# Association between SLCO1B1, apolipoprotein E and ABCG2 genes and lipid response to rosuvastatin: a meta-analysis

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***Objective*** **To investigate the effects of SLCO1B1, apolipoprotein E (APOE) and ABCG2 gene polymorphisms on the lipid-modulating efficacy of rosuvastatin.**

***Methods*** **Systematic searches were conducted in PubMed, Cochrane Library, Embase, Web of Science, PharmGKB, CNKI, VIP, and Wanfang databases (from database establishment to 1 March 2025). Studies on the correlation between SLCO1B1, APOE, ABCG2 gene polymorphisms and the lipid-modulating efficacy of rosuvastatin were collected, and meta-analysis was performed using RevMan 5.4 software.**

***Results*** **A total of 16 studies involving 6167 patients were included, covering APOE (p.C130R/rs429358, p.R176C/rs741), SLCO1B1 (p.V174A/rs4149056, p.N130D/rs2306283), and ABCG2 (p.Q141K/rs2231142) genes. The results showed that SLCO1B1 [AG+GG vs. AA, mean difference = −4.36, 95% confidence interval (CI): −7.92 to −0.80, $P = 0.02$], APOE (E2 vs. E3, mean difference = −5.58, 95% CI: −8.04 to −2.51, $P < 0.00001$] and ABCG2 (CA+AA vs. CC, mean difference = −7.07, 95% CI: −9.47 to −4.68, $P < 0.00001$) genotypes all significantly affected statin-induced low-density lipoprotein cholesterol (LDL-C) reduction; patients with ABCG2 CA+AA genotype had statistically significant differences in total cholesterol level changes (mean difference = −7.15, 95% CI: −8.78 to −5.53) and triglyceride level changes (mean difference = −7.37, 95% CI: −10.91 to −3.83) (both $P < 0.05$).**

***Conclusion*** **The lipid-lowering efficacy of rosuvastatin (especially the reduction of LDL-C level) is significantly affected by the polymorphisms of SLCO1B1 (c.388A>G), ApoE (c.388T>C, c.526C>T) and ABCG2 (c.421C>A) genes. *Pharmacogenetics and Genomics* XXX: XXXX–XXXX** 

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**Keywords: lipid-lowering efficacy, meta-analysis, polymorphism, rosuvastatin**

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## Introduction

Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of death and disability worldwide [1]. Dyslipidaemia constitutes a significant risk factor for atherosclerosis. Elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) represent pathogenic risk factors for ASCVD, with LDL-C being the primary atherogenic cholesterol component. Consequently, effective lipid regulation holds considerable importance for the prevention and treatment of cardiovascular disease.

Statins, as HMG-CoA reductase inhibitors, are widely employed in the treatment of dyslipidaemia. Among existing statins, rosuvastatin demonstrates superior lipid-lowering efficacy, with a higher proportion of patients achieving LDL-C target levels when treated with this medication [2,3]. Although the efficacy of rosuvastatin is well established, there exists considerable inter-individual variability in patients' lipid-lowering response. Some patients may fail to achieve target lipid levels or experience adverse reactions, thereby compromising treatment adherence and increasing the risk of cardiovascular events. Research indicates that this variation may be associated with polymorphisms in genes related to drug-metabolising enzymes, transporters, drug targets, and lipid metabolism. These genetic variations may influence the therapeutic response to rosuvastatin [4]. Against this backdrop, pharmacogenomics offers a viable pathway for understanding personalised medication. This field focuses on the impact of genetic polymorphisms on drug responses. By analysing patients' genetic information, it aids in understanding the distinct characteristics of drug responses across different individuals. This provides valuable guidance for drug selection, dose adjustment, and therapeutic



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monitoring, thereby assisting clinicians in the more rational use of rosuvastatin and enhancing treatment quality.

In recent years, the relationship between SLCO1B1, apolipoprotein E (APOE) and ABCG2 gene polymorphisms and the efficacy and safety of statin therapy has attracted considerable attention. These genes participate in the pharmacokinetics, pharmacodynamics or lipid metabolism processes of statins. The OATP1B1 transporter encoded by SLCO1B1 is crucial for hepatic uptake of rosuvastatin; APOE plays a central role in lipid metabolism, primarily regulating blood lipids by binding to its receptors; the BCRP protein encoded by ABCG2 influences both intestinal absorption and biliary excretion of rosuvastatin. However, existing research findings regarding the association between SLCO1B1, APOE and ABCG2 polymorphisms and the lipid-lowering efficacy of rosuvastatin remain inconsistent [5–9]. Therefore, it is necessary to further analyse the relationship between SLCO1B1, APOE and ABCG2 gene polymorphisms and the effects of rosuvastatin on TC, triglycerides, LDL-C and HDL-C levels, thereby providing additional scientific evidence for clinical drug use.

## Methods

### Data sources, search strategies and selection criteria

In this study, the genetic polymorphism studies related to rosuvastatin were collected by searching several databases, including systematic searches of PubMed, the Cochrane Library, Embase, PharmGKB, Web of Science, China Journal Full Text Database (CNKI), VIP and Wanfang databases. The search time frame was all from the establishment of each database to 1 March 2025.

We performed the literature search and study selection independently using a standardised approach, and any inconsistencies were resolved by discussing with each other. A study was included if it fulfilled the following criteria: (a) Study population: patients aged ≥18 years with dyslipidemia treated with rosuvastatin without the comorbid use of other lipid-modifying drugs (e.g. fibrates, ezetimibe, and atorvastatin). Sex, region, race and patients' hyperlipidaemia comorbidities and hyperlipidemia status were not restricted, and there was no language restriction. (b) Studies reporting specific information on SLCO1B1, APOE and/or ABCG2 genotypes were tested at any time and by any method. (c) Randomised controlled trials (RCTs), as well as prospective or retrospective cohort studies, were included. (d) Outcome metrics were provided: percentage change in at least one lipid metric (TC, triglyceride, LDL, and/or HDL) at baseline and post-treatment patient lipid metrics (LDL-C, HDL-C, TC, triglyceride).

