BMC Cardiovascular Disorders

SYSTEMATIC REVIEW

Open Access

Effect of ABCG2 c.421 C> A (rs2231142) single nucleotide polymorphisms on the lipid-modulating efficacy of rosuvastatin: a meta-analysis

Lingyan Liu[1], Yongkun Deng[1*†], Peng Li[2], Zhidan Zhang[3], Huiyou Li[1], Xingbiao Yang[1], Zhaoheng Yin[1] and Yong Lai[4,5,6*†]

Abstract

Background To systematically evaluate the effect of ABCG2 c.421 C > A (rs2231142) single nucleotide polymorphism (SNP) on the lipid-modulating efficacy of rosuvastatin (RST).

Methods Searches were conducted using the Wan Fang database, Web of Science, Embase, PubMed, Cochrane Library, and China Journal Full Text Database. The time frame for the search was from the database's creation to September 1, 2024. The RevMan 5.4 software was used to conduct a meta-analysis after the literature was filtered based on the inclusion and exclusion criteria, and pertinent data was extracted following methodological quality evaluation.

Results A total of 7 studies, including 1347 patients, were included. Meta-analysis showed that in a dominant model of inheritance, RST had a significant effect on low-density lipoprotein cholesterol (LDL-C) [MD = -7.23, 95% CI (-8.71, -5.75), $P < 0.05$], total cholesterol (TC) [MD = -7.15, 95% CI (-8.71, -5.75), $P < 0.05$], and triglyceride (TG) [MD = -7.34, 95% CI (-10.88, -3.80), $P < 0.05$] in patients harboring an A allele decreased significantly more than CC, but there was no significant difference in the change of high-density lipoprotein cholesterol (HDL-C) [MD = -2.22, 95% CI (-19.87, 15.43), $P = 0.81$]. The results of the sensitivity analysis suggested that all outcome indicators were stable. However, this study's small sample size may be heterogeneous, and more large-sample, multi-center studies are needed for future validation.

Conclusions The ABCG2 c.421 C > A (rs2231142) SNP significantly affected the lipid-modulating efficacy of RST, especially the down-regulation of LDL-C, TC, and TG.

Keywords ABCG2, BCRP, Rosuvastatin, Lipid-lowering efficacy, Single nucleotide polymorphisms

†Yongkun Deng and Yong Lai contributed equally as corresponding authors.

*Correspondence:
Yongkun Deng
745763076@qq.com
Yong Lai
laiyong8879@163.com
Full list of author information is available at the end of the article

Introduction

The primary chronic non-communicable disease that poses the greatest danger to human life and health globally is cardiovascular disease (CVD), for which hypercholesterolemia is a significant risk factor [1]. The mainstay of lipid reduction therapy is to effectively reduce atherosclerosis and cardiovascular risk by lowering LDL-C and TG levels and raising HDL-C levels in clinical practice. They are frequently used to avoid primary and secondary cardiovascular disorders and treat dyslipidemia [2]. The lipid-regulating effects of statins, however, vary significantly from person to person, according to specific research, and this variation is strongly linked to polymorphisms in the relevant drug genes, such as genetic variations of adenosine triphosphate binding transporter protein 2 (ABCG2) [3, 4].

The ABCG2 gene encodes the breast cancer resistance protein (BCRP), widely distributed in the human brain, kidney, liver, placenta, small intestine, and other tissues. It is the major efflux transporter of RST and can obtain energy through the hydrolysis of ATP and actively excrete endogenous and exogenous substances to the outside of the cell. Based on its location and function, ABCG2 is considered a "gatekeeper" that, on the one hand, facilitates the removal of endogenous chemicals and, on the other, shields tissues from the entry of dangerous compounds like toxins and xenobiotics. One of the most prevalent variations in the ABCG2 gene is the ABCG2 c.421C > A SNP. Polymorphism is created when cytosine (C) is changed to adenine (A), which causes glutamine (Gln) to replace lysine (Lys) in the BCRP polypeptide and reduces BCRP's transporter capacity for RST. Furthermore, the mutation may result in a 30–40% decrease in the expression of BCRP on the cell membrane, which lowers the efflux of RST from hepatocytes and intestinal cells and raises the in vivo concentration of RST with improved effects. The c.421C > A mutation frequency was 35% in Asians, much higher than in non-Asians (14%) [5–10]. Further research must determine how the c.421C > A mutation affects RST transport in Asian individuals.

Pharmacogenomics is one of the emerging approaches to precision medicine. By detecting individual genetic polymorphisms, pharmacogenomics provides precise guidance for drug selection, dosage adjustment, and medication monitoring. The prevalence of c.421C > A mutations in Asian populations and their consequences on RST transport underscore the significance of pharmacogenomics in personalized medicine.

Currently, studies on how the ABCG2 c.421C > A polymorphism affects the effectiveness of RST have produced mixed results. For example, Tomlinson et al. [11] showed that the ABCG2 c.421C > A SNP was linked to a significant dose-dependent decrease in LDL-C levels. Subjects with the AA genotype experienced a 6.9% greater drop in LDL-C levels than those with the CC genotype; this is comparable to the impact of doubling the RST dosage. Nevertheless, it has also been proposed that the ABCG2 c.421C > A SNP has no discernible impact on RST effectiveness [12]. To offer an evidence-based foundation for clinically tailored treatment, this work aims to employ the meta-analysis approach to systematically assess the impact of the AABCG2 c.421C > A SNP on the lipid-lowering efficacy of RST.

