting dose:178 (13.2)         | rs4149056 | 319/1462 a                     | NA NA |
| de Keyser et al. (2014)   | Simvastatin | Starting dose:417 (18.9)         | rs4149056 | 110/367 a                      | NA NA |
| de Keyser et al. (2014)   | Atorvastatin| Starting dose:450 (34.8)         | rs4149056 | 42/244 a                       | NA NA |
| Carr et al. (2013)        | Mixed       | Case:33.2 (15.7), control:30.6 (15.7) | rs4149056 | 76/372                         | 260/10 |
| Santos et al. (2012)      | Atorvastatin| Case:62.9 (20.5), control:61.0 (22.7) | rs4149056 | 14/129                         | 94/35 b |
| Linde et al. (2010)       | Mixed       | Multiple doses                  | rs2306283 | 14/129                         | 70/59 b |
| Marciani et al. (2011)    | Cerivastatin| Case:0.6 (0.2)                  | rs4149056 | 10/4 b                         | 4/30   |
| Brunham et al. (2012)     | Mixed       | Case:31.0 (23.0), control:36.0 (25.0) | rs4149056 | 25/83                          | 57/20  |
|                          | Cerivastatin| Case:6.0 (0.2)                  | rs4149056 | 27/19                          | 15/4   |
|                          | Cerivastatin| Case:0.6 (0.2)                  | rs4149056 | 65/716                         | 15/4   |
|                          | Simvastatin | NA                              | rs2306283 | 185/732                        | 15/4   |
|                          | Atorvastatin| NA                              | rs4149056 | 25/83                          | 57/20  |
|                          | Cerivastatin| NA                              | rs4149056 | 25/83                          | 57/20  |