### Data collection and quality assessment

The researcher first imported the literature into Noteexpress software and cross-checked the information such as title, author, year of publication, source, etc., and utilised the checking function of Noteexpress as well as manually eliminating duplicates. Then, two researchers independently screened titles, abstracts and full text according to set inclusion and exclusion criteria, excluding noncompliant literature to identify potentially relevant articles. If disagreements exist, the researchers will conduct a thorough discussion and full-text evaluation, and then independently extract data from eligible studies, including authors, sample size, study design, interventions and outcome metrics.

### Statistical analysis

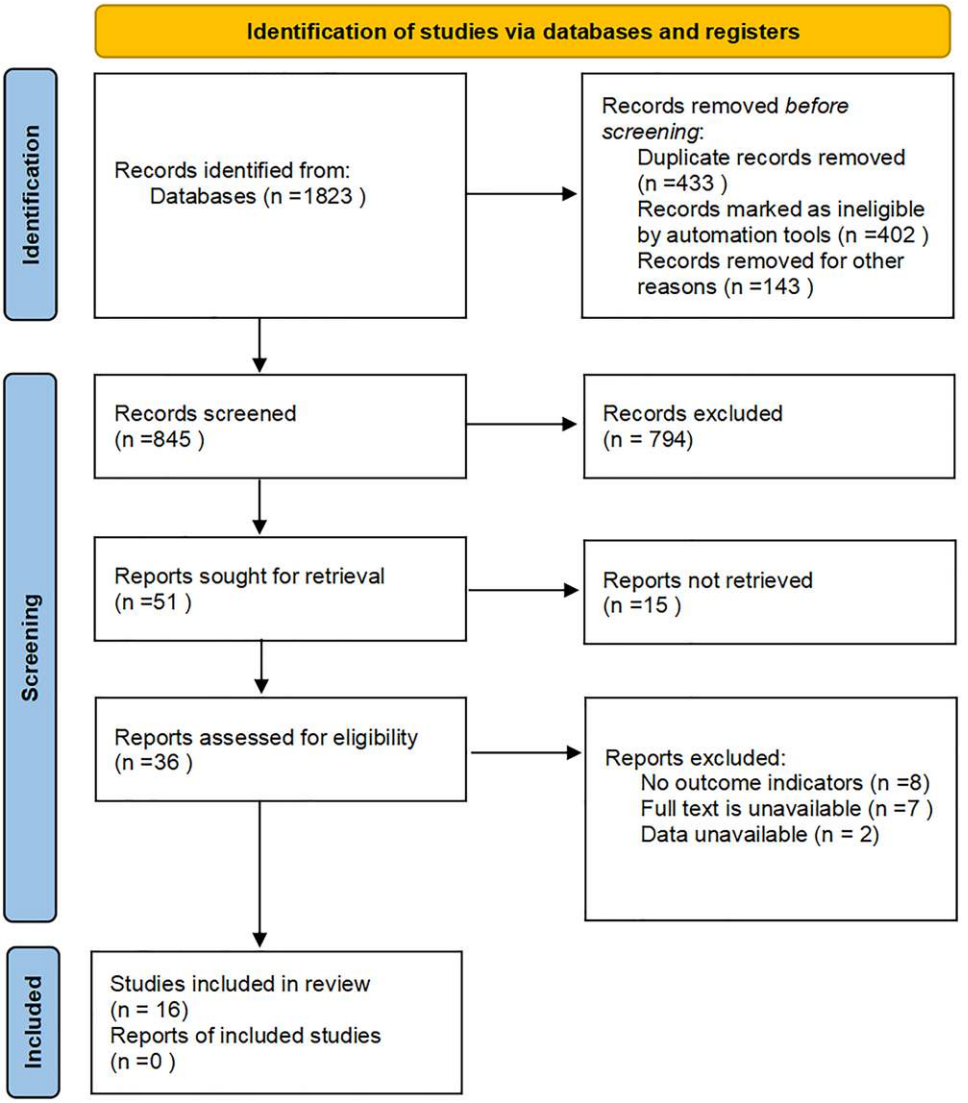
All extracted data were standardised as mean ± SD. Mean differences and their 95% confidence intervals (CIs) were used to assess the percentage change in lipid levels associated with SLCO1B1, APOE and ABCG2 genotypes within each individual study. The percentage change in lipid levels across different genotypes was calculated using the formula, $P = [(\text{post-treatment} - \text{baseline})/\text{baseline}] \times 100\%$. All statistical tests were conducted using Cochrane's meta-analysis software Review Manager 5.4 (RevMan; The Cochrane Collaboration, Oxford, UK) . As the majority of included studies presented lipid level changes and percentage lipid level changes using a parametric model, this parametric approach was adopted to ensure adequate statistical power. A $P$-value <0.05 was considered statistically significant. $Q$ test and $I^2$ test were used to analyse the statistical heterogeneity among studies; when $P \geq 0.1$ and $I^2 < 50\%$, it was considered that the heterogeneity among studies was small, and the fixed-effects model was used at this time; while when $P < 0.10$ or $I^2 \geq 50\%$, it was considered that the heterogeneity among studies was high, and the random-effects model was used; if the analytical results were more heterogeneous or the heterogeneity could not be eliminated, the method of eliminating the literature one by one could be used. Sensitivity analysis was performed to identify studies that could lead to heterogeneity.

## Results

### Literature search

The database search resulted in a preliminary search of 1823 articles, of which 581 were in Embase, 253 in PubMed, 169 in Cochrane Library, 758 in Web of Science, 88 in CNKI, 45 in VIP and 88 in WanFang. Duplicates of 433 articles were screened and excluded. The titles and abstracts were read according to the inclusion and exclusion criteria, and 16 studies that met the criteria were finally included [9–23]. The literature screening process is detailed in Fig. 1.

**Fig. 1**




Flow diagram of the literature search and trials selection process.