Methods

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Inclusion criteria

(1) Study subjects: patients with dyslipidemia treated with RST and not combined with other lipid-lowering drugs (e.g., fibrates, nicotinic acid, ezetimibe, etc.); (2) patients were tested for ABCG2 c.421C > A (rs2231142) polymorphisms, with unlimited detection time and methods; (3) the study provided patients with ABCG2 c.421C > A genotype information; (4) it provided the outcome metrics: the mean percentage change in patients' lipid indices (LDL-C, HDL-C, TC, TG) before and after treatment with RST.

Exclusion criteria

(1) reviews, conference papers, case reports, letters, and animal experiments; (2) duplicate publications; (3) patients with incomplete information; (4) studies with experimental data that could not be extracted or were not available.

Literature search strategy

PubMed, the Cochrane Library, Embase, Web of Science, the Chinese Journal Full Text Database, and the Wan Fang database were all thoroughly searched using the following search terms: ABCG2, BCRP, RST, lipid-lowering effectiveness, and single nucleotide polymorphisms. Citation search was also used to search the reference lists and pertinent literature manually. Searching was restricted from the database's creation to September 1, 2024.

Literature screening and data extraction

Two investigators independently evaluated the literature based on the inclusion and exclusion criteria, and a third investigator assessed the literature through discussion or intervention if there was disagreement. First author, publication year, research nation, sample size, treatment plan, genotyping technique, study design, and outcome measures were among the extracted data.

Evaluation of the quality of the included literature

The Newcastle–Ottawa scale (NOS), which assessed the quality of the included literature, was based on study population selection, between-group comparability, and evaluation of exposure/outcome factors. The total score was 9, with 1–4 denoting low-quality literature, 5–6 denoting moderate-quality literature, and 7–9 denoting high-quality literature.

Statistical methods

Meta-analysis was performed using RevMan 5.4 software. All extracted continuous data were as mean ± standard deviation. To determine the percentage change in lipid levels between rs2231142 genotypes, the mean difference (MD) and its 95% confidence interval (CI) were employed.

Statistical heterogeneity among studies was analyzed using the χ2 test and the I^2 test; when $P \geq 0.1$ and $I^2 < 50\%$, it indicated that the heterogeneity among studies was small and a fixed-effects model was used; conversely ($P < 0.$ 10 or $I^2 \geq 50\%$), a random-effects model was used; if the analytical results were more heterogeneous or the heterogeneity could not be eliminated, sensitivity analyses were performed using a literature-by-literature exclusion method. Since most of the included studies presented lipid level changes and percentage of lipid level changes in a dominant model (CA + AA vs. CC), a dominant model was used to ensure adequate statistical power, and $P < 0.05$ was considered statistically significant.

Results

Literature search results

A database search was conducted to retrieve an initial 300 literature items, and 150 duplicates were screened and excluded. Titles and abstracts were read according to the inclusion and exclusion criteria, and 135 studies were removed. Seven studies that satisfied the criteria were included after the remaining 15 publications were examined in full text; four studies failed to give outcome indicators, 1 study for which the complete text was unavailable, and three studies for which the necessary data were unavailable were eliminated. The literature screening process is detailed in Fig. 1.

Basic information on included studies

This meta-analysis comprised seven studies, including two randomized controlled trials [11, 13] and five cohort studies [12, 14–17]. Four were from China, two from Korea, and one from the United Kingdom. 1413 participants, including 703 wild-type (CC) patients and 644 mutant (CA + AA) patients, were treated with RST 10 mg/day or 20 mg/day. Treatment duration was > 3 weeks in all studies (Table 1).

Results of the quality assessment of the included literature

Two studies were of high quality [11, 13], two studies were of low quality [12, 14], and three studies were of moderate quality [15–17].

Effect of ABCG2 c.421C > A SNP on LDL-C levels

A total of seven studies evaluated the effect of the ABCG2 c.421C > A SNP on LDL-C changes, and statistical heterogeneity among studies was small *(*$P = 0.08$, I2 = 48%), so they were meta-analyzed using a fixed-effects model. The results of the analysis showed that patients with the CA + AA genotype had a greater reduction in LDL-C levels compared with the CC genotype [MD = −7.23, 95% CI (−8.71, −5.75), $P < 0.05$], and the difference was statistically significant. Subgroup analyses showed that the differences were still statistically significant for both 10 mg [MD = −7.14, 95% CI (−8.70, −5.59), $P < 0.05$] and 20 mg [MD = −8.09, 95% CI (−12.92, −3.26), $P < 0.05$] at the different RST doses (Fig. 2).

Effect of ABCG2 c.421C > A SNP on HDL-C levels

Two investigations documented the impact of the ABCG2 c.421C > A SNP with RST on HDL-C modulation. Due to their substantial heterogeneity ($P = 0.005$, I2 = 81%), a random-effects model was used to examine these trials. The findings demonstrated that there was no statistically significant difference in the level of HDL-C improvement between patients with the CA + AA genotype and those with the CC genotype [MD = −2.22, 95% CI (−19.87, 15.43), $P = 0.81$] (Fig. 3).

Effect of ABCG2 c.421C > A SNP on TC levels

A fixed-effects model was used to meta-analyses the four studies that assessed the impact of the ABCG2 c.421C > A SNP on the TC-lowering effect of RST because there was minimal statistical heterogeneity between them ($P = 0.64$, I2 = 0%). The findings demonstrated a statistically significant difference in TC improvement between patients with the CA + AA genotype and those with the CC genotype [MD = −7.15, 95% CI (−8.78, −5.53), $P < 0.05$]. At both RST doses, 10 mg [MD = −6.95, 95% CI (−8.67, −5.23), $P < 0.05$] and 20 mg [MD = −9.02, 95% CI (−14.18, −3.85), $P < 0.05$], subgroup analysis revealed that the differences were still statistically significant (Fig. 4).