Table 1 continued

Study (first author, year) | Country | Ethnicity | Study design | Definition of adverse drug reactions | Population disease | Source of participants |
|---------------------------|---------|-----------|--------------|--------------------------------------|-------------------|------------------------|
| Marciante et al. (2011)   | Case: US, Canada; control: US | Caucasian for case, control 1 (CHS), control 2 (HVH): 90.8, 84.5, 89.4% | Case–control | Definite rhabdomyolysis defined as muscle pain or weakness associated with CK > 10 × ULN | Dyslipidemia | Population |
| Brunham et al. (2012)     | Netherlands | Caucasian 100% | Case–control | Plasma CK > 10 × ULN | Dyslipidemia | Hospital |
| Study (first author, year) | Effect estimate (95 % CI) | CC vs. TT | TC vs. TT | TC/CC vs. TT | CC vs. TT/TC | Additive | C vs. T | Adjusting factors |
|---------------------------|--------------------------|-----------|-----------|-------------|-------------|----------|--------|------------------|
| Voora et al. (2009)       | 4.24 (1.03–17.43)         | 1.57 (0.95–2.57) | 1.70 (1.04–2.80) | 3.73 (0.92–15.20) | 1.70 (1.11–2.61) | 1.67 (1.10–2.52) | Race, gender |
| NA                        | NA                       | 2.76 (1.26–6.02) | NA         | NA          | NA          | NA       | –     |
| NA                        | NA                       | 1.55 (0.65–3.70) | NA         | NA          | NA          | NA       | –     |
| NA                        | NA                       | 1.03 (0.41–2.57) | NA         | NA          | NA          | NA       | –     |
| Danik et al. (2013)       | 1.13 (0.65–1.97)          | 0.90 (0.72–1.12) | NA         | NA          | 0.95 (0.79–1.15) | NA       | –     |
| Donnelly et al. (2011)    | 1.75 (0.97–3.15)          | 1.04 (0.86–1.27) | 1.09 (0.90–1.32) | 2.05 (1.02,4.09) | 1.12 (0.94–1.33) | 1.12 (0.94–1.32) | Statin adherence, study duration, maximum dose, prescription for other lipid-regulating drugs, cyp3a4 inhibiting drugs, age, and rs2306283 |
|                           | 0.76 (0.58–1.01)           | 0.98 (0.81–1.19) | 0.93 (0.77–1.11) | 0.71 (0.52,0.96) | 0.90 (0.79–1.02) | 0.90 (0.79–1.02) | –     |
| Link et al. (2008)        | 1690 (470–61 10)          | 4.97 (2.41–10.24) | 6.76 (3.46–13.20) | 9.52 (2.72–33.28) | 4.50 (2.60–7.70) | 5.65 (3.32–9.62) | –     |
| de Keyser et al. (2014)   | 1.74 (1.05–2.88)          | 0.77 (0.58–1.02) | NA         | NA          | NA          | NA       | –     |
| de Keyser et al. (2014)   | 1.49 (0.54–4.10)          | 1.17 (0.77–1.79) | NA         | NA          | NA          | NA       | –     |
| de Keyser et al. (2014)   | 1.38 (0.34–5.71)          | 0.74 (0.45–1.24) | NA         | NA          | NA          | NA       | –     |
| de Keyser et al. (2014)   | NA                       | 0.97 (0.68–1.40) | NA         | NA          | NA          | NA       | –     |
| Carr et al. (2013)        | 432 (182–10.43)           | 1.93 (1.14–3.27) | 2.09 (1.27–3.45) | 2.81 (1.01–7.86) | 2.08 (1.35–3.23) | 1.93 (1.29–2.89) | Statin type, previous history of type 2 diabetes, asthma, hypertension |
|                           | 633 (160–25.02)           | 1.78 (0.97–3.37) | 2.03 (1.13–3.63) | 5.05 (1.31–19.43) | 2.13 (1.29–3.54) | 1.95 (1.23–3.10) | –     |
| Santos et al. (2012)      | 231 (0.10–52.59)          | 2.23 (0.60–8.32) | 2.05 (0.55–7.58) | 1.89 (0.09–41.74) | 1.91 (0.56–65.4) | 1.66 (0.52–5.28) | –     |
| NA                        | NA                       | 2.24 (0.47–10.72) | NA         | NA          | NA          | NA       | –     |
| NA                        | NA                       | 2.08 (0.62–7.00) | NA         | NA          | NA          | NA       | –     |
| Linde et al. (2010)       | 3.21 (0.12–85.20)         | 3.21 (0.84–12.35) | 3.48 (0.92–13.25) | 2.21 (0.09–57.14) | 3.44 (0.95–12.53) | 2.98 (0.90–9.89) | –     |
| Marciante et al. (2011)   | NA                       | NA         | NA         | NA          | 0.96 (0.75,1.24) | NA       | –     |
| NA                        | NA                       | NA         | NA         | NA          | NA          | NA       | –     |
### Table 1 continued

| Study (first author, year) | Effect estimate (95% CI) | Genotyping methods | Deviation from HWE |
|---------------------------|--------------------------|-------------------|-------------------|
|                           | CC vs. TT | TC vs. TT | TC/CC vs. TT | CC vs. TT/TC | Additive | C vs. T | Adjusting factors |
| Brunham et al. (2012)     | 1.27 (0.23–6.92)  | 1.52 (0.56–4.12) | 1.50 (0.58–3.69) | 1.12 (0.21–5.91)  | 1.26 (0.63–2.51)  | 1.32 (0.62–2.81)  | – |
|                           | 2.70 (0.20–35.75) | 3.24 (0.81–13.02) | 4.50 (0.73–27.59) | 1.68 (0.14–20.35) | 2.19 (0.79–6.12)  | 2.29 (0.82–6.38)  | – |
|                           | 1.14 (0.10–12.79) | 0.98 (0.17–5.83) | 1.06 (0.22–4.80) | 1.15 (0.11–12.43) | 1.04 (0.36–3.07)  | 1.06 (0.30–3.70)  | – |

