

Effect and safety of combination lipid-lowering therapies based on statin treatment versus statin monotherapies on patients with high risk of cardiovascular events

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Abstract

This study aimed to compare the effect and safety of statin monotherapies and combination therapies on lipid-lowering therapies. We searched for published randomized controlled trial (RCT) reports of statin monotherapies and combination therapies in patients with high risk of cardiovascular events, and extracted lipid levels to perform meta-analysis. A total of 12 RCT reports were included in this study. According to the new guidelines (low-density lipoprotein cholesterol [LDL-C] < 100 mg/dL, high-density lipoprotein cholesterol [HDL-C] > 130 mg/dL), the percent of LDL-C attaining goals in combination therapy is more than that of monotherapy (risk ratio [RR] = 1.43, 95% confidence interval [CI]: 1.13 to 1.82, $P = 0.003$), and the percent of LDL-C and HDL-C attaining goals in combination therapy is greater than that of monotherapy (RR = 1.43, 95% CI: 1.24 to 1.65, $P = 0.000$). The changing level of blood lipid had significant statistical difference between the two groups. The degree of blood lipid lowered by combination therapy was larger than in monotherapy (standard mean difference [SMD] = -0.45 , 95% CI: -0.75 to -0.14 , $P = 0.004$; SMD = -0.72 , 95% CI: 0.04 to 1.39, $P = 0.039$; and SMD = -0.71 , 95% CI: -1.12 to -0.3 , $P = 0.001$ in LDL-C, HDL-C, and triglyceride, respectively). The incidence of adverse events was not significantly different between the two groups (RR = 1.15, 95% CI: 0.91 to 1.37, $P = 0.096$; RR = 1.5, 95% CI: 0.55 to 4.1, $P = 0.427$; RR = 0.63, 95% CI: 0.33 to 1.24, $P = 0.181$ in incidence of total adverse events, drug-related treatment, and myalgia, respectively). Combination therapy can bring better effect in reducing lipid. It does not increase the incidence of adverse events, so it can be used widely and safely.

KEYWORDS

cardiovascular events, combination therapy, lipid-lowering, statin monotherapies

1 | INTRODUCTION

Coronary heart disease (CHD) has been the main threat to people's health in recent years. While the major factor for CHD is

atherosclerosis, the most relevant factor of atherosclerosis is low-density lipoprotein cholesterol (LDL-C) level. Many clinical trials have confirmed that statin treatment could lower LDL-C levels and substantially reduce the morbidity and mortality of atherosclerotic

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cardiovascular disease (ASCVD).¹ Moreover, even with high-dose statin therapies, the residual risk of major adverse cardiovascular events still exists.²

Studies have indicated that many factors, such as dyslipidemia, smoking, hypertension, diabetes, metabolic disorder, and alcohol, account for most of the risk of vascular events. Dyslipidemia is the major factor among these risks.³ Lowering LDL-C levels by statins reduces cardiovascular events after acute coronary syndrome,⁴ while dyslipidemia is characterized by high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels, and an accumulation of cholesterol-rich remnant particles with high levels of apolipoprotein B.⁵ Although lowering the LDL-C level in these patients is the primary goal, in order to reduce cardiovascular risk,⁶ recent therapy guidelines have emphasized consideration of other lipoprotein abnormalities as well as non-lipid risk factors (including smoking, blood pressure, and weight management) that contribute to global risk.⁷ There are also patients who have no response or sensitivity to monotherapy drugs, such as statins, because of their own physical fitness. Furthermore, high-dose monotherapy statins can increase the incidence of adverse drug events as well as therapy costs and they can be hard for some patients to tolerate.

This study aimed to find other lipid-lowering drugs to evaluate the effect and safety from all of the available data. Statins are hydroxymethylglutaryl coenzyme A reductase inhibitors, inhibiting the synthesis of cholesterol.⁸ Other LDL-C-lowering agents include niacin, omega-3, and fibrate. Fibrates activate the peroxisome proliferator-activated receptor α , a transcription factor that regulates the expression of a number of genes involved in multiple metabolic pathways, including lipid metabolism, ultimately reducing plasma TG concentrations and enhancing HDL levels. Fibrates have a beneficial action on the atherogenic dyslipidemia.⁹ Niacin inhibits the activity of phosphodiesterase, and reduces the synthesis of TG and the secretion of very-low-density lipoprotein; it can raise the activity of lipoprotein lipase (LPL), resulting in the hydrolysis of TG, and lowering the synthesis of apolipoprotein B. It can also enhance HDL level, lower TG level, and lower α -lipoprotein.¹⁰ The differences in action mechanisms of all kinds, resulting in different pharmacological effects and an improvement of different components of the lipid profile, provide a rationale for their use in combination in patients with high residual cardiovascular risk related to atherogenic dyslipidemia and persisting after single therapy, such as patients with metabolic syndrome, type 2 diabetes, or kidney disease.

