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REVIEW ARTICLE

Lowering of Blood Lipid Levels with a Combination of Pitavastatin and Ezetimibe in Patients with Coronary Heart Disease: A Meta-Analysis

Ruping Cai[1], Chen Chang[2], Xingjie Zhong[1,a] and Qiang Su[2,a]

[1]*Department of Rehabilitation Medicine, The Second Nanning People's Hospital, Nanning, 530031, China*
[2]*Department of Cardiology, Guilin Medical University Affiliated Hospital, Guilin, 541000, China*

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Abstract

Objectives: According to the findings of randomized controlled trials, blood lipid levels in patients with coronary heart disease (CHD) can be significantly decreased through a combination of pitavastatin and ezetimibe; however, the effects and clinical applications of this treatment remain controversial. This meta-analysis was aimed at objectively assessing the efficacy and safety of pitavastatin and ezetimibe in lowering blood lipid levels.

Design: Relevant studies were retrieved from electronic databases, including PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure, VIP, and WanFang Data, from database inception to June 8, 2022. The levels of low-density lipoprotein cholesterol, total cholesterol, triglycerides, and high-density lipoprotein cholesterol in patients' serum after treatment were the primary endpoint.

Results: Nine randomized controlled trials (2586 patients) met the inclusion criteria. The meta-analysis indicated that pitavastatin plus ezetimibe resulted in significantly lower levels of LDL-C [standardized mean difference (SMD) = −0.86, 95% confidence interval (CI) (−1.15 to −0.58), P<0.01], TC [SMD = −0.84, 95% CI (−1.10 to −0.59), P<0.01], and TG [SMD = −0.59, 95% CI (−0.89 to −0.28), P<0.01] than pitavastatin alone.

Conclusions: Pitavastatin plus ezetimibe significantly decreased serum LDL-C, TC, and TG levels in patients with CHD.

Keywords: Pitavastatin; Ezetimibe; Coronary heart disease; Blood lipid

[a]Xingjie Zhong and Qiang Su contributed equally to this work.

Correspondence: **Xingjie Zhong**, Department of Rehabilitation Medicine, The Second Nanning People's Hospital, Nanning, 530031, China. E-mail: 54814372@qq.com; and **Qiang Su**, Department of Cardiology, Guilin Medical University Affiliated Hospital, Guilin, 541000, China. E-mail: suqiang1983@glmc.edu.cn, https://orcid.org/0000-0002-5173-7921

Introduction

Coronary heart disease (CHD), a cardiovascular disease, is the leading cause of death in both developed and developing nations [1]. According to a 2009 report by the World Health Organization, cardiovascular diseases account for 17.3 million deaths annually [2]. Over the past decade, the number of

hospitalizations due to CHD in China has tripled [3]. Visceral fat is often converted into cholesterol, usually low-density lipoprotein cholesterol (LDL-C), in the body; it accumulates in older people and can cause a variety of cardiovascular diseases, among which coronary heart disease is most serious and fatal [3]. With China's aging population, cardiovascular disease morbidity and mortality will continue to rise over the next decade, thus making cardiovascular disease a major public health concern [4]. Risk factors for CHD include sex, age, dyslipidemia, smoking, diabetes, hypertension, and obesity, among which dyslipidemia is the most important. Shen Li et al. [5] have reported that the lipid-associated protein NECTIN2 is a potential marker of atherosclerosis progression. Elevated LDL-C has also been identified as an independent CHD risk factor [6, 7].

Studies have indicated that even after standard doses of pitavastatin are administered to some patients with CHD, their LDL-C levels remain above 1.8 mmol/L. Doubling the statin dose to decrease LDL-C levels has been found to result in adverse effects, such as elevated transaminase and creatine kinase levels, and the LDL-C compliance rate did not improve significantly [8, 9]. Thus, for patients with CHD, doubling the dose of pitavastatin to decrease LDL-C is not an optimal solution; consequently, combination therapy has become a new treatment choice. The Heart Institute of Japan PRoper level of lipid lOwering with Pitavastatin and Ezetimibe in acute coRonary syndrome (HIJ-PROPER) study has indicated that, without increasing the incidence of adverse cardiovascular events, the standard dose of pitavastatin in combination with ezetimibe, compared with the standard dose of pitavastatin alone, significantly decreases LDL-C to <70 mg/dL (1.8 mmol/L) in patients with CHD [10].

Although the efficacy and safety of this combination treatment have been demonstrated in some studies [11–19], controversies remain. For example, Hollingworth et al. and Luo et al. [20, 21] have reported that ezetimibe can result in musculoskeletal and connective tissue disorders, as well as gastrointestinal disorders. The most often reported adverse effects of pitavastatin include back pain, diarrhea, constipation, myalgia, and pain in the extremities. Reports have also indicated myopathy and rhabdomyolysis, which can lead to acute renal failure. Pitavastatin use can also lead to abnormal laboratory results, including elevated creatine phosphokinase, transaminases (aspartate aminotransferase [AST]/serum glutamic-oxaloacetic transaminase or alanine aminotransferase [ALT]/serum glutamic-pyruvic transaminase), alkaline phosphatases, bilirubin, and glucose [8, 22]. Even if the combination of drugs lowers blood cholesterol levels to a normal range, if the aforementioned severe adverse effects occur, the damage to patient health outweighs any benefits. Therefore, whether the efficacy of the drug combination damages patient health must be considered. Whether drugs should be combined warrants an in-depth investigation. Therefore, we used meta-analysis methods to objectively assess the efficacy and safety of concomitant lipid-lowering drugs to provide a scientific basis for clinical practice.