| Study (first author, year) | Statin type | Genotyping methods |
|---------------------------|------------|--------------------|
| Voora et al. (2009)       | Mixed      | NA                 |
|                           | Simvastatin| NA                 |
|                           | Atorvastatin| NA                |
|                           | Pravastatin| NA                 |
| Danik et al. (2013)       | Rosuvastatin| NA               |
| Donnelly et al. (2011)    | Mixed (simvastatin major) | TAQMAN assays |
| Link et al. (2008)        | Simvastatin| PCR-fluorescence   |
| de Keyser et al. (2014)   | Simvastatin| Microarray genotyping procedures |
| de Keyser et al. (2014)   | Atorvastatin| Microarray genotyping procedures |
| de Keyser et al. (2014)   | Simvastatin| TaqMan allelic discrimination |
| de Keyser et al. (2014)   | Atorvastatin| TaqMan allelic discrimination |
| Carr et al. (2013)        | Mixed      | TaqMan real-time PCR SNP genotyping assays |
|                           | Simvastatin|                 |
|                           | Atorvastatin| No               |
| Santos et al. (2012)      | Atorvastatin| PCR-HRM           |
| Linde et al. (2010)       | Mixed      | PCR and DNA sequencing |
| Marcicante et al. (2011)  | Cerivastatin| Illumina Goldengate custom panel; Taqman 5′ nuclease discrimination assay; pyrosequencing on the PyroMark Q26MD platform |
| Brunham et al. (2012)     | Mixed      | Illumina Goldengate genotyping assay |

CI confidence interval, NA not available, HWE Hardy–Weinberg equilibrium, PCR polymerase chain reaction

- Case/size of cohort;
- The frequency of TC/CC;
- The estimates were calculated using the original data;
- Hazard ratio (HR);
- The adjusted effect estimates
of ADRs caused by various statins, which is consistent with that of one previous meta-analysis (Carr et al. 2013). However, the synthesis heterogeneity was generally large under the different genetic models except for the recessive model. So we could not draw a strong conclusion that the association between the rs4149056 polymorphism and the ADRs induced by statins was a class effect. Upon closer review of each selected original study, it was found that results according to different statin types were inconsistent. Thus, we conducted a stratification analysis to explore that.

After stratification analysis by the statin type, significant associations between the $-521T>C$ polymorphism and ADRs among simvastatin users for the allele contrast, the homozygote comparison, the dominant model, the recessive model and the additive model were observed, while no significant effect was found among patients treated with atorvastatin in any of the six genetic models. The results were in line with those of one previous meta-analysis by Carr et al. (2013), in which patients who carried at least one minor allele showed a more than three-fold higher risk for simvastatin-induced side effects compared with the reference TT genotype, whereas in contrast, the relationship did not reach statistical significance within atorvastatin users. The results from the original studies indicated that the $-521C$ minor allele was not a risk factor for rosuvastatin-induced myalgia (HR = 0.95, 95 % CI 0.79–1.15 per allele, $P = 0.59$) (Danik et al. 2013) or pravastatin-induced adverse events (TC/CC vs. TT: OR = 1.03, 95 % CI 0.41–2.57, $P = 0.948$) (Voora et al. 2009). On the contrary, an additional copy of the minor allele was associated with the risk of cerivastatin-associated rhabdomyolysis (OR = 2.45, 95 % CI 1.61–3.75, $P = 3.11E–05$) (Marciante et al. 2011). However, as there was only one study investigating cerivastatin, rosuvastatin and pravastatin respectively, we did not perform a meta-analysis to provide evidence for their relationship.