Effect of ABCG2 c.421C > A SNP on TG levels

A fixed-effects model was used for meta-analysis after three studies assessed the impact of the ABCG2 c.421C > A SNP on the TG-lowering effect of RST. The

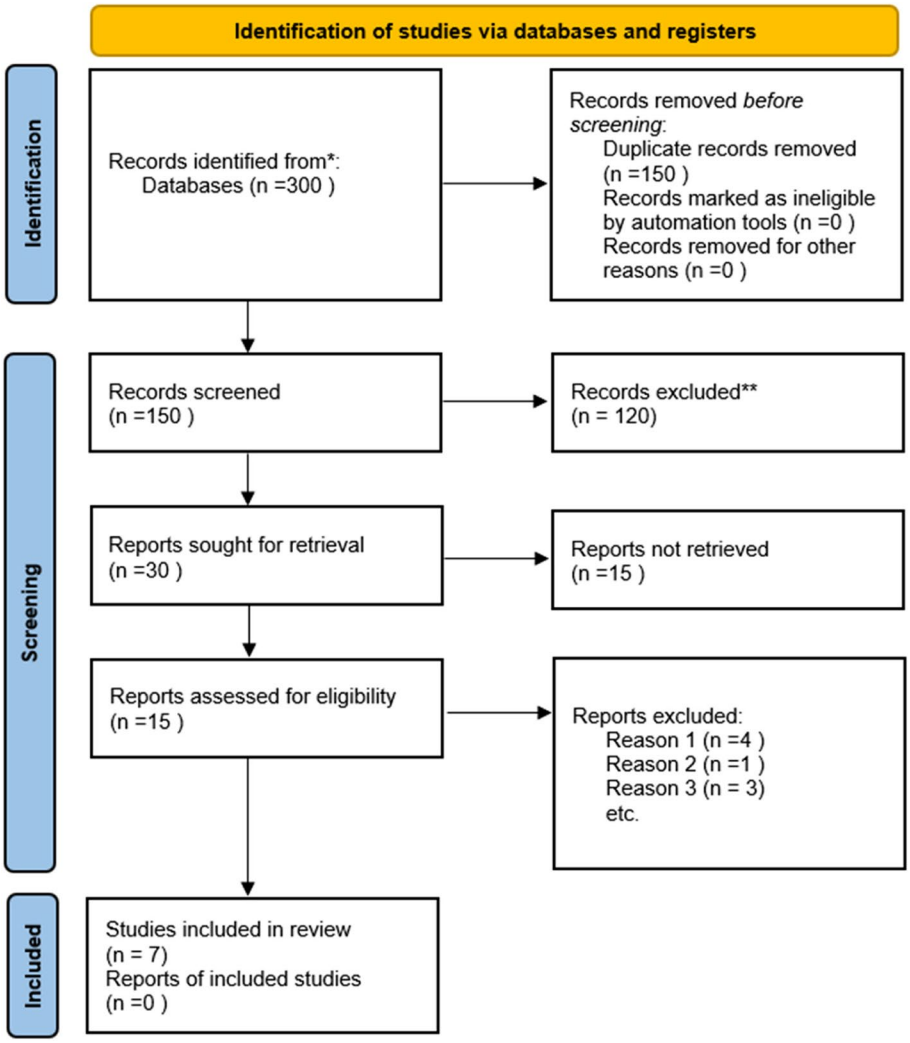

Fig. 1 PRISMA Flowchart for selection of relevant studies

Table 1 provides details of the characteristics included in this study

First author	Year	Country	Number of patients		treatment	dose/day	Gene sequencing methods	outcomes	NOS
			CC	CA + AA					
Bailey [13]	2010	United Kingdom	239	71	12 weeks	10 mg	PCR	③	7
Kim TE [14]	2017	Korea	14	4	8 weeks	20 mg	PCR	①②③④	4
Kim Y [12]	2019	Korea	10	9	3 weeks	20 mg	PCR	①②③④	4
Lee HK [15]	2013	China	129	147	> 4 weeks	10 mg	PCR	③	5
Tomlinson [11]	2010	China	158	147	> 4 weeks	10 mg	PCR	②③	7
Zhang [16]	2020	China	75	194	> 4 weeks	10 mg	Sanger Dideoxy DNA sequencing	①③④	5
Ma [17]	2020	China	78	72	6 weeks	10 mg	PCR	①②③④	5