Methods

Search Strategy

We searched electronic databases, including PubMed, Cochrane Library, Embase, NCKI, VIP, and WanFang Data, from database inception until June 8, 2022. We used the following keywords and corresponding MeSH terms without language limitations: "pitavastatin/pitavastatin calcium/pitavastatin lactone," "ezetimibe/ezetrol/SCH-58235/zetia," and "coronary heart disease/CHD." The above-mentioned Chinese keywords were used to search the three Chinese databases, NCKI, VIP, and WanFang Data. Searching of the Chinese and English literature, as well as reference lists in other similar publications, yielded additional potentially relevant data. The protocol was registered with INPLASY(INPLASY202150072).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) all randomized controlled trials (RCTs); (2) follow-up time of ≥8 weeks; (3) patient age ≥18 years; (4) oral pitavastatin and ezetimibe treatment in the experimental group, and oral pitavastatin in the control group, in accordance with conventional CHD treatment; and (5) a diagnosis of CHD according to the criteria

established by the included literature. The exclusion criteria were as follows: (1) meta-analyses, case reports, reviews, nonrandomized controlled trials, and animal testing; (2) no reporting of original data; (3) hemodynamic instability, such as hypotension, pulmonary edema, congestive heart failure, acute mitral regurgitation, or ventricular rupture; or ischemic events (stroke, recurring cardiac ischemia symptoms, or acute vascular occlusion); (4) arrhythmic events (ventricular fibrillation, persistent ventricular tachycardia, or advanced heart block); (5) pregnancy; (6) active liver disease or unexplained persistent elevated serum transaminase levels; (7) current use of immunosuppressive agents such as cyclosporine, tacrolimus, thiazole, or long-term oral corticosteroids; history of alcohol or drug abuse; and (8) allergy to any statins or ezetimibe. Each study was evaluated independently on the basis of the inclusion and exclusion criteria. When multiple publications on the same study were reported, the RCT with the longest follow-up period or the most comprehensive endpoint was selected. Disagreements regarding the inclusion or exclusion of a study were resolved via discussion. The third investigator (Qiang Su) was consulted if any doubts remained.

Data Extraction

Two researchers (Ruping Cai and Chen Chang) collected the data independently and in duplicate. In cases of disagreement, all authors discussed the results and reached a consensus. The primary endpoints were levels of LDL-C, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) in the serum in patients. The registration number, study type, data source of the primary endpoint, drugs received by patients in the experimental and control groups, and follow-up time of each study included in the analysis were investigated.

Quality Assessment

The risk-of-bias assessment tool recommended by the Cochrane Manual 5.1.0 [23] was used to evaluate the quality of the included RCTs:

1. Random sequence generation
2. Allocation concealment
3. Blinding of personnel and participants
4. Incomplete outcome data
5. Selective reporting
6. Blinding of outcome assessment
7. Other bias

High-bias, low-bias, and unclear judgments were made for the seven items above.

Statistical Analysis

Stata 16 software was used for meta-analysis. Measurement data including the standardized mean difference (SMD) and its 95% confidence interval (CI) were used for analysis and statistics. Intervention effects were defined according to the SMD and 95% CI in serum blood lipid levels between the experimental and control groups, and random effects models were used to evaluate the combined effects. The P value of heterogeneity was calculated to determine whether statistical heterogeneity existed between studies. A P value >0.1 indicated no statistical heterogeneity between studies; in contrast, $P<0.1$ implied heterogeneity among studies. $I^2>50\%$ indicated significant heterogeneity among studies. The effects of pitavastatin and ezetimibe on blood lipids were analyzed through meta-regression. A subgroup analysis was performed on the basis of the participants' follow-up time (≤12 weeks or >12 weeks), health status (diabetic or nondiabetic), and dose of pitavastatin administered. We conducted sensitivity analysis by altering the effect model and performing elimination tests. Egger's test was used to examine publication bias, wherein $P>0.05$ indicated no clear publication bias, whereas $P<0.05$ indicated publication bias. In the case of publication bias, a trim-and-fill analysis was performed to detect the influence of bias on the overall effect.

Results

Search Results and Fundamental Characteristics of the Included Studies

A total of 538 studies were identified through an electronic search (Figure 1). A total of 324 duplicate studies were eliminated, 162 studies were removed after reading of the title and abstract, and only 52 studies remained. Finally, nine

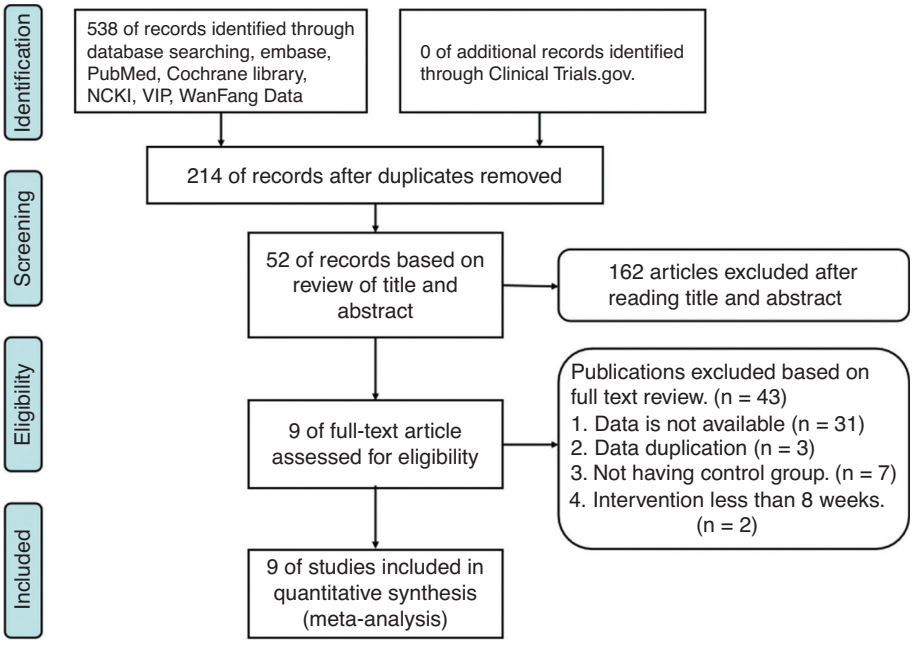

Figure 1 Flow Chart of Study Selection.

studies involving 2586 patients [9, 20, 21, 24–29] were included in this meta-analysis. The fundamental characteristics described in the literature are presented in Table 1. Most of the included studies were from China, and two studies were from Japan. All the included studies were RCTs, and the follow-up period ranged from 8 weeks to 156 weeks. All patients had coronary heart disease with or without diabetes. The experimental group was treated with pitavastatin plus ezetimibe, and the control group was treated with pitavastatin monotherapy. The monitored indicators included LDL-C, HDL-C, TC, TG, ALT, and creatine kinase.

Inclusion and Exclusion Criteria

In some studies [10, 24, 26, 30–34], low-risk sequences were generated with the random number table method. Using LDL-C levels for grouping resulted in elevated risk [25]. In one study [34], patients in both the experimental and control groups withdrew without explaining a reason, thus indicating a high risk. In nine studies [10, 24–26, 30–34], other biases were not found. In general, literature with a low risk of bias and uncertainty represented a larger proportion than literature with a high risk of bias and uncertainty, thus indicating that the overall risk of bias in the included literature was low. All studies were of high quality. The assessment of the quality of studies is presented in Figure 2.