There remains uncertainty about the biological mechanisms underlying the statin-associated myopathy but statin concentrations in the blood was one possible reason (Stewart 2013). A non-synonymous coding SNP, rs4149056 in the SLCO1B1 gene encodes a valine-to-alanine substitution that leads to a less active form of the OATP1B1 transporter and hence increases the plasma drug concentration (Kameyama et al. 2005; Tirona et al. 2001; Nozawa et al. 2002; Iwai et al. 2004). A previous study showed that in transient expression systems of HEK293 and HeLa cells using statins as substrates, the transporting activities of those expressing SLCO1B1 $-521C$ allele decreased significantly (Kameyama et al. 2005). Furthermore, there are differences in the effects of SLCO1B1 $-521T>C$ polymorphism on the pharmacokinetics of various statins. In patients with homozygous minor allele genotype, the observed plasma areas under the curve of active simvastatin acid, pitavastatin, atorvastatin, pravastatin, and rosuvastatin have been 221, 162–191, 144, 57–130, and 62–117 % higher respectively than that in patients with the wild-type genotype (Wilke et al. 2012). This may partially account for the disparate roles of rs4149056 variant in the development of ADRs during different types of statin therapy. Several case–control (Link et al. 2008; de Keyser et al. 2014; Carr et al. 2013) and cohort studies (de Keyser et al. 2014) provide evidence for this relationship.