①TG: triglycerides

②TC: total cholesterol

③LDL-C: low-density lipoprotein cholesterol

④HDL-C: high-density lipoprotein cholesterol

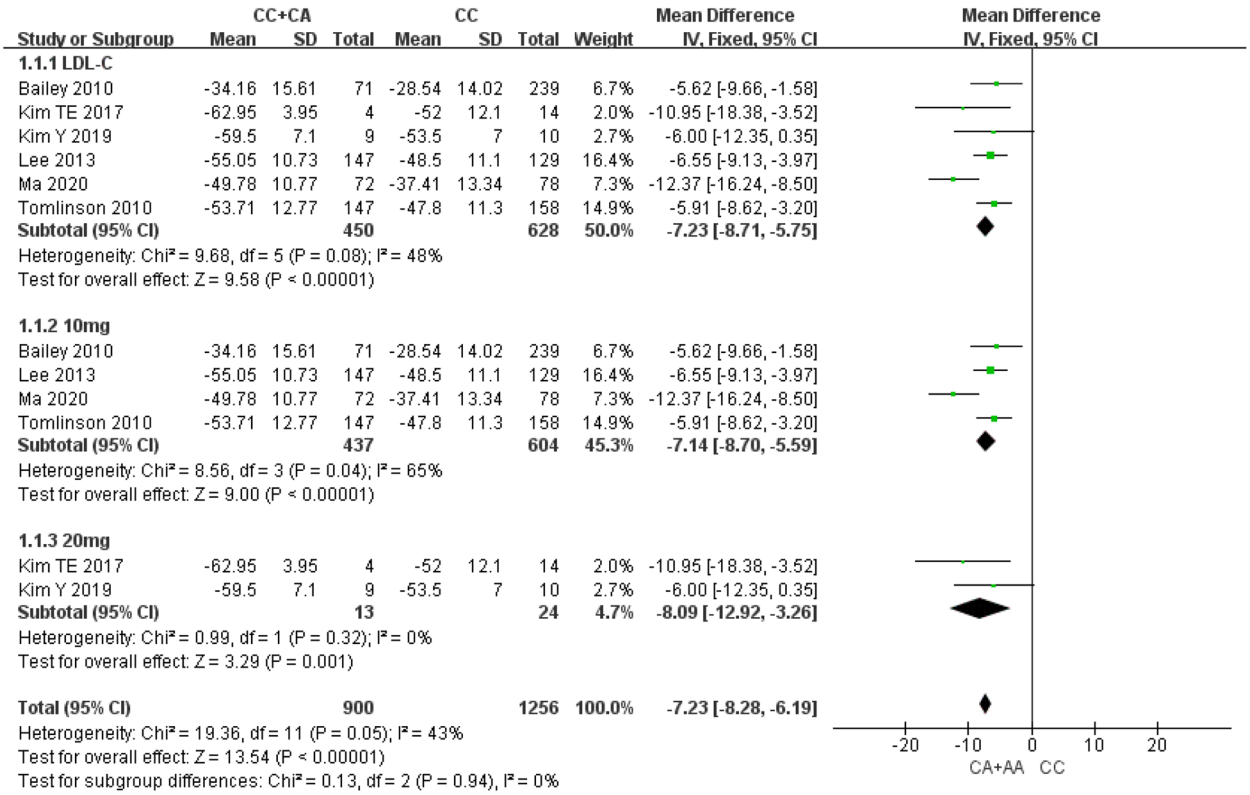

Fig. 2 The effect of ABCG2 c.421C > A SNP on LDL-C level lowering by RST

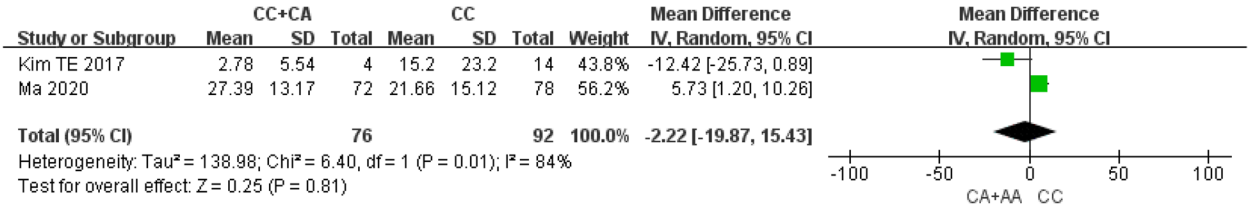

Fig.3 The effect of ABCG2 c.421C > A SNP on the elevation of HDL-C level by RST

results showed that the effect was statistically less diverse among the trials ($P=0.26$, I2 = 25%). The findings demonstrated that patients with the CA + AA genotype had a statistically significant improvement in TG compared to those with the CC genotype [MD = −7.34, 95% CI (−10.88, −3.80), $P<0.05$]. The improvement of HDL-C at 20 mg of RST dosage did not differ significantly between mutant and wild-type patients, according to subgroup analysis [MD = −2.44, 95% CI (−12.42, 7.54), $P=0.63$] (Fig. 5).

Sensitivity analysis

Sensitivity analysis was carried out by excluding individual studies in turn. After excluding literature with high heterogeneity, the LDL-C differences remained statistically significant, indicating that the analysis was relatively stable. Building on existing sensitivity analyses to further explore the impact of different study quality on the results, it became clear that low-quality studies did not significantly impact the overall results (Table 2).

Discussion

This study showed that it significantly lowered LDL-C, TC, and TG in CA + AA type patients compared to CC type. Our study is consistent with the findings of Liu et al. [18] that the A allele variant significantly affects lipid levels. Still, our study clarifies the link between RST and ABCG2 more clearly.

LDL-C is a significant risk factor for CVD. It is regarded as a primary target for treatment, with a