Main Outcome and Subgroup Analysis

Effect of Pitavastatin Plus Ezetimibe on LDL-C Levels

After treatment, nine studies reported changes in LDL-C levels in the ezetimibe plus pitavastatin (combination treatment group) and pitavastatin treatment groups (pitavastatin monotherapy group). Among these, six studies [10, 25, 30–33] reported randomized controlled trials of 10 mg of ezetimibe combined with 2 mg of pitavastatin (10 mg of EZE + 2 mg of PIT) and 2 mg of pitavastatin alone (2 mg of PIT); two studies [33, 34] performed comparative analysis of 10 mg of EZE + 1 mg of PIT and 4 mg of PIT alone; and one study [26] compared 10 mg of EZE + 10 mg of PIT to 10 mg of PIT alone. The heterogeneity among studies was $I^2 = 85.39\%$ ($P < 0.1$) (Figure 3A). A random effects model was used. The LDL-C levels decreased more significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD = −0.86, 95% CI = −1.15 to −0.58, $P < 0.001$). For sensitivity analysis, the random effects model was replaced with a fixed effects model. The LDL-C levels decreased more

Table 1 Randomized Controlled Trials Included in the Systematic Review and Meta-Analysis.

Author (and reference)	Year	Country	Design	Inclusion patients	Duration	Pitavastatin + ezetimibe			Pitavastatin monotherapy			Outcomes
						Intervention	N	Age	Intervention	N	Age	
Hagiwara, N [24]	2017	Japan	Prospective RCT	ACS+HL	156W	PIT/EZE 2*/10 mg	864	65.70±11.70	PIT 2† mg	857	65.60±11.90	①⑤⑥
Hibi, K [25]	2018	Japan	Prospective RCT	ACS	52W	PIT/EZE 2 /10 mg	50	63.00±10.00	PIT 2 mg	53	63.00±12.00	①②③④
Li Haili [26]	2019	China	Prospective RCT	Older CHD+T2DM	8W	PIT/EZE 2/10 mg	55	83.29±0.81	PIT 2 mg	55	82.36±0.75	①②③④
Feng Weijie [9]	2020	China	Prospective RCT	CHD+HL	12W	PIT/EZE 2 /10 mg	51	63.45±8.14	PIT 2 mg	51	62.57±8.31	①②③④
Zhou Jing [20]	2019	China	Prospective RCT	Older CHD+T2DM	12W	PIT/EZE 2/10 mg	45	70.90±8.70	PIT 2 mg	44	69.70±7.30	①②③④⑤
Zhao Ju [21]	2019	China	Prospective RCT	CHD+HL	12W	PIT/EZE 1/10 mg	45	65.30±2.50	PIT 2–4‡ mg	45	65.20±2.20	①②③④
Liu Jinfa [27]	2018	China	Prospective RCT	CHD+HL	12W	PIT/EZE 1 /10 mg	53	61.78±9.45	PIT 2–4‡ mg	53	62.12±9.01	①②③④
Hu Guanghui [28]	2016	China	Prospective RCT	Older CHD+T2DM	24W	PIT/EZE 2 /10 mg	60	85.00±3.50	PIT 2 mg	55	85.00±3.00	①②③⑤
Dong Tao [29]	2018	China	Prospective RCT	Older CHD+T2DM	12W	PIT/EZE 10 /10 mg	75	72.70±8.60	PIT 10 mg	75	73.60±8.30	①②③④

*The starting dose of pitavastatin was 2 mg; the dosage was adjusted to target LDL-C of 70 mg/dL.
†The starting dose of pitavastatin was 2 mg; the dosage was adjusted to target LDL-C between 90 mg/dL and 100 mg/dL.
‡The dosage was appropriately increased for patients with no significant decrease in LDL-C; the maximum daily dose was 4 mg.
RCT: randomized controlled trial; ACS: acute coronary syndrome; HL: hyperlipidemia; CHD: coronary heart disease; T2DM: type 2 diabetes; PIT: pitavastatin; EZE: ezetimibe; ① low density lipoprotein cholesterol (LDL-C) ② high density lipoprotein cholesterol (HDL-C) ③ total cholesterol (TC) ④ triglyceride (TG) ⑤ alanine aminotransferase (ALT) ⑥ creatine kinase (CK).

significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD=−0.77, 95% CI=−0.86 to −0.68, P<0.01), in agreement with the original analysis results, thus indicating that the original meta-analysis results showed stability and high reliability.

Effect of Pitavastatin Plus Ezetimibe on TC Levels

Eight studies [24–26, 30–34] reported changes in TC levels in the combined treatment and pitavastatin monotherapy groups after treatment. The heterogeneity among studies was I^2=70.02% (P<0.1) (Figure 3B). With a random effects model, the TC levels were found to decrease more significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD=−0.84, 95% CI=−1.10 to −0.59, P<0.001). The random effects model was replaced with a fixed effects model for sensitivity analysis. The TC levels decreased more significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD=−0.79, 95% CI=−0.93 to −0.65, P<0.01), in agreement with the original analysis results, thus indicating that the original meta-analysis results showed stability and high reliability.

Effect of Pitavastatin Plus Ezetimibe on TG Levels

Seven studies [24, 26, 30–34] reported changes in TG levels in the combined treatment and pitavastatin monotherapy groups after treatment. The heterogeneity among studies was I^2=76.38% (P<0.1) (Figure 4A). With the random effects model, the TG levels were found to decrease more significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD=−0.59, 95% CI=−0.89 to −0.28, P<0.001). The random effects model was replaced with a fixed effects model for sensitivity analysis. The TG levels decreased more significantly in the combined treatment group than in the pitavastatin monotherapy group (SMD=−0.57, 95% CI=−0.72 to −0.42, P<0.01), in agreement with the original analysis results, thereby indicating that the original meta-analysis results showed stability and high reliability.