### Basic information on included studies

A total of 16 studies were included in this meta-analysis, including 2 randomised controlled trials [10,11] and 14 cohort studies [12–23]. Twelve of these were from China, one from the UK, two from South Korea and one from Russia with a total of 6167 patients included. The treatment regimen was rosuvastatin 10 mg/day or 20 mg/day. Treatment duration was greater than 3 weeks in all studies. See table 1 for details.

### Inclusion in literature quality assessment

For included observational studies (cohort studies), we employed the Newcastle–Ottawa Scale to assess cohort study quality. Evaluation focused on three aspects: selectivity (including representativeness of the exposed cohort, selection of the unexposed cohort, confirmation of exposure and occurrence of outcome events prior to study commencement), comparability (comparability of cohorts) and outcome assessment (including evaluation of outcome events, adequacy of follow-up to observe outcomes and completeness of follow-up). This ensured study reliability. The total score was out of 9 points, with scores >7 indicating high-quality studies, 1–4 indicating low-quality literature, 5–6 indicating moderate-quality literature and 7–9 indicating high-quality literature. Results: Ten studies were of high quality; five studies were of moderate quality.

**Table 1 Basic characteristics of the included literature**

| First authors | Particular year | Countries | Reported genetic | Prophylacticmedication | Treatments | Dosages | Median age | Outcome indicator | Quality score |
|---|---|---|---|---|---|---|---|---|---|
| Bailey *et al.* [11] | 2010 | UK | ABCG2 (421C>A) SLCO1B1 (521T>C) | Secondary | 12 weeks | 10 mg | 61.98 | ③ | 8 |
| Hu *et al.* [17] | 2010 | China | ABCG2 (421C>A) | Secondary | >6 weeks | 10 mg | 55.7 | ③ | 8 |
| Tomlinson *et al.* [10] | 2010 | China | ABCG2 (421C>A) | Secondary | >4 weeks | 10 mg | 56.7 | ①②③④ | 8 |
| Hu *et al.* [16] | 2012 | China | SLCO1B1 (521T>C, 388A>G) | Secondary | 6 weeks | 10 mg | 55.7 | ③ | 7 |
| Lee *et al.* [15] | 2013 | China | ABCG2 (421C>A) SLCO1B1 (521T>C, 388A>G) | Secondary | >4 weeks | 10 mg | 55.9 | ③ | 9 |
| Zhang *et al.* [18] | 2016 | China | SLCO1B1 (521T>C) | Secondary | 6 weeks | 10 mg | 66.16 | ①②③④ | 5 |
| Wang *et al.* [19] | 2016 | China | APOE (ε3, ε2, ε4) | Secondary | 8 weeks | 10 mg | 60.5 | ③ | 6 |
| Tian [12] | 2019 | China | SLCO1B1 (521T>C) APOE (ε3, ε2, ε4) | Secondary | 6 months | 10 mg | 63.52 | ①②③ | 9 |
| Ma [22] | 2020 | China | SLCO1B1 (521T>C) ABCG2 (421C>A) | Secondary | 6 weeks | 10 mg | 48.5 | ①②③④ | 7 |
| Zhang *et al.* [20] | 2020 | China | SLCO1B1 (521T>C, 388A>G) | Secondary | 8 weeks | – | – | ①②③④ | 5 |
| Du *et al.* [13] | 2021 | China | APOE (ε3, ε2, ε4) | Secondary | 12 weeks | 10 mg | 60.12 | ①②③④ | 8 |
| Yang *et al.* [14] | 2023 | China | APOE (ε3, ε2, ε4) | Secondary | 6 months | 10 mg | 63.63 | ①②③④ | 7 |
| Han *et al.* [21] | 2022 | China | APOE (ε3, ε2, ε4) SLCO1B1 (521T>C, 388A>G) | Secondary | 6 months | 20 mg | 58.38 | ①②③④ | 8 |
| Kim *et al.* [9] | 2019 | Korea | ABCG2 (421C>A) | Primary | 3 weeks | 20 mg | – | ①②③④ | 5 |
| Kim *et al.* [24] | 2017 | Korea | ABCG2 (421C>A) | Primary | 8 weeks | 20 mg | – | ①②③④ | 5 |
| Sivkov *et al.* [23] | 2021 | Russia | SLCO1B1 (521T>C) | Secondary | 4 months | 10 mg | – | ②③ | 8 |

① Percentage change in triglyceride level; ② Percentage change in total cholesterol level; ③ Percentage change in LDL level; ④ Percentage change in HDL level; –: unknown.

## Meta-analysis results

### *Effect of SLCO1B1 (521T>C, 388A>G) single nucleotide polymorphism on lipid levels*

This study evaluated the impact of the SLCO1B1 (521T>C) polymorphism on the lipid-lowering efficacy of rosuvastatin, with results presented in Fig. 2. Analysis revealed that patients carrying the C allele (TC+CC) exhibited statistically significant changes in HDL-C levels compared to those with the TT genotype: HDL-C levels increased more markedly (mean difference = 5.23, 95% CI: 2.15–8.31, $P < 0.05$). However, no significant differences were observed in LDL-C (mean difference = –2.46, 95% CI: –6.48 to 1.55), triglyceride (mean difference = –1.76, 95% CI: –4.99 to 1.46, $P > 0.05$) and TC (mean difference = 0.02, 95% CI: –4.96 to 5.00, $P > 0.05$).

Additionally, the study assessed the impact of another SLCO1B1 mutation site, 388A>G, on the lipid response to rosuvastatin, as shown in Fig. 3. Analysis of all lipid parameters revealed low heterogeneity ($I^2 = 0\%$), thus a fixed-effect model was employed. Results demonstrated a statistically significant difference in LDL-C reduction between patients with the AG+GG genotype compared to the AA genotype (mean difference = –4.36, 95% CI: –7.92 to –0.80, $P = 0.02$), suggesting this genotype may be associated with a more pronounced LDL-C decrease. However, no statistically significant differences were observed between the AG+GG and AA genotypes in terms of changes in TC, triglyceride, or HDL-C ($P > 0.05$).