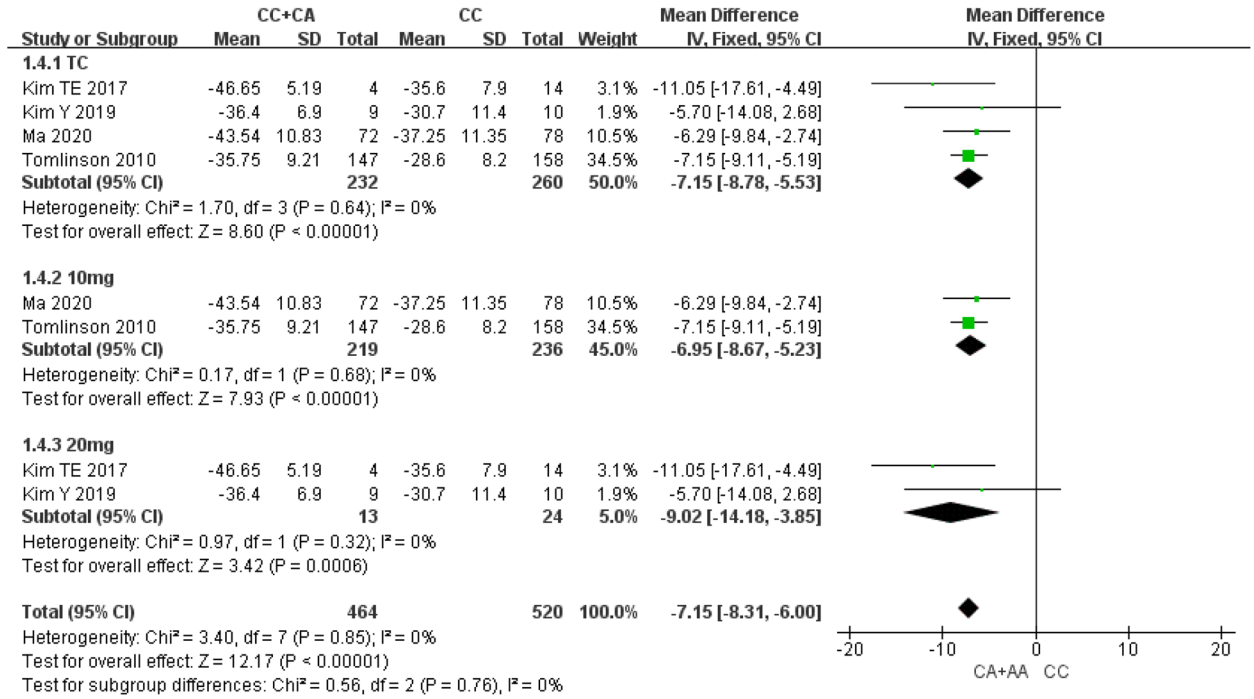

Fig. 4 The effect of ABCG2 c.421C> A SNP on TC level lowering by RST

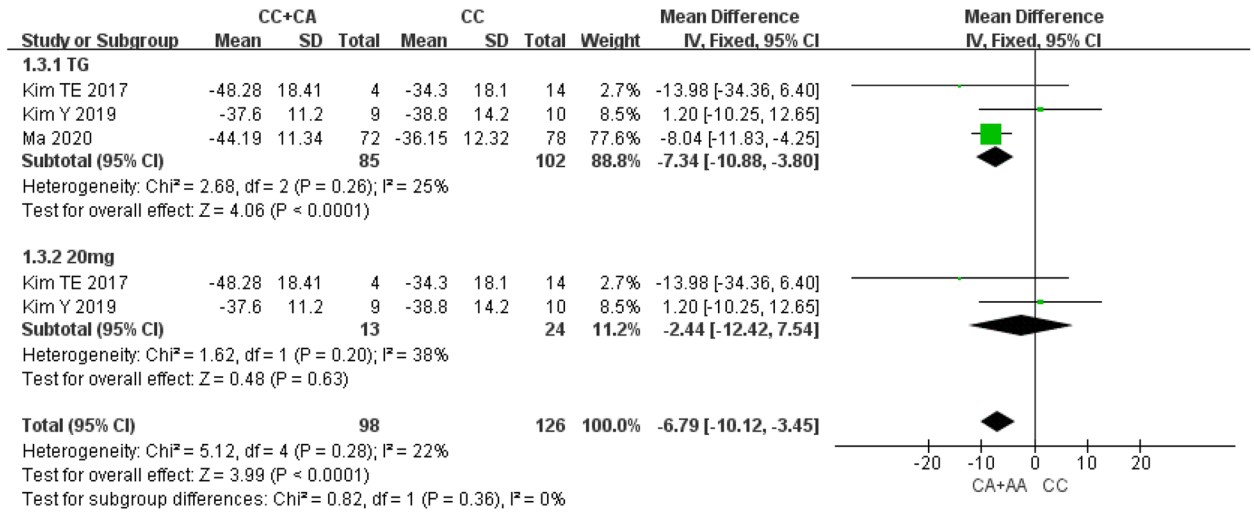

Fig. 5 The effect of ABCG2 c.421C> A SNP on TG level lowering by RST

Table 2 Test of heterogeneity Publication bias

outcome	No. of study	95%CI	P value	I^2(%)
LDL(10 mg)	Ma2020 [17]	[−7.83, −4.44]	0.0001	0
LDL	Kim Y [12]	[−10.28,−5.22]	0.00001	58
	Kim TE [14]	[−9.64, −4.90]	0.00001	54
TG	Kim Y [12]	[−11.96,−4.52]	0.0001	0
	Kim TE [14]	[−10.72,−3.53]	0.0001	56

20%−23% decrease in CVD events for every one mmol/L reduction in LDL-C [19], according to the 2018 ACC/AHA [20], 2019 ESC/EAS [21], and Adult Treatment Group III (ATP III) cholesterol guidelines [22]. Therefore, LDL cholesterol reduction was used as a surrogate for cardiovascular risk reduction. According to this study, the rs2231142 A allele considerably enhanced RST's ability to decrease LDL-C in dyslipidemic people, indicating

that those who carry the allele have superior CVD prevention with RST.

Other lipids are regarded as secondary or complementary therapeutic targets. HDL-C levels are negatively correlated with the incidence of cardiovascular disease (CVD). In the context of atherosclerosis, the primary protective function of HDL-C is its role as a dynamic molecular complex that facilitates reverse cholesterol transport, the transport of excess cholesterol from the peripheral cells back to the liver, and its excretion into the bile [23, 24]. In addition, TG is an independent risk factor for ASCVD and is also used as a risk factor for enhanced risk of ASCVD when risk stratification is performed. Patients with high TG after LDL-C compliance should be treated with concomitant TG-lowering therapy to reduce the risk of ASCVD further. In addition, in patients with severe high TG, lowering TG may reduce the risk of pancreatitis [25].