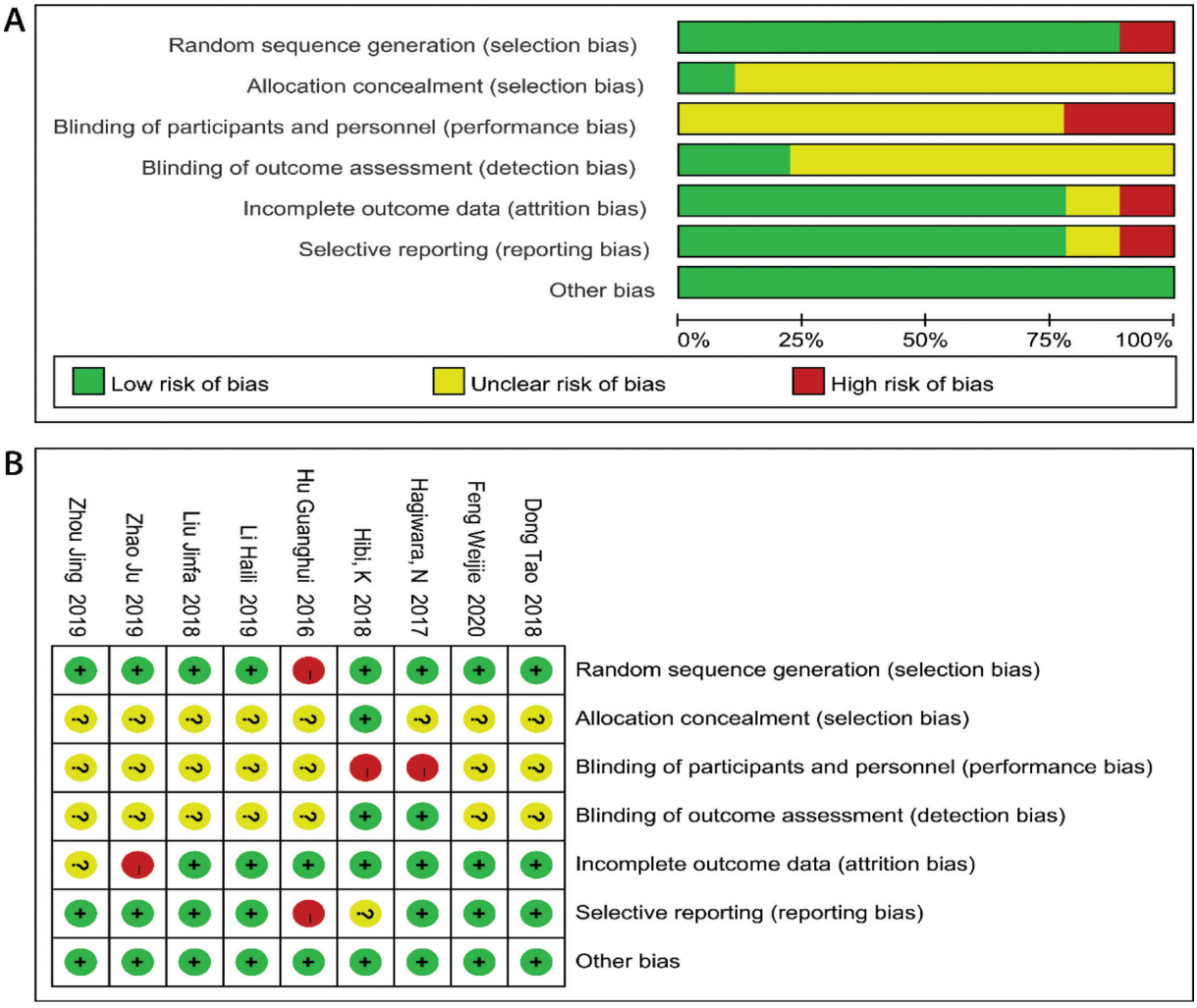

Figure 2 Risk of Bias.
(A) Risk of bias graph: authors' judgements for each risk of bias item are expressed as percentages across all included studies.
(B) Risk of bias summary: authors' judgements for each risk of bias item for each included study are indicated.

Effect of Pitavastatin Plus Ezetimibe on HDL-C Levels

Eight studies [24–26, 30–34] reported changes in HDL-C levels in the combined treatment and pitavastatin monotherapy groups after treatment. The heterogeneity among studies was I^2=89.03% (P<0.1) (Figure 4B). A random effects model indicated that HDL-C levels did not increase in the combined treatment group relative to the pitavastatin monotherapy group (SMD=0.45, 95% CI=0.03–0.87, P=0.04), and the difference was statistically significant. The random effects model was replaced with a fixed effects model for sensitivity analysis. HDL-C levels did not increase in the combined therapy group compared with the pitavastatin monotherapy group (SMD=0.39, 95% CI=0.25–0.53, P<0.001); the difference was statistically significant, in agreement with the original analysis results, thus indicating that the original meta-analysis results showed stability and high reliability.

Elevation of Alanine Aminotransferase and Creatine Kinase Levels

One study [10] found that patients in both groups had ALT levels three or more times the normal upper limit. The combined treatment and pitavastatin monotherapy groups contained 28 and 15 patients, respectively. No significant difference was observed between groups (P=0.05). Two studies [25, 33] found mildly elevated ALT levels with no statistically significant difference between groups (P>0.05). In a study comparing ≥10-fold differences