### *Effect of apolipoprotein E on lipid levels*

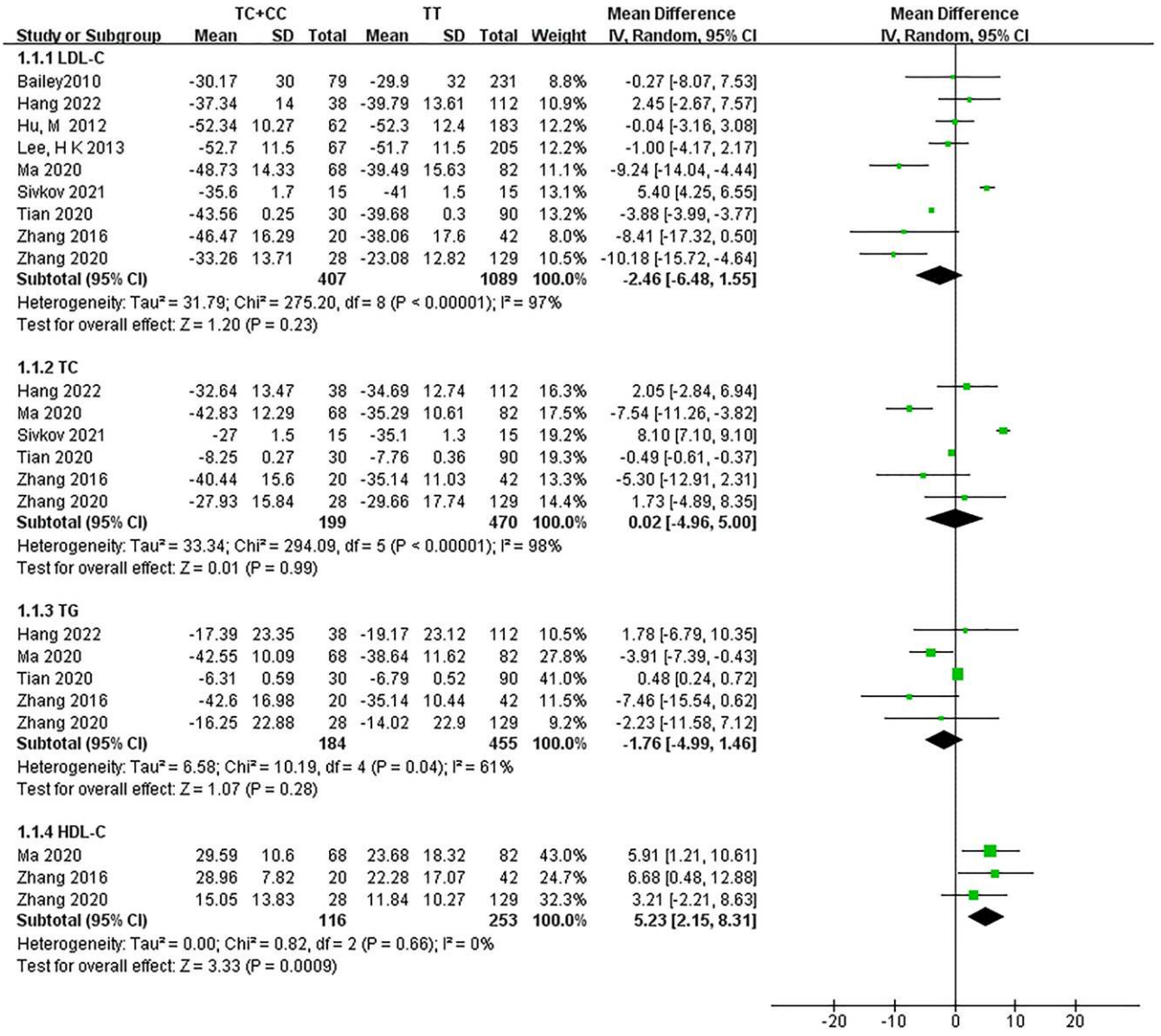
The ApoE gene is determined by two sites, c.388T>C and c.526C>T, giving rise to three major subtypes: E2, E3 and E4 [25]. This study compared the effects of mutant subtypes E2 and E4 versus the wild-type subtype E3 on the lipid response to rosuvastatin (Figs. 4 and 5). Given the high heterogeneity of the data, we employed a random-effects model for analysis. Results revealed that patients with the E2 subtype exhibited a greater reduction in LDL-C compared to those with the E3 subtype (mean difference = –5.58, 95% CI: –8.04 to –2.51, $P < 0.05$), while exhibiting a greater increase in HDL-C (mean difference = 3.30, 95% CI: 0.64–5.97, $P < 0.05$). However, no statistically significant differences were observed between E2 and E3 subtypes for TC and triglyceride levels ($P > 0.05$).

It is noteworthy that, compared with the E3 genotype group, resveratrol demonstrated inferior lipid-lowering efficacy in carriers of the E4 allele (mean difference = 9.58, 95% CI: 0.12–19.03, $P = 0.05$). However, no statistically significant differences were observed between the two groups regarding changes in TC, triglycerides and high-density lipoprotein cholesterol (HDL-C) ($P > 0.05$).