While RST is a hydrophilic medication, it depends heavily on drug transporter proteins to pass across cell membranes and reach its site of action, unlike other statins. It primarily consists of the efflux transporter BCRP and the uptake transporter protein organic anion transporting polypeptide family 1B1 (OAT1B1), and the associated pharmacogenetic polymorphisms are a significant contributor to individual variations in RST. Of these, the ABCG2 SNP has the most significant impact on RST pharmacokinetics, especially in subjects carrying 2 A alleles, and the lipid-lowering efficacy of RST increased with increasing plasma concentrations [15]. Because of the lower frequency of SLCO1B1 mutations in Asians, this observation suggests that the ABCG2 421C > A SNP is more likely to be the key genetic factor influencing the pharmacokinetic changes of RST in Asian populations [26, 27].

The frequency of genetic variants in ABCG2 was notably elevated in Asians compared to non-Asians. Furthermore, Asian and European individuals harboring the ABCG2 c.421C > A SNP variant exhibited heightened plasma concentrations of RST, particularly those with the AA genotype, in contrast to those with CA and CC genotypes. However, despite sharing the same ABCG2 genotype, Asian individuals were still more exposed to RST than their European counterparts, potentially due to a heightened absorption of statins within this population [28]. The studies included in our meta-analysis focused on Asian populations, but when analyzed in conjunction with the above information, the findings can be reasonably extrapolated to other ethnic groups.

Furthermore, two recent genome-wide association studies (GWAS) [29, 30] demonstrated that in people given RST, the A allele of ABCG2 rs2199936 reduced LDL-C levels. In the same genomic region of the ABCG2 gene, rs2231142 (chromosome: 4; location: 89,052,323) and rs2199936 (chromosome: 4; location: 89,264,355) are in linkage disequilibrium. Because alleles at these two loci tend to occur together when inherited by offspring, linkage disequilibrium suggests that they may have comparable biological activities or be regulated by the exact mechanisms [31, 32]. This study confirms that the effect of the A allele of rs2231142 on the lipid-lowering efficacy of RST echoes this.

BCRP is a widely distributed hepatic and intestinal transporter protein that recognizes and binds various substrates, including RST. It influences their distribution and concentration in vivo through an active transport mechanism. The ABCG2 c.421C > A mutation inhibits ABCG2 function, which lowers BCRP activity and expression. This alteration reduces drug efflux in the biliary tract while increasing RST absorption in the gastrointestinal tract. Although the precise molecular mechanisms and signaling routes are unknown, the combination of increased absorption and slower hepatic clearance causes RST to accumulate in the systemic circulation, enhancing its ability to lower cholesterol [33].

The Pharmacogenomic Knowledge Base (PharmGKB) assigns an evidence level of 2A (meaning essential pharmacogenetic gene with multiple study replicates but small sample size or differences not statistically significant) to the ABCG2 c.421C > A SNP and the efficacy of lipid modulation of RST [33, 34]. Due to a lack of data, there currently needs to be a consensus or pertinent professional guideline that suggests testing for ABCG2 before taking RST in dyslipidemic patients to advise customized therapy. Therefore, by conducting a meta-analysis of the effects of ABCG2 c. 421 C > A polymorphisms on the lipid-lowering efficacy of RST, this study sought to provide evidence-based evidence for the association between ABCG2 and C421A polymorphisms on the lipid-lowering efficacy of RST. Additionally, it sought to provide a reference basis for elucidating whether or not to consider the effect of ABCG2 c.421C > A SNP in the individualization of clinical dosage of RST.

The potential impact of ABCG2 (c.421C > A) gene polymorphisms with altered RST kinetics on the risk of myopathy is controversial. Marco et al. [35] showed that statin-induced elevation of creatine kinase (CK) was not associated with polymorphisms in the ABCG2 (c.421C > A) gene and that the A allele did not significantly correlate with a high risk of myopathy [36, 37]. However, a case–control study demonstrated that the c.421C > A SNP increased the risk of RST-associated myotoxicity and hepatotoxicity approximately twofold [38]. Adverse effects and safety assessments were not performed in this study because the effect of each genotype on drug safety could not be statistically analyzed due

to the small number of enrolled patients or mild reactions. Our study suggests the need to monitor the muscle status of dyslipidemic patients in the clinical management of RST and to adjust the dosage or consider alternative treatments based on genotypic test results to ensure patient safety and maximize efficacy.

The results of the present study showed that ABCG2 c.421C > A SNP significantly affected the lipid-lowering effect of RST, especially in the downregulation of LDL-C, TC, and TG. However, this study has some limitations: (1) Small sample size and heterogeneity problem: The small sample size of the included studies may lead to heterogeneity problems. Future studies should include more large-sample, multicenter studies to reduce heterogeneity and improve the reliability of the results. In addition, the inclusion of low-quality studies in this study may have impacted the results, and it is recommended that future studies prioritize high-quality studies to improve the stability of the results. (2) No publication bias analysis was performed: Due to the limited number of studies, no publication bias analysis was performed. Nevertheless, we preliminarily assessed the risk of bias through funnel plots, and the results showed that the bias was negligible. Future studies should increase the sample size to assess publication bias more comprehensively. (3) Lack of safety data: This study should have discussed adverse reactions and safety in detail. Although existing studies suggest a controversial relationship between the ABCG2 c.421C > A SNP and RST-related adverse reactions (e.g., myopathy), future studies should incorporate safety data to assess tolerability in patients with different genotypes comprehensively. (4) Insufficient racial diversity: This study was primarily based on Asian populations and lacked analysis of other races (e.g., European populations). Future studies should include more cross-racial studies to verify the generalizability of the results. (5) Gene-environment interaction: This study did not explore the interaction between genotype and lifestyle (e.g., diet and exercise). Future studies should further analyze the interaction between genes and environmental factors to more fully explain the lipid-lowering effect of RST.