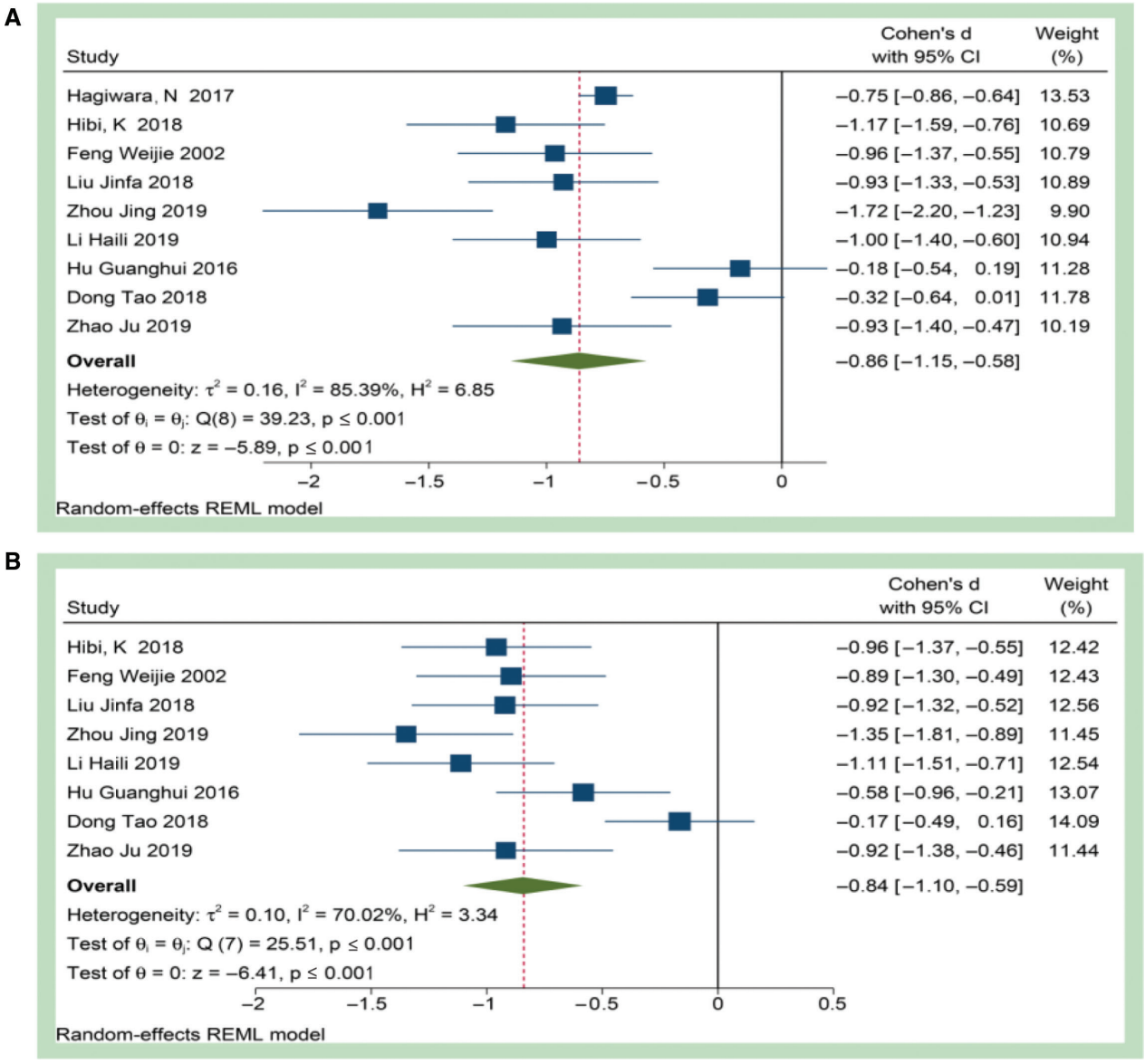

Figure 3 Forest Plots.
(A) Forest plot showing the effect of pitavastatin plus ezetimibe on serum LDL-C levels. (B) Forest plot showing the effect of pitavastatin plus ezetimibe on serum total cholesterol levels.

in CK levels from baseline between two regimens [10], eight cases were identified in the combination therapy and pitavastatin monotherapy groups. The results showed no significant difference between treatment regimens (P=0.99).

Meta-Regression and Subgroup Analysis

To investigate the source of heterogeneity, we performed a subgroup analysis on the basis of participants' follow-up times (≤12 weeks or >12 weeks), health status (diabetic or nondiabetic), and the dose of pitavastatin administered. The effect of pitavastatin and ezetimibe on lowering LDL-C, TC, and TG levels was found to be unaffected by follow-up time, health status, and administered pitavastatin dose (Table 2). The effect of the elevation of HDL-C levels in the experimental group, in contrast, was significantly influenced by patients' health status, follow-up time, and administered pitavastatin dose. The effect of the elevation of HDL-C levels with the combination of pitavastatin and ezetimibe was more significant in patients with diabetes (SMD=0.135, 95% CI=−0.413 to 0.682), whereas the drug combination had no effect in patients without diabetes (SMD=0.764,

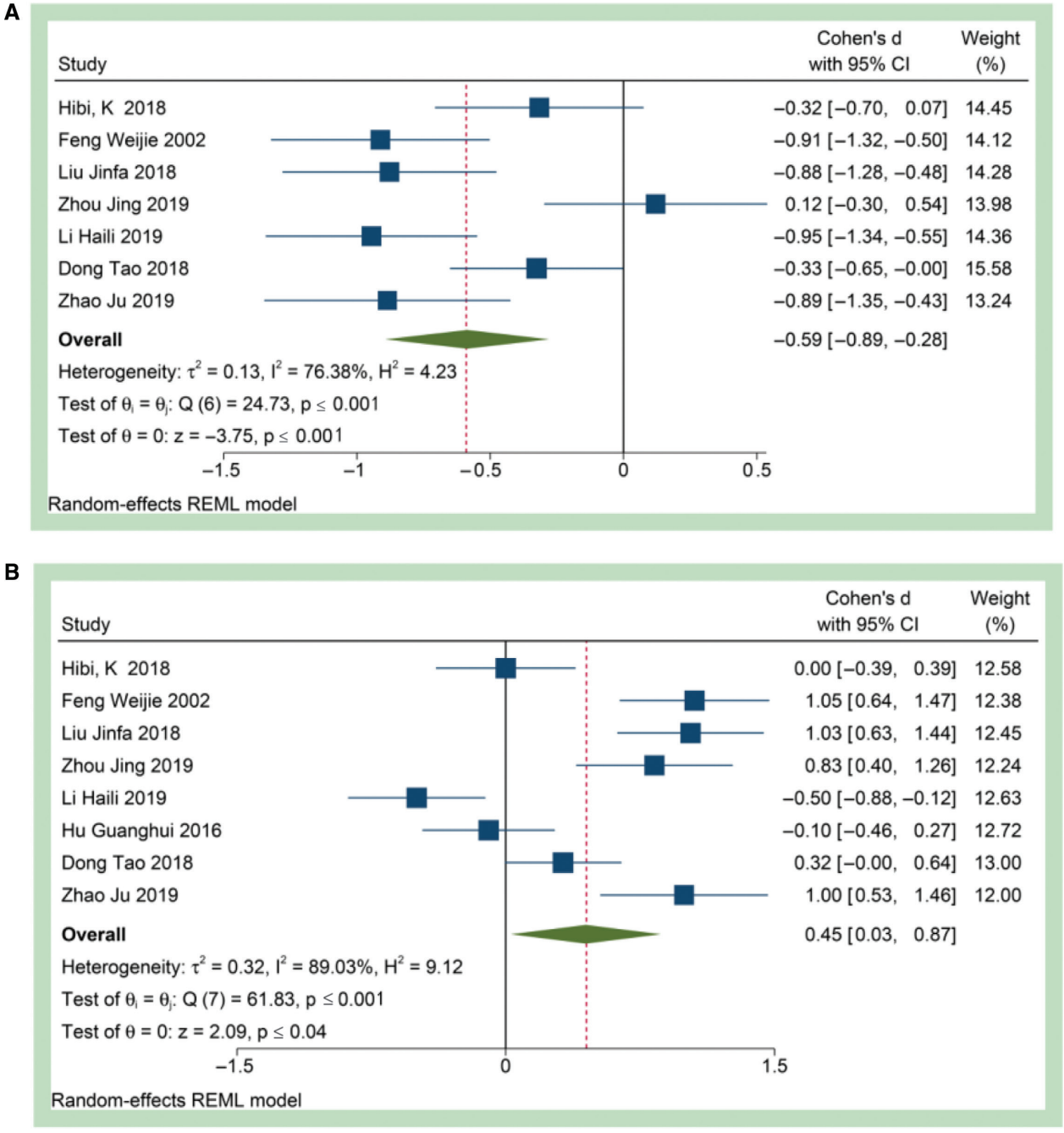

Figure 4 Forest Plots II.
(A) Forest plot showing the effect of pitavastatin plus ezetimibe on serum triglyceride levels. (B) Forest plot showing the effect of pitavastatin plus ezetimibe on serum HDL-C levels.