### *Effect of ABCG2 (c.421C>A) gene on lipid levels*

A total of seven studies evaluated the effect of ABCG2 (c.421C>A) single nucleotide polymorphism on LDL-C changes, and statistical heterogeneity among studies was small ($P = 0.08$, $I^2 = 47\%$), so they were meta-analysed using a fixed model. The results of the analysis showed a greater reduction in LDL-C levels in patients with the CA+AA genotype compared with the

**Fig. 2**



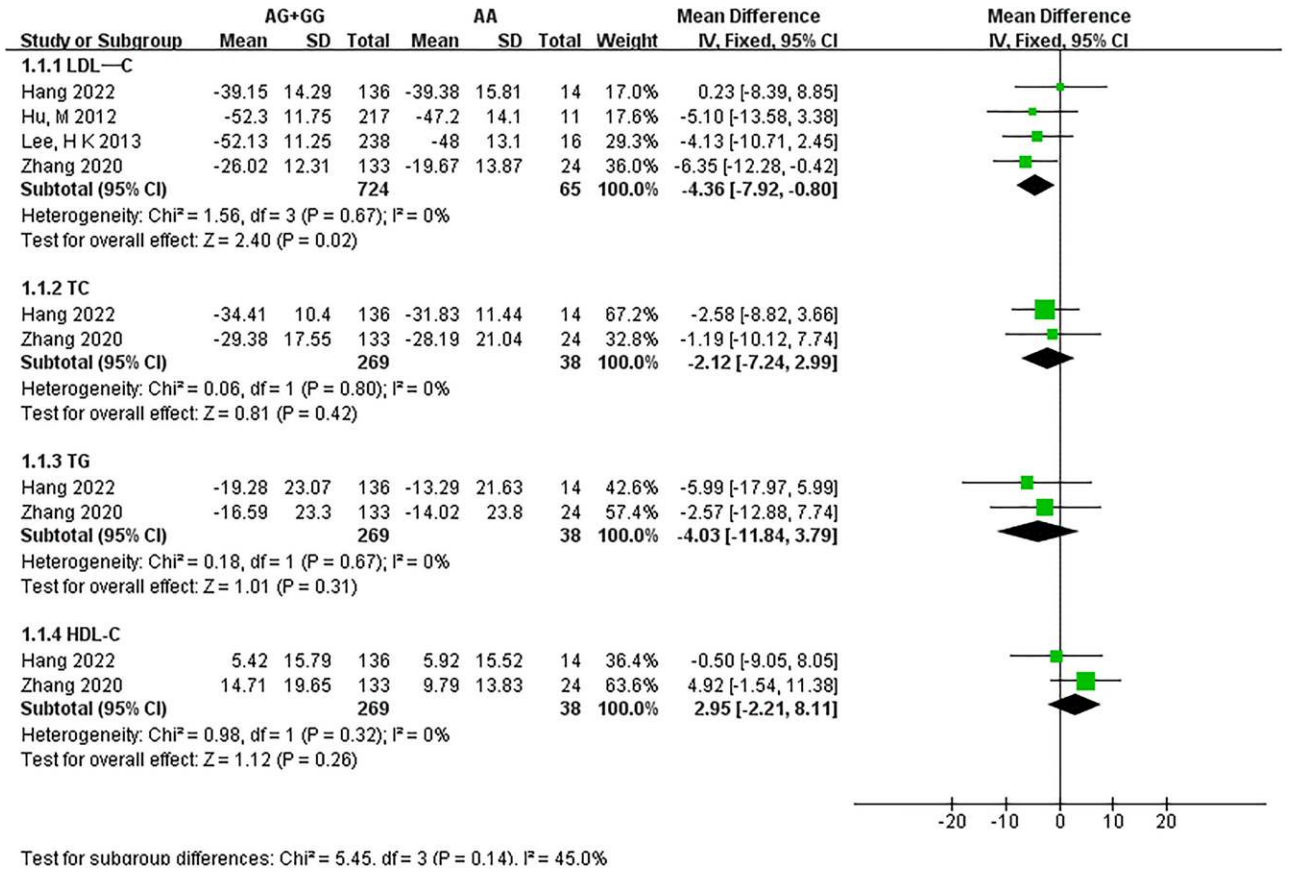

Forest plot of meta-analysis of the effect of SLCO1B1 (521T>C) genotype on lipid profiles in patients with rosuvastatin. CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Mean, mean change rate of blood lipids by genotype after treatment; TC, total cholesterol; TG, triglyceride. Total, the total sample size.

CC genotype (mean difference = −6.61, 95% CI: −7.92 to −5.31, $P < 0.05$), and the difference was statistically significant (Fig. 6). In addition, by evaluating the percentage changes in other lipids (TC, triglyceride and HDL-C), we found that carriers of the variant A allele had statistically significant differences in the changes in TC levels (mean difference = −7.15, 95% CI: −8.78 to −5.53, $P < 0.05$) and triglyceride levels (mean difference = −7.37, 95% CI: −10.91 to −3.83, $P < 0.05$) in patients with the CA+AA genotype compared to patients with the wild-type gene, whereas changes in HDL-C levels (mean difference = −3.03 to −3.83) were statistically significant, and changes in HDL-C levels ($P < 0.05$) were statistically significant. 95% CI: −10.91 to −3.83, $P < 0.05$] were statistically significant, whereas there was no statistically significant difference in the change in HDL-C level (mean difference = 3.03, 95% CI: −1.13 to 7.18, $P > 0.05$).

## Discussion

Based on existing published research, we investigated the association between polymorphisms in the SLCO1B1, ApoE and ABCG2 genes and the effects of rosuvastatin on TC, triglycerides, LDL-C and HDL-C levels. Results indicate that the AG+GG genotype at the

**Fig. 3**




Forest plot of meta-analysis of the effect of SLCO1B1 (388A>G) genotype on lipid profile in patients with rosuvastatin. CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Mean, mean change rate of blood lipids by genotype after treatment; TC, total cholesterol; TG, triglyceride. Total, the total sample size.