### Table 2 Methodological quality assessment of included studies based on the Newcastle–Ottawa Scale

| Author (years) | Study design | Selection | Comparability | Exposure/outcome | Total |
|---------------|--------------|-----------|---------------|------------------|-------|
| Link et al. (2008) | Case–control | * * * * | ** | * | ******** |
| Carr et al. (2013) | Case–control | * * * * | * | * | ******** |
| Marcian et al. (2011) | Case–control | * * * | * | * | ***** |
| Brunham et al. (2012) | Case–control | * * * * | ** | * | ******** |
| Voora et al. (2009) | Cohort | * * * | * | * | ******** |
| Danik et al. (2013) | Cohort | * * * | * | * | ******** |
| Donnelly et al. (2011) | Cohort | * * * | * | * | ******** |
| de Keyser et al. (2014) | Cohort | * * * | * | * | ******** |
| de Keyser et al. (2014) | Cohort | * * * | * | * | ******** |
| de Keyser et al. (2014) | Cohort | * * * | * | * | ******** |
| Santos et al. (2012) | Cohort | * * * | * | * | ******** |
| Linde et al. (2010) | Cohort | * * * | * | * | ***** |
| Polymorphism | Statin type | Genetic model | N  | Effect estimate (95 % CI) | Z    | P value | I² % | P_{het} | Effect model | Begg's test | Egger's test | P  |
|--------------|-------------|---------------|----|--------------------------|------|---------|------|---------|--------------|-------------|--------------|----|
| −521T>C      | C vs T      | 6             | 1.99 (1.20–3.29) | 2.69 | 0.007 | 86.90 % | <0.001 | R       |              | 0.38        | 0.707        | 1.91 | 0.129 |
|              | CC vs TT    | 10            | 2.21 (1.41–3.47) | 3.45 | 0.001 | 55.20 % | 0.017  | R       |              | 0.54        | 0.592        | 1.32 | 0.223 |
|              | TC vs TT    | 10            | 1.26 (0.96–1.65) | 1.69 | 0.091 | 75.80 % | <0.001 | R       |              | 1.97        | 0.049        | 2.36 | 0.046 |
|              | TC/CC vs TT | 8             | 1.85 (1.20–2.85) | 2.80 | 0.005 | 80.70 % | <0.001 | R       |              | 1.11        | 0.266        | 2.15 | 0.075 |
|              | CC vs TT/TC | 6             | 2.76 (1.73–4.39) | 4.27 | <0.001 | 13.60 % | 0.327  | F       |              | 0.00        | 1.000        | 0.31 | 0.769 |
|              | Additive    | 8             | 1.76 (1.25–2.50) | 3.19 | <0.001 | 86.10 % | <0.001 | R       |              | 0.087       | 0.386        | 2.97 | 0.025 |
|              | C vs T      | 3             | 3.00 (1.39–6.48) | 2.80 | 0.005 | 77.90 % | 0.011  | R       |              | 0.00        | 1.000        | 0.01 | 0.993 |
|              | CC vs TT    | 5             | 3.62 (1.33–9.83) | 2.52 | 0.012 | 69.10 % | 0.012  | R       |              | –0.24       | 1.000        | 1.06 | 0.367 |
|              | TC vs TT    | 5             | 1.58 (0.78–3.19) | 1.28 | 0.200 | 86.50 % | <0.001 | R       |              | 1.22        | 0.221        | 2.07 | 0.130 |
|              | TC/CC vs TT | 4             | 3.43 (1.80–6.52) | 3.76 | <0.001 | 59.60 % | 0.060  | R       |              | 0.34        | 0.734        | 0.32 | 0.777 |
|              | CC vs TT/TC | 3             | 5.98 (2.53–14.13)| 4.07 | <0.001 | 0.00 %  | 0.453  | F       |              | 1.04        | 0.296        | 2.06 | 0.288 |
|              | Additive    | 3             | 2.87 (1.67–4.94) | 3.81 | <0.001 | 52.80 % | 0.120  | R       |              | 0.00        | 1.000        | 0.17 | 0.892 |
|              | C vs T      | 2             | 1.35 (0.58–3.15) | 0.69 | 0.491 | 0.00 %  | 0.605  | F       |              | –          | –            | –   | –    |
|              | CC vs TT    | 3             | 1.49 (0.61–3.65) | 0.87 | 0.383 | 0.00 %  | 0.941  | F       |              | 0.00        | 1.000        | 0.23 | 0.858 |
|              | TC vs TT    | 3             | 1.23 (0.83–1.82) | 1.03 | 0.303 | 0.00 %  | 0.635  | F       |              | 0.00        | 1.000        | 0.52 | 0.697 |
|              | TC/CC vs TT | 5             | 1.11 (0.82–1.52) | 0.69 | 0.492 | 0.00 %  | 0.606  | F       |              | 0.73        | 0.462        | 2.60 | 0.081 |
|              | CC vs TT/TC | 2             | 1.38 (0.21,9.13) | 0.33 | 0.738 | 0.00 %  | 0.803  | F       |              | –          | –            | –   | –    |
|              | Additive    | 2             | 1.36 (0.60–3.05) | 0.74 | 0.460 | 0.00 %  | 0.468  | F       |              | –          | –            | –   | –    |
|              | C vs T      | 1             | 1.13 (0.65–1.97) | –    | –      | –      | –      | –       |              | –          | –            | –   | –    |
|              | TC vs TT    | 1             | 0.90 (0.72–1.12) | –    | –      | –      | –      | –       |              | –          | –            | –   | –    |
|              | Additive    | 1             | 0.95 (0.79–1.15) | –    | –      | –      | –      | –       |              | –          | –            | –   | –    |
|              | TC/CC vs TT | 1             | 1.03 (0.41–2.57) | –    | –      | –      | –      | –       |              | –          | –            | –   | –    |
|              | Additive    | 1             | 2.45 (1.61–3.75) | –    | –      | –      | –      | –       |              | –          | –            | –   | –    |
| −388A>G      | Statins     | 2             | 0.94 (0.79–1.13) | 0.63 | 0.526 | 40.10 % | 0.196  | F       |              | –          | –            | –   | –    |
|              | Additive    | 2             | 0.91 (0.81–1.02) | 1.58 | 0.114 | 0.00 %  | 0.649  | F       |              | –          | –            | –   | –    |