95% CI=0.252 to 1.277). Pitavastatin 2 mg plus ezetimibe 10 mg had a significantly greater effect on the elevation of HDL-C than pitavastatin 1 mg plus ezetimibe 10 mg (SMD=0.25, 95% CI=−0.31 to 0.82). The drug combination did not achieve the goal of increasing the levels of HDL-C when the follow-up time was ≤12 weeks (SMD=0.615, 95% CI=0.120–1.109). Except for HDL-C levels, no significant interstudy heterogeneity was evident in the nondiabetic subgroup [LDL-C: I^2=34.08%, P=0.268; TC: I^2=0.00, P=0.997; TG: I^2=50.75%, P=0.107], whereas the heterogeneity P in the diabetic group was less than 0.1. The study heterogeneity therefore might have been due to the participation of patients with diabetes. When the follow-up time was ≤12 weeks, the heterogeneity P among LDL-C, TC, TG, and HDL-C levels was less than 0.1. Hence, the follow-up time of ≤12 weeks might

Table 2 Subgroup Analysis of the Effects of Pitavastatin Plus Ezetimibe on Blood Lipids.

	No. Of Studies	SMD	[95% Conf. Interval]	P value	I^2	P for heterogeneity
LDL-C						
Health status						
Diabetic	4	−0.787	−1.470, −0.104	0.024	92.010	≤0.001
Nondiabetic	5	−0.883	−1.058, −0.708	≤0.001	34.080	0.268
Duration						
≤12 weeks	6	−0.956	−1.312, −0.600	≤0.001	78.180	≤0.001
>12 weeks	3	−0.695	−1.231, −0.160	0.011	89.900	0.001
The dose of pit						
2 mg	5	−0.990	−1.480, −0.510	≤0.001	0.855	≤0.001
1 mg	2	−0.930	−1.203, −0.630	≤0.001	0.000	0.984
TC						
Health status						
Diabetic	4	−0.786	−1.309, −0.263	0.003	86.490	≤0.001
Nondiabetic	4	−0.923	−1.132, −0.715	≤0.001	≤0.001	0.997
Duration						
≤12 weeks	6	−0.876	−1.210, −0.541	≤0.001	75.740	≤0.001
>12 weeks	2	−0.761	−1.129, −0.393	≤0.001	43.670	0.183
The dose of pit						
2 mg	5	−0.960	−1.210, −0.700	0.293	45.100	0.122
1 mg	2	−0.920	−1.220, −0.620	0.293	0.000	0.990
TG						
Health status						
Diabetic	3	−0.386	−0.981, 0.209	0.204	86.690	0.001
Nondiabetic	4	−0.740	−1.034, −0.446	≤0.001	50.750	0.107
Duration						
≤12 weeks	6	−0.633	−0.982, −0.284	≤0.001	78.530	≤0.001
>12 weeks	1	−0.316	−0.705, 0.073	0.111	-	-
The dose of pit						
2 mg	4	−0.510	−1.010, −0.020	0.001	83.500	0.000
1 mg	2	−0.880	−1.180, −0.580	0.001	0.0	0.979
HDL-C						
Health status						
Diabetic	4	0.135	−0.413, 0.682	0.630	88.450	≤0.001
Nondiabetic	4	0.764	0.252, 1.277	0.003	83.500	≤0.001
Duration						
≤12 weeks	6	0.615	0.120, 1.109	0.015	89.190	≤0.001
>12 weeks	2	−0.050	−0.316, 0.215	0.711	≤0.001	0.725
The dose of pit						
2 mg	5	0.250	−0.310, 0.820	0.000	90.200	0.000
1 mg	2	1.020	0.710, 1.320	0.000	0.0	0.909

have been a source of heterogeneity. With meta-regression, we determined that duration of follow-up (P>0.05), health status (P>0.05), and dose of pitavastatin (P>0.05) were not factors influencing heterogeneity (Table 3).

Sensitivity Analysis and Publication Bias

The random effects model was replaced by a fixed effects model for sensitivity analysis. The outcomes

Table 3 Meta-Regression of the Effects of Pitavastatin Plus Ezetimibe on Blood Lipids.

	[95% Conf. Interval]		P
LDL-C			
Health status (Diabetic or Nondiabetic)	−0.730	1.125	0.608
Duration (≤12 weeks or >12 weeks)	−1.334	0.838	0.583
The dose of pit/mg	−0.506	0.627	0.794
TC			
Health status (Diabetic or Nondiabetic)	−1.132	0.872	0.737
Duration (≤12 weeks or >12 weeks)	−0.956	0.841	0.868
The dose of pit/mg	−0.461	1.194	0.286
TG			
Health status (Diabetic or Nondiabetic)	−1.186	2.130	0.432
Duration (≤12 weeks or >12 weeks)	−2.340	1.231	0.396
The dose of pit/mg	−1.159	1.226	0.935
HDL-C			
Health status (Diabetic or Nondiabetic)	−1.895	0.745	0.293
Duration (≤12 weeks or >12 weeks)	−0.539	1.841	0.203
The dose of pit/mg	−1.181	1.025	0.854

demonstrated that the combination of pitavastatin and ezetimibe did not significantly change the overall effects on LDL-C (SMD=−0.77, 95% CI=−0.86 to −0.68, P<0.01), TC (SMD=−0.79, 95% CI=−0.93 to −0.65, P<0.01), TG (SMD=−0.57, 95% CI=−0.72 to −0.42, P<0.01), and HDL-C (SMD=0.39, 95% CI=0.25–0.53, P<0.001) levels, thereby suggesting that the original meta-analysis results showed stability and high reliability. Studies were individually excluded to determine whether the overall effect might change. After elimination of each study, the overall effect of LDL-C, TC, TG, and HDL-C levels on the test group did not change significantly (Figure 5). Egger's test indicated no publication bias in the LDL-C (Egger's: P=0.196), TG (Egger's: P=0.487), and HDL-C levels (Egger's: P=0.06), but clear publication bias in the TC level (Egger's: P<0.0001). In accordance with the trim-and-fill analysis, we added a study to the right side of the TC study to fix the asymmetry. Despite the adjustment of the trim-and-fill analysis, the pitavastatin plus ezetimibe did not significantly change the overall effects on TC from the funnel plot (Figure 6).