Conclusion

In summary, although the current study provides important evidence for the effect of ABCG2 c.421C > A SNP on the lipid-lowering effect of RST, more large-sample, multicenter studies are needed to validate the reliability of the results. Future studies should focus on sample size, ethnic diversity, safety data, and gene-environment interactions to provide more comprehensive clinical guidance.

Abbreviations

ABCG2	ATP-binding cassette superfamily G member 2
SNP	Single nucleotide polymorphism
RST	Rosuvastatin
CVD	Cardiovascular disease
BCRP	Breast cancer resistance protein
TG	Triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
Gln	Glutamine
Lys	Lysine
MD	Mean difference
CI	Confidence interval
OAT1B1	Organic anion transporting polypeptide family 1B1
PCR	Polymerase Chain Reaction
GWAS	Genome-wide association study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PharmGKB	Pharmacogenomic Knowledge Base

Acknowledgements
Not applicable.

Clinical trial number
Not applicable.

Authors' contributions
Yongkun Deng and Yong Lai contributed to the study conception and design. Peng Li and Zhidan Zhang analyzed and interpreted data, and made substantial intellectual contribution to paper revision. Lingyan Liu was major contributors in writing the manuscript. Xingbiao Yang, Huiyou Li and Zhaoheng Yin collected data and prepared material. All authors read and approved the final manuscript. manuscript. Xingbiao Yang, Huiyou Li and Zhaoheng Yin collected data and prepared material. All authors read and approved the final manuscript.

Funding
This study did not receive any funding in any form.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Medical Protection Center, The 926, Hospital of Joint Logistics Support Force of Chinesepeople'S Liberation Army, Kaiyuan, Yunan, China. [2]Department of Clinical Laboratory, The 926, Hospital of Joint Logistics Support Force of Chinese People'S Liberation Army, Kaiyuan, Yunan, China. [3]Department of Cardiology, The 926, Hospital of Joint Logistics Support Force of Chinese People'S Liberation Army, Kaiyuan, Yunan, China. [4]Yunnan Provincial Key Laboratory of Entomological Biopharmaceutical R&D, Dali University, Dali, Yunnan Province, China. [5]National-Local Joint Engineering Research Center of Entomoceutics, Dali University, Dali, Yunnan Province, China. [6]College of Pharmacy Dali University, Dali, Yunnan, China.

Received: 6 November 2024 Accepted: 26 February 2025
Published online: 13 March 2025

References

1. Navarese EP, Robinson JG, Kowalewski M, Kolodziejczak M, Andreotti F, Bliden K, et al. Association Between Baseline LDL-C Level and Total and