N number of included studies in the meta-analysis, CI confidence interval, P_{het} value of heterogeneity, F fixed-effect model, R random-effect model
et al. 2014) as well as our meta-analysis confirmed the positive correlation between −521C minor allele and simvastatin-induced adverse effects. Link et al. (2008) observed that the OR for myopathy of 4.5 (95 % CI 2.6–7.7, $P = 2 \times 10^{-9}$) per copy of the C allele in patients taking 80 mg of simvastatin daily in the SEARCH study was approximately 2 times of that in those taking 40 mg daily within the Heart Protection Study (OR = 2.6, 95 % CI 1.3–5.0, $P = 0.004$). Besides, Carr et al. (2013) discovered in the stratification analysis for dose (a cut-off point of 40 mg), the significant increased risk associated with rs4149056 variant was only found in patients receiving ≥ 40 mg/day simvastatin. These provided evidence for dose-genotype interaction in simvastatin treatment. Consequently, the Clinical Pharmacoeconomics Implementation Consortium (CPIP) Guideline for SLCO1B1 and Simvastatin-Induced Myopathy (2012) (Wilke et al. 2012) recommends that prescribing physicians should be alerted to the FDA advice on avoiding high-dose simvastatin. In our analyses, all of extracted or de novo effect estimates for atorvastatin-related ADRs showed a consistent and no significant association. While in one of the included studies by de Keyser et al. (2014), an association between the −521T>C polymorphism and dose decrease or switching to another cholesterol-lowering drug in the highest-dose category (> 20 mg) was found (the adjusted HR = 3.26, 95 % CI: 1.47–7.25, $P = 0.004$), however, we extracted the HR for whole population, which showed no significance, other than the outcome of stratification analysis. Therefore, we could anticipate that a significant higher risk would appear if patients are prescribed to high dose atorvastatin. Puccetti et al. (2010) conducted a case–control study to explore specific genetic and/or environmental factors to statin intolerance and they found a significant association between the C allele of rs4149056 SNP in the SLCO1B1 and myopathy in atorvastatin-treated patients (OR = 2.7, 95 % CI 1.3–4.9, $P < 0.001$). Since the genetic model under which the reported OR had been calculated was not available, we did not incorporate this study into our meta-analysis, which may influence our results.

The −388A>G is another common variant in the SLCO1B1 gene, which is in strong linkage disequilibrium with the −521T>C SNP (Link et al. 2008). Unlike

| Study ID | ES (95% CI) | Weight |
|---------|-------------|--------|
| 1       | 1.70 (1.04, 2.80) | 15.07  |
| 2       | 1.09 (0.90, 1.32) | 18.13  |
| 3       | 6.76 (3.46, 13.20) | 12.95  |
| 4       | 2.09 (1.26, 3.45) | 14.99  |
| 5       | 1.50 (0.58, 3.69) | 10.09  |
| 6       | 3.48 (0.92, 13.25) | 6.71   |
| 7       | 2.24 (0.47, 10.72) | 5.43   |
| 8       | 0.97 (0.68, 1.40)  | 16.62  |
| Overall | 1.85 (1.20, 2.85)  | 100.00 |

**NOTE:** Weights are from random effects analysis.

![Fig. 2](image-url) Association between SLCO1B1 −521T>C polymorphism and risk of adverse drug reactions caused by any statin. Dominant genetic model (TC/CC vs. TT). The ES is odds ratio (OR) or hazard ratio (HR); the size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.
rs4149056, rs2306283 SNP enhances liver uptake of pravastatin bringing about a reduced area under the curve for plasma pravastatin concentration (Niemi et al. 2004). The synthesis of studies on \(-388A>G\) polymorphism yielded a non-statistically significant protective effect on ADRs caused by any statin. But the results should be interpreted with caution because there were only two available studies incorporated to the meta-analyses. Therefore, more well-designed large sample size original studies are needed to identify the association.

When we performed the meta-analyses on association between \(SLCO1B1\ −521T>C\) and ADRs caused by various statins, high heterogeneity was present in all genetic models except for the recessive model. The disparate definitions of ADRs, study design, characteristics of participants (i.e., age, sex, BMI, health status), statin type, dose and duration of treatment, and some other factors maybe the potential explanation. Unfortunately, we could only conduct the subgroup analysis for statin type but not other factors owing to the limited available data and small number of original studies. After stratification analyses, the \(\hat{I}^2\) values were decreased to zero in the atorvastatin group but for the simvastatin the heterogeneity remained almost the same. In order to further explore the source of heterogeneity and to investigate the influence of individual study to the overall results, sensitivity analysis was performed. When we removed studies by de Keyser et al. (2014) respectively, the pooled effect estimates changed to be statistically significant in the heterozygote comparison. Both of the two studies reported insignificant reduced risk of dose decrease or switches in TC carriers, which may take place by chance, and might contributed more to the overall insignificant result. For simvastatin users, no significant association between \(-521T>C\) polymorphism and ADRs was found with the exclusion of one study by Carr et al. (2013) for the homozygote contrast. Possible explanation was that in this study, borderline statistically significant differences between cases and controls in terms of previous history of type 2 diabetes (\(P = 0.046\)), asthma (\(P = 0.080\)), and hypertension (\(P = 0.087\)) were determined, which might be confounders making the calculated OR biased consequently influencing the pooled result.