Discussion

CHD is a prevalent cardiovascular condition. The incidence and mortality of CHD continue to rise annually [35, 4]. Statin monotherapy at recommended dosages is the conventional method for decreasing lipid levels. However, numerous investigations have concluded that the optimal treatment consists of a combination of drugs [11, 29, 36]. Consequently, a combination of a standard dose of pitavastatin and the cholesterol absorption inhibitor ezetimibe play crucial roles in treatment. Pitavastatin, a novel member of the statin family, has potent antagonist and inhibitory action on hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, and efficiently inhibits cholesterol formation in HepG2 liver cells, thereby inhibiting cholesterol synthesis [28]. Ezetimibe selectively inhibits cholesteryl ester transfer protein, thereby drastically lowering cholesterol absorption in the intestine, liver cholesterol storage, and plasma cholesterol concentrations [12]. Both drugs affect the synthesis and absorption of cholesterol and exert good synergistic effects. Therefore, the standard dose of pitavastatin in conjunction with the usual dose of ezetimibe may be an effective method for lowering blood cholesterol levels in patients with CHD.

This study quantitatively analyzed the efficacy and safety of the use of pitavastatin and ezetimibe in China and internationally with meta-analysis methods. Pitavastatin plus ezetimibe treatment was

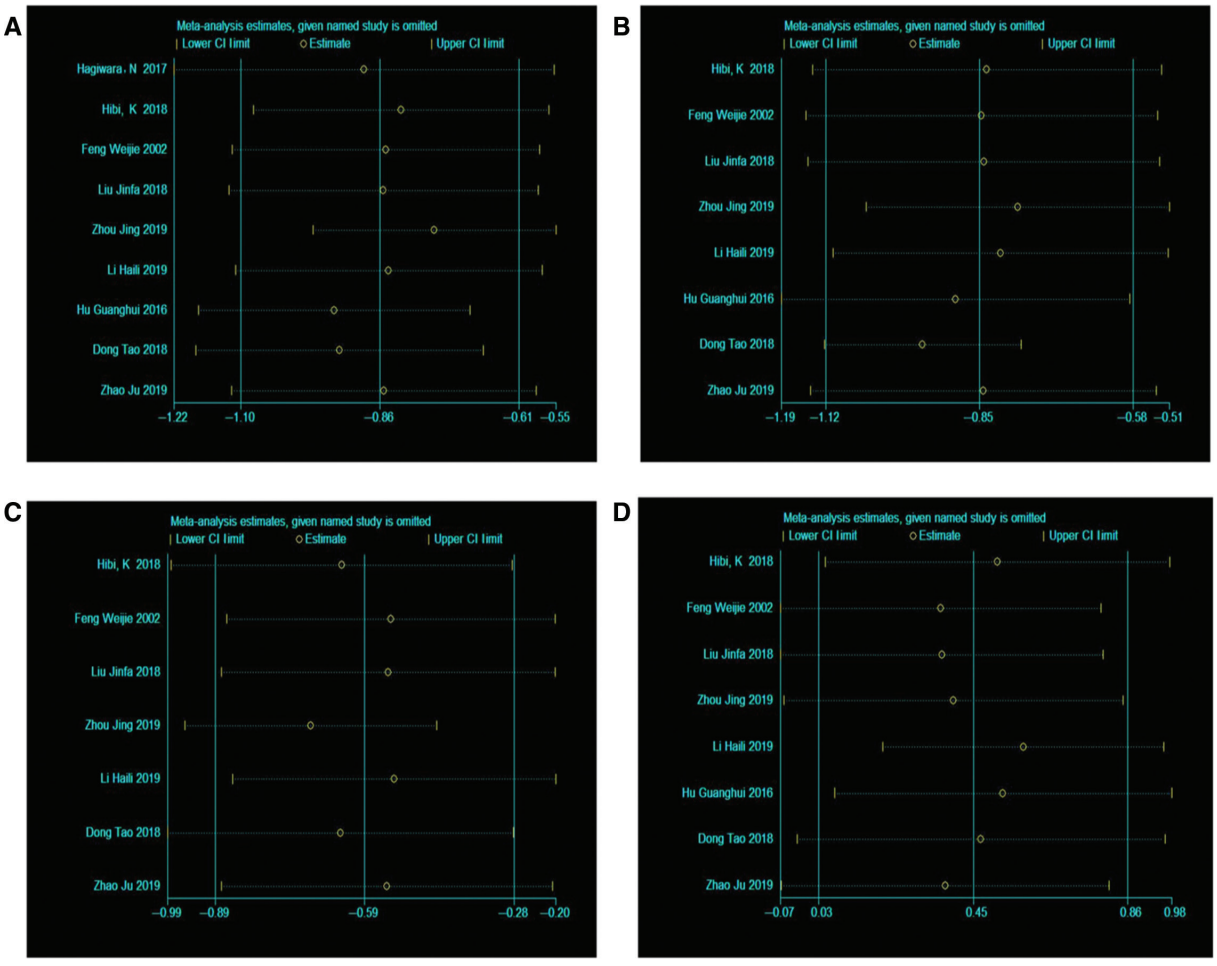

Figure 5 Effects of Eliminating a Single Test.
(A) Effects of eliminating a single test on LDL-C results. (B) Effects of eliminating a single test on TC results. (C) Effects of eliminating a single test on TG results. (D) Effects of eliminating a single test on HDL-C results.