Cardiovascular Mortality After LDL-C Lowering: A Systematic Review and Meta-analysis. JAMA. 2018;319(15):1566–79.
2. Li JJ, Zhao SP, Zhao D, Lu GP, Peng DQ, Liu J, et al. 2023 Chinese guideline for lipid management. Front Pharmacol. 2023;14:1190934.
3. Guan ZW, Wu KR, Li R, Yin Y, Li XL, Zhang SF, et al. Pharmacogenetics of statins treatment: Efficacy and safety. J Clin Pharm Ther. 2019;44(6):858–67.
4. Hirota T, Fujita Y, Ieiri I. An updated review of pharmacokinetic drug interactions and pharmacogenetics of statins. Expert Opin Drug Metab Toxicol. 2020;16(9):809–22.
5. Kukal S, Guin D, Rawat C, Bora S, Mishra MK, Sharma P, et al. Multidrug efflux transporter ABCG2: expression and regulation. Cell Mol Life Sci. 2021;78(21–22):6887–939.
6. Sarkadi B, Homolya L, Hegedus T. The ABCG2/BCRP transporter and its variants - from structure to pathology. FEBS Lett. 2020;594(23):4012–34.
7. Dudas B, Decleves X, Cisternino S. ABCG2/BCRP transport mechanism revealed through kinetically excited targeted molecular dynamics simulations. Comput Struct Biotechnol. 2022;20:4195–205.
8. Homolya L. Medically Important Alterations in Transport Function and Trafficking of ABCG2. Int J Mol Sci. 2021;22(6):2786.
9. Taylor NMI, Manolaridis I, Jackson SM, Kowal J, Stahlberg H, Locher KP. Structure of the human multidrug transporter ABCG2. Nature. 2017;546(7659):504–9.
10. Jackson SM, Manolaridis I, Kowal J, Zechner M, Taylor NMI, Bause M, et al. Structural basis of small-molecule inhibition of human multidrug transporter ABCG2. Nat Struct Mol Biol. 2018;25(4):333–40.
11. Tomlinson B, Hu M, Lee VW, Lui SS, Chu TT, Poon EW, et al. ABCG2 polymorphism is associated with the low-density lipoprotein cholesterol response to rosuvastatin. Clin Pharmacol Ther. 2010;87(5):558–62.
12. Kim Y, Yoon S, Choi Y, Yoon SH, Cho JY, Jang IJ, et al. Influence of OATP1B1 and BCRP polymorphisms on the pharmacokinetics and pharmacodynamics of rosuvastatin in elderly and young Korean subjects. Sci Rep. 2019;9(1):19410.
13. Bailey KM, Romaine SP, Jackson BM, Farrin AJ, Efthymiou M, Barth JH, et al. Hepatic metabolism and transporter gene variants enhance response to rosuvastatin in patients with acute myocardial infarction: the GEOSTAT-1 Study. Circ Cardiovasc Genet. 2010;3(3):276–85.
14. Kim TE, Shin D, Gu N, Jung BH, Kim J, Cho YM, et al. The Effect of Genetic Polymorphisms in SLCO2B1 on the Lipid-Lowering Efficacy of Rosuvastatin in Healthy Adults with Elevated Low-Density Lipoprotein. Basic Clin Pharmacol Toxicol. 2017;121(3):195–201.
15. Lee HK, Hu M, Lui S, Ho CS, Wong CK, Tomlinson B. Effects of polymorphisms in ABCG2, SLCO1B1, SLC10A1 and CYP2C9/19 on plasma concentrations of rosuvastatin and lipid response in Chinese patients. Pharmacogenomics. 2013;14(11):1283–94.
16. Zhang D, Ding Y, Wang X, Xin W, Du W, Chen W, et al. Effects of ABCG2 and SLCO1B1 gene variants on inflammation markers in patients with hypercholesterolemia and diabetes mellitus treated with rosuvastatin. Eur J Clin Pharmacol. 2020;76(7):939–46.
17. Zhanqing Ma. Effect of nuclear receptor and transporter gene polymorphisms on the lipid-lowering efficacy of Rosuvastatin[J]. Cardiovascular Disease Control. 2020;20(02):139–42.
18. Liu Y, Chen Y, Wei B, Li H, Peng Y, Luo Z. Impacts of ABCG2 loss of function variant (p. Gln141Lys, c.421 C > A, rs2231142) on lipid levels and statin efficiency: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2024;24(1):202.
19. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association between lowering LDL-C and Cardiovascular risk reduction among different therapeutic interventions: a systematic review and Meta-analysis[J]. jama. 2016;316(12):1289–1297.
20. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082–143.
21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111–88.
22. National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143–421.
23. Kjeldsen EW, Thomassen JQ, Frikke-Schmidt R. HDL cholesterol concentrations and risk of atherosclerotic cardiovascular disease - Insights from randomized clinical trials and human genetics. Biochim Biophys Acta Mol Cell Biol Lipids. 2022;1867(1):159063.
24. Hancock-Cerutti W, Millar JS, Valentini S, et al. Assessing HDL Metabolism in Subjects with Elevated Levels of HDL Cholesterol and Coronary Artery Disease. Molecules. 2021;26(22):6862.
25. Xu D, Xie L, Cheng C, Xue F, Sun C. Triglyceride-rich lipoproteins and cardiovascular diseases. Front Endocrinol (Lausanne). 2024;15:1409653.
26. Hu M, To KK, Mak VW, Tomlinson B. The ABCG2 transporter and its relations with the pharmacokinetics, drug interaction and lipid-lowering effects of statins. Expert Opin Drug Metab Toxicol. 2011;7(1):49–62.
27. Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010;87(1):130–3.
28. Birmingham BK, Bujac SR, Elsby R, et al. Impact of ABCG2 and SLCO1B1 polymorphisms on pharmacokinetics of rosuvastatin, atorvastatin and simvastatin acid in Caucasian and Asian subjects: a class effect? Eur J Clin Pharmacol. 2015;71(3):341–55.
29. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Circ Cardiovasc Genet. 2012;5(2):257–64.
30. Chu AY, Guilianini F, Barratt BJ, Nyberg F, Chasman DI, Ridker PM. Pharmacogenetic determinants of statin-induced reductions in C-reactive protein. Circ Cardiovasc Genet. 2012;5(1):58–65.
31. Li X, Meng X, He Y, Spiliopoulou A, Timofeeva M, Wei WQ, et al. Genetically determined serum urate levels and cardiovascular and other diseases in UK Biobank cohort: A phenome-wide mendelian randomization study. PLoS Med. 2019;16(10):e1002937.
32. Lehtisalo M, Taskinen S, Tarkiainen EK, Neuvonen M, Viinamaki J, Paile-Hyvarinen M, et al. A comprehensive pharmacogenomic study indicates roles for SLCO1B1, ABCG2 and SLCO2B1 in rosuvastatin pharmacokinetics. Br J Clin Pharmacol. 2023;89(1):242–52.
33. Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 2022;111(5):1007–21.
34. Professional Committee of Laboratory Medicine of Chinese Society of Integrative Medicine and Western Medicine, Professional Committee of Clinical Immunodiagnosis of Zhejiang Society of Immunology, Professional Committee of Therapeutic Drug Monitoring and Research of Zhejiang Society of Pharmacology. Expert consensus on SLCO1B1 and ApoE gene polymorphism detection and clinical application of statins. Chinese Journal of Laboratory Medicine, 2023, 46(07):672–680.
35. Ferrari M, Guasti L, Maresca A, et al. Association between statin-induced creatine kinase elevation and genetic polymorphisms in SLCO1B1, ABCB1 and ABCG2. Eur J Clin Pharmacol. 2014;70(5):539–47.
36. Bai X, et al. Effects of SLCO1B1 and GATM gene variants on rosuvastatin-induced myopathy are unrelated to high plasma exposure of rosuvastatin and its metabolites. Acta Pharmacol Sin. 2019;40:492–9.
37. Sreter KB, Barisic B, Popovic-Grle S. Pharmacogenomics and tailored polypharmacy: an 80-year-old lady with rosuvastatin-associated rhabdomyolysis and maprotiline-related Ogilvie's syndrome. Int J Clin Pharmacol Ther. 2017;55:442–8.
38. Merćep I, Radman I, Trkulja V, et al. Loss of function polymorphisms in SLCO1B1 (c.521T>C, rs4149056) and ABCG2 (c.421C>A, rs2231142) genes are associated with adverse events of rosuvastatin: a case-control study. Eur J Clin Pharmacol. 2022;78(2):227–236.

Publisher's Note