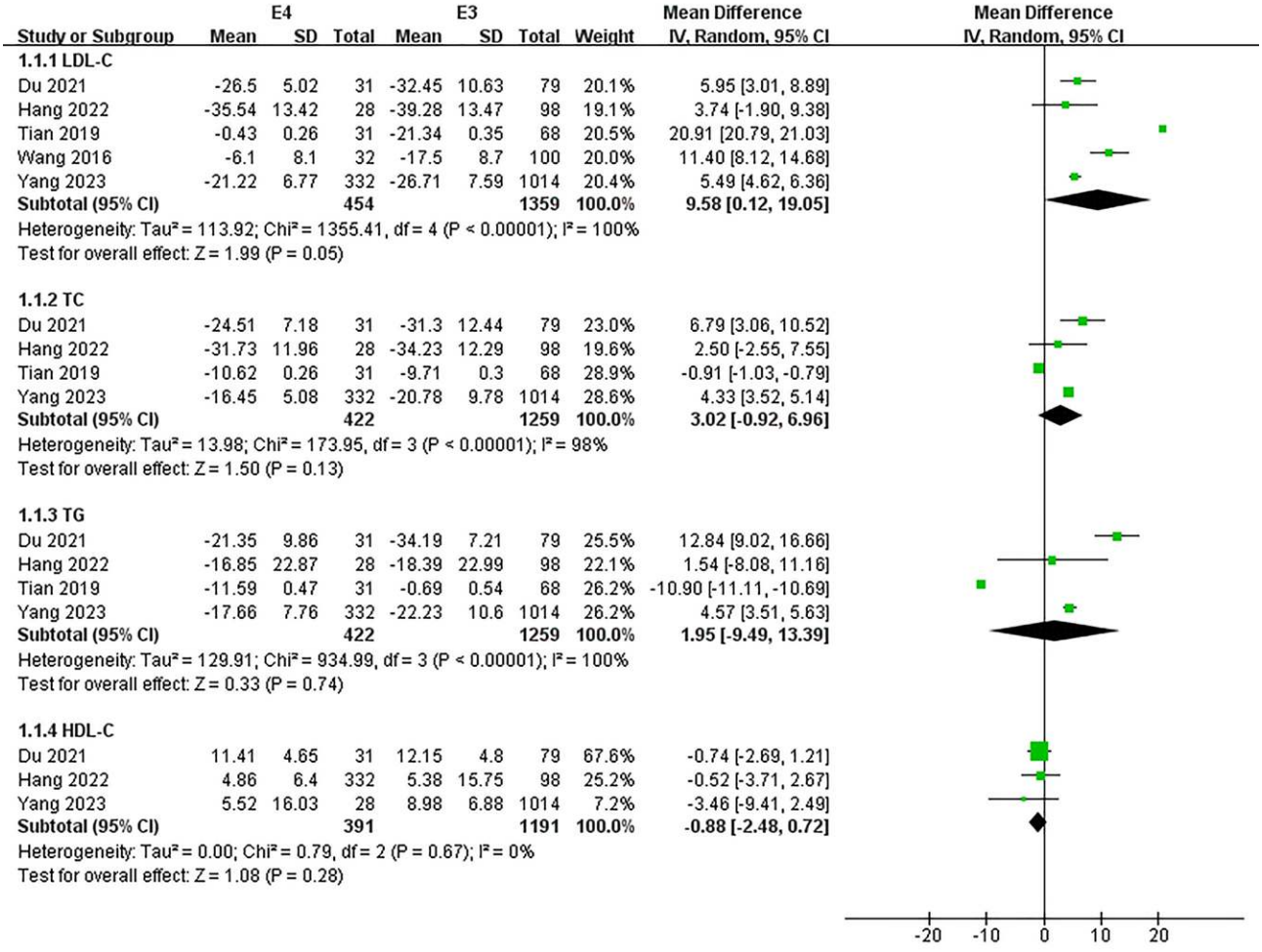
SLCO1B1 c.388A>G locus is also significantly associated with variations in LDL-C levels, whereas the C allele at the SLCO1B1 c.521T>C locus exhibits no significant influence on LDL-C level changes.

APOE gene polymorphisms significantly influence the efficacy of rosuvastatin in lowering LDL-C. Compared with the E3 genotype, patients with the E2 genotype exhibited greater reductions in LDL-C, whereas those with the E4 genotype demonstrated smaller decreases. Apart from statistically significant changes in HDL-C among E2 genotype patients, APOE polymorphisms had no significant effect on alterations in TC or triglyceride. Furthermore, the ABCG2 c.421C>A polymorphism also significantly influenced the efficacy of rosuvastatin in reducing TC, triglyceride and LDL-C. These findings provide additional evidence for understanding the role of SLCO1B1, ApoE and ABCG2 gene polymorphisms in the lipid-modulating effects of rosuvastatin.

Current major expert consensus in Europe and America emphasises the importance of rosuvastatin in the treatment and prevention of ASCVD, establishing LDL-C as the primary therapeutic target [26,27]. Other lipid parameters such as TC and triglycerides are regarded as secondary or supplementary targets. Although current evidence does not support treating HDL-C as a therapeutic target, its levels retain predictive value for ASCVD risk [28,29].

Rosuvastatin, being a hydrophilic compound, requires active transport via uptake and efflux transporters to effectively cross the cell membrane and exert its effects. The absorption of rosuvastatin is limited by ABCG2 expressed on the apical membrane of intestinal epithelial cells [30]. ABCG2 mediates the efflux of rosuvastatin back into the small intestinal lumen, and reduced ABCG2 function may lead to increased rosuvastatin exposure. For instance, carriers of the ABCG2 c.421A allele exhibit a 144% higher area under the concentration–time curve (AUC) compared to wild-type individuals [31]. The more pronounced reductions in LDL-C, TC and triglyceride observed in patients with the CA+AA genotype in this study may be attributed to increased systemic drug