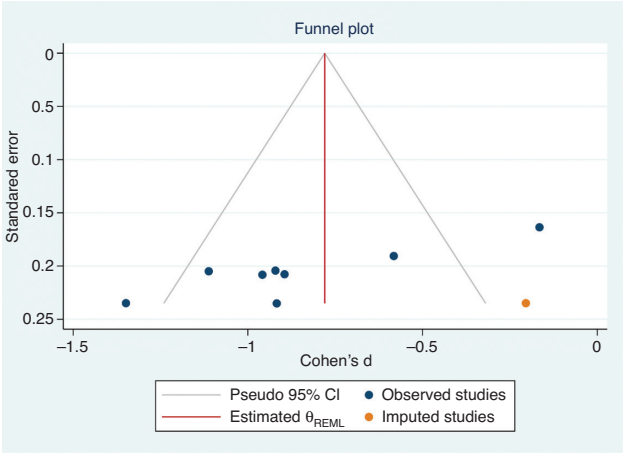

Figure 6 Analysis of the Publication Bias Regarding TC with the Trim-and-Fill Method.

found to result in significantly lower LDL-C, TC, and TG levels than pitavastatin treatment alone. However, combination therapy did not increase HDL-C levels. We obtained additional insights through subgroup analysis. The effect of the elevation of HDL-C levels in the experimental group was significantly influenced by patients' health status, follow-up time, and the pitavastatin dose administered. The effect of the elevation of HDL-C levels with the combination of pitavastatin and ezetimibe was more significant in patients with diabetes, whereas the drug combination had no effect in patients without diabetes. Pitavastatin 2 mg plus ezetimibe 10 mg had a significantly greater effect on the elevation of HDL-C than pitavastatin 1 mg plus ezetimibe 10 mg. The drug combination did not achieve the goal of increasing the levels of HDL-C when the follow-up time was ≤12 weeks, thus demonstrating that the increase in HDL-C levels was time-dependent. We also studied the safety of pitavastatin plus ezetimibe. The combination of pitavastatin and ezetimibe did not increase ALT and

creatine kinase levels. With meta-regression, we determined that the duration of follow-up ($P>0.05$), health status ($P>0.05$), and dose of pitavastatin ($P>0.05$) were not factors influencing heterogeneity (Table 3). Regression and subgroup analyses yielded inconsistent results because their underlying statistical models were not the same. The logarithm of the effect index was used as the dependent variable, whereas the factors that might have led to heterogeneity were used as the independent variables. The results of meta-regression analysis were therefore unstable, that is, inconsistent with the findings of subgroup analysis, owing to the presence of too many independent variables.

Statins may affect glucose metabolism and thus the development of diabetes. Prior research has demonstrated that, in contrast to a regular statin regimen, an intensive statin regimen increases the chance of developing new-onset diabetes [27, 37]. The result of the meta-analysis indicated that the combined regimen allows for lower LDL levels without the risk of high-dose statins, and thus may be particularly advantageous in improving cardiovascular outcomes in patients with coronary heart disease. A subgroup analysis of the meta-analysis also supported this view. The results of the subgroup analysis revealed that the effects of pitavastatin and ezetimibe on lowering LDL-C and TC levels were not affected by diabetes (Table 2). We also found an interesting phenomenon at the primary end point, wherein LDL-C, TC, and TG levels decreased after intensive treatment, but HDL-C levels remained unchanged. According to Van de Woestijne et al., the intensity of cholesterol-lowering therapies may affect the association between HDL-C and vascular events [38]: low HDL-C levels have been associated with higher vascular risk in patients who take no or low-dose lipid-lowering drugs, but not in patients who take high-dose lipid-lowering drugs. In our investigation, the level of HDL-C was not increased by the intensity of the lipid-lowering drug treatment. Consequently, the HDL-C index could not be used to evaluate the success of intensive lipid-lowering drugs. The outcome of the meta-analysis supports the perspective of the aforementioned study.

In some studies [10, 24, 26, 30–34], low-risk sequences were generated with a random number table method. Use of LDL-C levels for grouping resulted in elevated risk [25]. In one study [34], patients in both the experimental and control groups withdrew without explaining the reason, thus indicating a high risk. In nine studies [10, 24–26, 30–34], other biases were not found. Consequently, other potential threats to validity posed minimal risk. In general, literature with a low risk of bias and uncertainty represented a larger proportion than literature with a high risk of bias and uncertainty, thus indicating that the overall risk of bias in the included literature was low. Figure 2 provides detailed information regarding the assessment of research quality.

This study has several limitations. First, the findings revealed publication bias in the TC group (Egger's: $P<0.0001$). To equalize the asymmetry, a study needed to be added to the right side of the TC study. Second, several studies concentrated solely on short-term changes in blood lipid markers, and the follow-up period was insufficient. Consequently, in the subgroup analysis, HDL-C levels with the medication combination did not increase when the follow-up duration was less than 12 weeks. Third, commonly used lipid-lowering medications include atorvastatin, rosuvastatin, simvastatin, whereas pitavastatin and ezetimibe are rarely used in clinical settings. Few clinical trials have compared the effectiveness and safety of pitavastatin plus ezetimibe versus pitavastatin alone in decreasing lipids, and evidence from large RCTs is lacking. Fourth, some research was of poor quality and did not specify blinding and allocation concealment techniques, thus leading to measurement and selection bias.

Conclusions

According to this meta-analysis, patients with CHD may benefit from with ezetimibe and pitavastatin in combination at the recommended doses to decrease blood cholesterol levels, notably LDL-C, TC, and TG. However, the increase in HDL-C may be affected by diabetes and short treatment durations. The combination of pitavastatin and ezetimibe does not increase the levels of ALT and creatine kinase. Therefore, more investigations involving patients with diabetes and longer follow-up periods are essential. To gather better data and adequately guide clinical practice, more high-quality, large-sample, multicenter, long-term clinical RCTs are required to

confirm the safety and long-term therapeutic benefits of combination therapy.

Abbreviations

ACS, acute coronary syndrome;
ALT, alanine aminotransferase;
AST, aspartate aminotransferase;
CHD, coronary heart disease;
CIs, confidence intervals;
CK, creatine kinase;
CKD, chronic kidney disease;
EZE, ezetimibe;
HDL-C, high-density lipoprotein cholesterol;
HL, hyperlipidemia;
LDL-C, low-density lipoprotein cholesterol;
NCKI, China National Knowledge Infrastructure;
NPC1L1, Niemann-Pick C1-Like 1;
PCI, percutaneous coronary intervention;
PIT, pitavastatin;
RCT, randomized controlled trial;
SMD, standardized mean difference;
T2DM, type 2 diabetes;
TC, total cholesterol;
TG, triglyceride.

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Data availability statement

All data generated and analyzed in the study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RPC made substantial contributions to the conception and design of the study; RPC and CC searched the literature, extracted data from the collected literature, and analyzed the data; RPC wrote the manuscript; XJZ and QS revised the manuscript; Qiang Su and Xingjie Zhong contributed equally to this work. All authors approved the final version of the manuscript.

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