Several limitations in our study may affect the results. Firstly, it is noteworthy that the definitions of statin-induced ADRs varied among individual studies, which contributed to the presence of heterogeneity to a large extent. Further studies using uniform definitions are required to reach more definitive conclusions. Secondly, the crude and adjusted effect estimates were combined together due to the limited available data from the original studies. Moreover, the adjusting factors for each

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### Table 1

| Study ID | ES (95% CI)            | Weight |
|---------|------------------------|--------|
| 1       | 2.76 (1.26, 6.02)      | 27.03  |
| 2       | 6.76 (3.46, 13.20)     | 30.26  |
| 3       | 2.03 (1.13, 3.63)      | 32.91  |
| 4       | 4.50 (0.73, 27.59)     | 9.80   |

Overall (\(I^2 = 59.6\%, p = 0.060\))

**Fig. 3** Association between \(SLCO1B1\ −521T>C\) polymorphism and risk of adverse drug reactions caused by simvastatin. Dominant genetic model (TC/CC vs. TT). The ES is odds ratio (OR); the size of the square is proportional to the weight of each study; horizontal lines represent the 95% CI.
effect estimate were not completely consistent. As such, some potential confounding risk factors may be introduced to influence our pooled results, such as the differences in statin therapy including dose and duration of treatment. It is indicated that methodological improvement in the individual studies should be focused. Thirdly, the data from original studies were insufficient. We could not perform further stratification analyses to explore dose-, gender-, age-, BMI- and comedication-gene interactions. Additionally, the limited number of studies on $-388A>G$ polymorphism lowered our power and the results of meta-analyses should be interpreted with caution. Fourthly, we only included articles published in English in four databases, relevant articles published in other databases and in other languages and unpublished studies may have been missed. What’s more, as the number of included studies was small, the power of detecting the publication bias in Begg’s and Egger’s test was low. Finally, the original studies were entirely or predominantly based on Caucasians, thus additional researches in other ethnicities are needed to generalize the findings.

In conclusion, our meta-analysis suggests that SLCO1B1 $-521T>C$ polymorphism may be significantly associated with increased risk of statin-induced adverse reactions, especially in the simvastatin therapy. Conversely, the $-521C$ minor allele might not modify the risk of atorvastatin-associated adverse effects. Besides, there may be no significant association between $-388A>G$ polymorphism and statin-related adverse reactions. However, the finding should be interpreted with caution because of the small number of studies and small sample sizes. Well-designed epidemiological studies with large sample size in the treatment of various statins among different ethnicities should be carried out to confirm these associations and interaction between dose-, sex-, BMI-, extensive physical exercise-, comedication-gene should also be further investigated.

Authors’ contributions
All authors contributed in the writing of this paper. JJJ: Literature search, data extraction and production of manuscript, QT: Literature search, data extraction and production of manuscript, JF: Literature search, data extraction and production of manuscript, RD: Final approval of the version to be published, YW: Conception of idea and production of manuscript, YY: Production of manuscript and senior author, XT: Conception of idea and production of manuscript, CD: Result interpretation, made discussion and conclusion, HZ: Senior author for literature search and production of manuscript, YZ: Result interpretation, made discussion and conclusion, FZ: Conception of idea, production of manuscript and senior author. All authors read and approved the final manuscript.
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Competing interests
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