**Fig. 4**

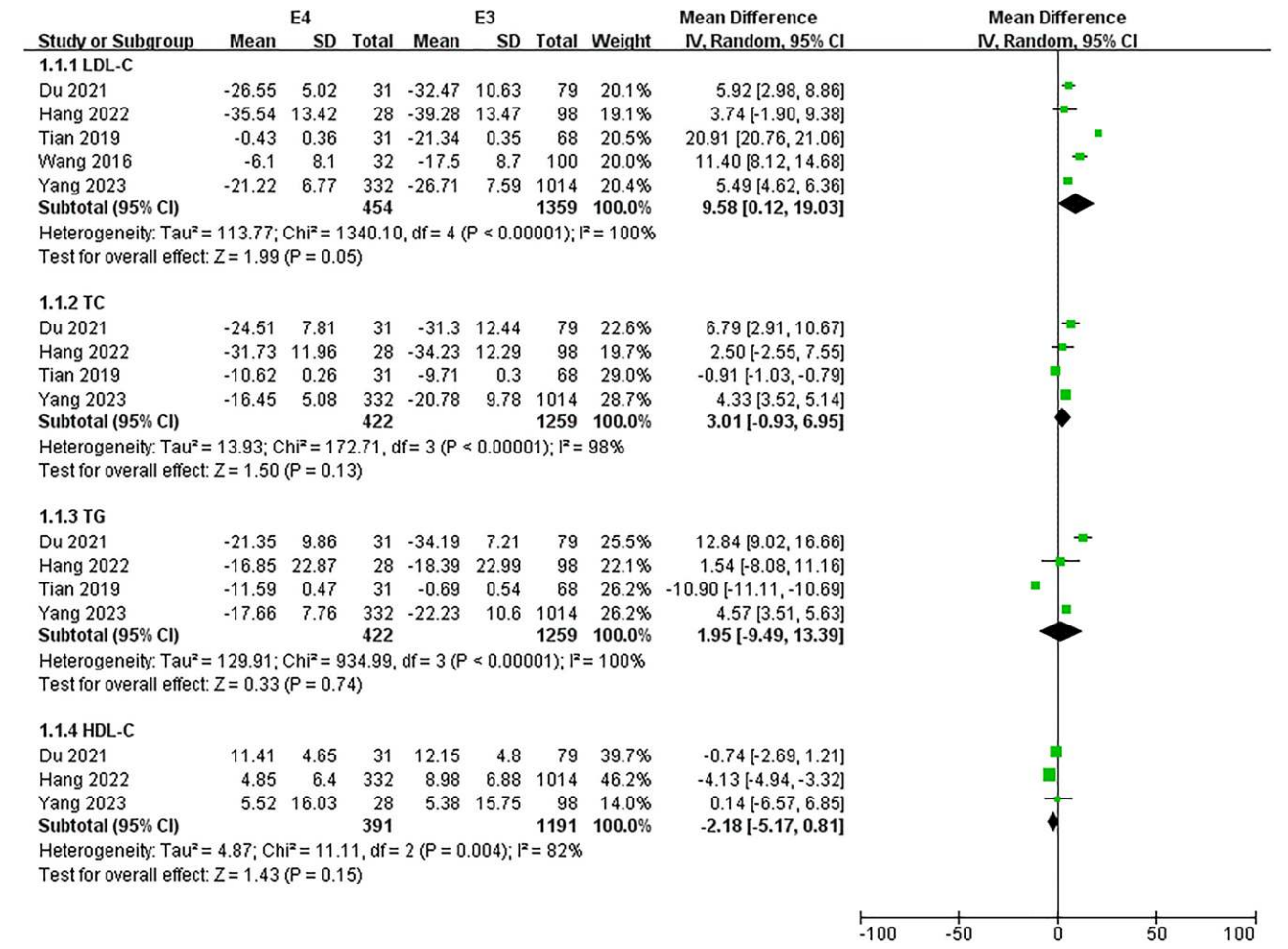



Forest plot of meta-analysis of the effect of APOE genotype on lipid profile in patients with rosuvastatin. APOE, apolipoprotein E; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Mean, mean change rate of blood lipids by genotype after treatment; TC, total cholesterol; TG, triglyceride. Total, the total sample size.

exposure due to ABCG2 dysfunction, thereby amplifying its lipid-lowering effects. The uptake of rosuvastatin into hepatocytes is primarily mediated by the organic anion transporter polypeptide OATP1B1, encoded by SLCO1B1 [30]. As statins exert their primary cholesterol-lowering effects within hepatocytes, reduced uptake from the bloodstream into the liver via OATP1B1 due to SLCO1B1 genetic variants may diminish the pharmacological efficacy of rosuvastatin. However, observational studies indicate that carriers of SLCO1B1 alleles such as c.521T>C and c.388A>G exhibit significantly elevated plasma $C_{max}$ and AUC for rosuvastatin, with paradoxically enhanced lipid-lowering effects [32,33]. This may be intrinsically linked to the reduced functionality of this transporter, which significantly increases systemic and hepatic exposure to statins [34]. This likely enhances HMG-CoA reductase inhibition and promotes LDL-C clearance by upregulating LDL receptor expression. It also explains the functional reduction in OATP1B1 protein activity associated with the c.388A>G and c.521T>C variants forming the SLCO1B1*5 (388A-521C) and *15 (388G-521C) haplotypes, leading to elevated serum drug concentrations following statin administration. This, in turn, increases the risk of adverse reactions such as abnormal liver transaminases, myopathy and even rhabdomyolysis.

The APOE gene is characterised by two common genetic polymorphic sites (rs429358 T>C, rs7412 C>T) and generate three allelic combinations: e2 (Cys 112, Cys158), e3 (Cys 112, Arg158) and e4 (Arg 112, Arg158), yielding three heterozygous APOE genotypes (E2, E3, E4). APOE gene polymorphisms influence individual lipid levels by affecting lipid clearance and metabolic

**Fig. 5**

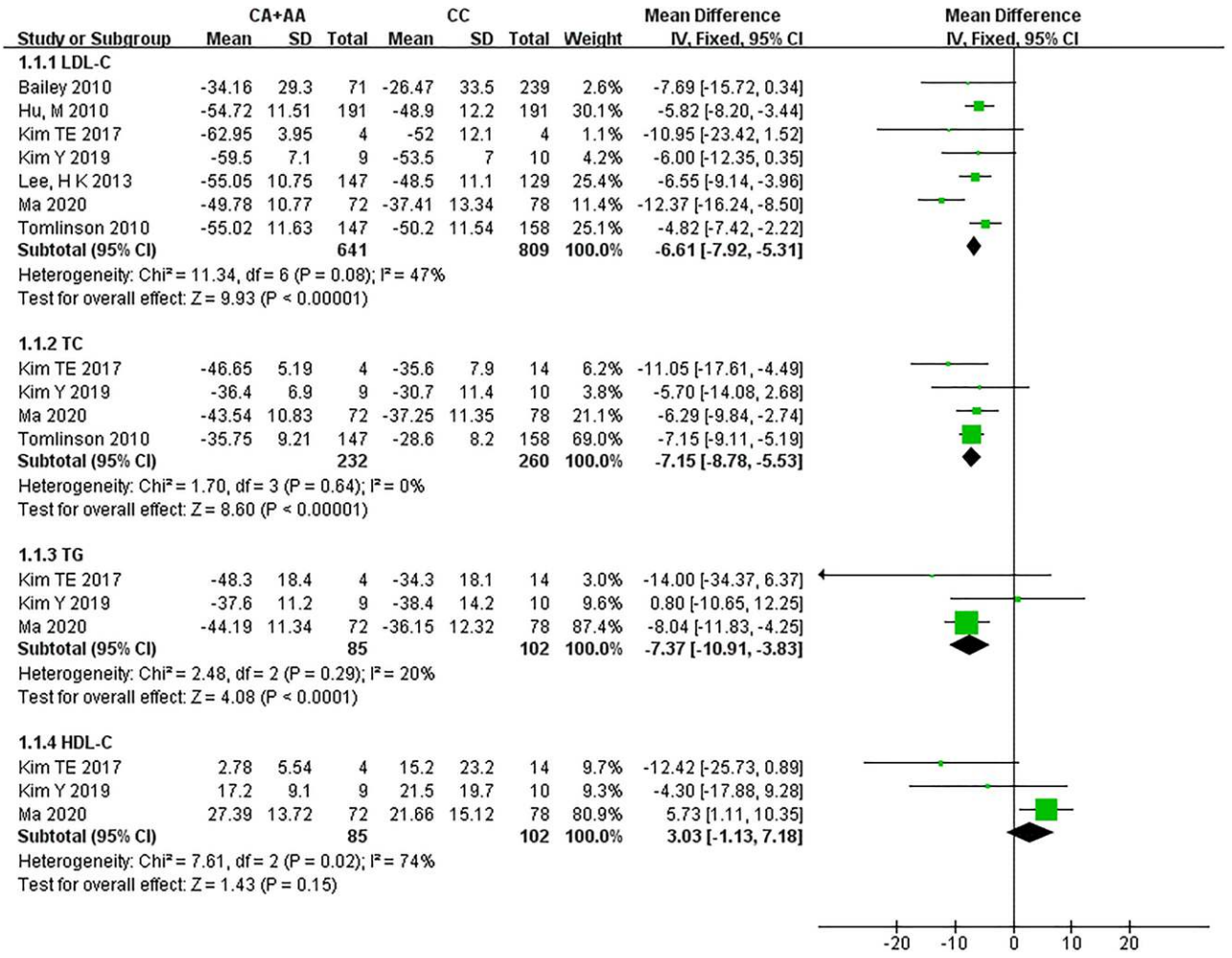



Forest plot of meta-analysis of the effect of APOE genotype on lipid profile in patients with rosuvastatin. APOE, apolipoprotein E; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Mean, mean change rate of blood lipids by genotype after treatment; TC, total cholesterol; TG, triglyceride. Total, the total sample size.

capacity [35]. The effects of APOE genetic polymorphisms on blood lipid levels have been reported in numerous studies, though conclusions remain inconsistent. Our findings indicate that the lipid-lowering efficacy of statins (LDL-C) is influenced by APOE genotype, with the E2 subtype exhibiting the best response, the E3 subtype showing intermediate efficacy and the E4 subtype demonstrating the poorest response.

A comparison of numerous prior studies examining the impact of genetic polymorphisms across different populations worldwide on the pharmacokinetics of rosuvastatin [36–46] revealed that ABCG2 genotypes exert a greater percentage effect on rosuvastatin AUC compared to polymorphisms in genes such as SLCO1B1. Alterations in the pharmacokinetics of statins are likely to directly influence both their therapeutic efficacy and toxicity. Consequently, we hypothesise that ABCG2 polymorphisms may exert a more pronounced influence on rosuvastatin's lipid-lowering efficacy. This may relate to ABCG2's expression in the liver and gut, where it participates in the majority of rosuvastatin's intestinal absorption and biliary excretion [3,47]. Finally, it should be noted that this study has the following limitations: (a) Individual variability in drug response is influenced not only by genetic factors but also by other non-genetic factors such as age, lifestyle and comorbidities. (b) Factors including gender, ethnicity, research methodology, statin dosage and treatment duration may influence outcomes, leading to considerable heterogeneity between studies. Future investigations should account for these multifaceted influences by incorporating more multicentre, multi-population, large-sample studies and conducting comprehensive subgroup analyses to enable more reliable prediction of the response between rosuvastatin and lipids. (c)

**Fig. 6**




Forest plot of meta-analysis of the effect of ABCG2 genotype on lipid profile in patients with rosuvastatin. CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Mean, mean change rate of blood lipids by genotype after treatment; TC, total cholesterol; TG, triglyceride. Total, the total sample size.

The combined effects of relevant genes on rosuvastatin were not considered. Future research should investigate interactions between genes to gain a more comprehensive understanding of the mechanisms by which genetic polymorphisms influence the efficacy of rosuvastatin.

## Conclusion

Polymorphisms in SLCO1B1, ApoE and ABCG2 may influence the lipid-lowering efficacy of rosuvastatin. Specifically, SLCO1B1 (c.388A>G), ApoE (c.388T>C, c.526C>T) and ABCG2 (c.421C>A) variants significantly affect the extent of LDL-C reduction.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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