2 | MATERIALS AND METHODS

2.1 | Search strategy

We searched the major medical databases, such as PubMed, Embase, Ovid, ScienceDirect, Springer, and Web of Science, for randomized controlled trials (RCTs) comparing combination lipid-lowering therapies based on statin treatment with statin monotherapies for major cardiovascular events. We included articles published from January 2000 to April 2018, and the search terms used were: “statin

monotherapies”, “combination”, “ASCVD”, “lipid-lowering therapies”, “randomized controlled trial” and so on.

2.2 | Criteria selection and data extraction

Inclusion criteria were as follows: (a) RCT study design, (b) recruited patients had ASCVD or were at high risk of ASCVD, (c) study compared statin monotherapies with combination therapy based on statin, (d) article reported the data of major adverse cardiovascular events, and (e) entire follow-up intervals were ≥ 6 weeks.

Data were abstracted using predefined data fields. The following data were extracted from each study: details of participant characteristics (age, sex, basic disease, and lifestyle), the number of patients in each group, duration of follow-up, baseline lipid levels (including TC, LDL-C, HDL-C, and TG), treatment and drug dosage, incidence of adverse events, and the percent of attaining goals.

2.3 | Statistical analysis

Standard mean difference (SMD) and risk ratio (RR) were used for the analysis of continuous and dichotomous variables, respectively. The chi-square test was used to evaluate heterogeneity among the studies, and I^2 was used to quantify the inconsistency. There were two models: the fixed effect model and the random effect model. The fixed effect model was used when the effects were deemed to be homogeneous ($P > 0.1$, $I^2 < 50\%$); otherwise, the random effects model was used. The Z test was used to compare the overall difference. The confidence interval (CI) was established at 95%, and P values < 0.05 were considered to indicate statistical significance. Begg's test and Egger's test were performed in order to evaluate the publication bias (in Begg's test $P > 0.05$ and in Egger's test $P > 0.05$ and 95% CI includes 1; it is thought that there was no publication bias). Statistical analyses were performed using STATA 12.0 (meta module; StataCorp., College Station, TX, USA).

3 | RESULTS

3.1 | Characteristics of study selection

In total, 12 papers of RCTs that compared statin monotherapies with combination therapies were selected.¹¹⁻²² The characteristics of each RCT are presented in Table 1. This meta-analysis included 6227 patients with ASCVD risk, 3108 of whom were given statin plus another drug therapy (including coenzyme A, ezetimibe, niacin, and fenofibrate) and 3119 of whom were given statin monotherapy.

3.2 | Effect of modifying lipid

3.2.1 | The percent of attaining goals

The US National Cholesterol Education Program released the third report of the Adult Treatment Panel, stating that patients with metabolic syndrome achieved a target LDL-C < 100 mg/dL as the primary

TABLE 1 Characteristics of included studies (combination/monotherapy)

Study	Follow-up (weeks)	Patients (n)	Treatment (mg/d)	Patient characteristics				
				Age (years)	Women (%)	Diabetes (%)	Hypertension (%)	
Lai et al ¹¹	8	118/94	Statin + CoA 400 U/moderate-dose statin ^a	55.6 ± 11.6/53.6 ± 13.1	44.9/37.2	17.8/24.5	47.5/42.6	
Torimoto et al ¹²	12	39/36	Rosuvastatin 2.5 + ezetimibe/10/rosuvastatin 5	66.3 ± 11.7/63.0 ± 13.0	38.0/56.0	100.0/100.0	72.0/64.0	
Insull et al ¹³	12	114/79	Niacin + simvastatin ^b /atorvastatin (40)	55.1 ± 12.1/51.5 ± 11.1	62.3/48.1	21.1/12.7	48.2/36.7	
Weinstein et al ¹⁴	16	140/140	FA45 + R/R ^c	65.1 ± 10.35/67.4 ± 11.15	55.7/50.7	59.3/55.7	93.6/93.6	
Farnier et al ¹⁵	12	123/125	Fenofibrate 160 + pravastatin 40/pravastatin 40	57.8 ± 9.3/58.1 ± 9.3	30.1/29.6	26.0/29.0	76.0/78.0	
Ballantyne et al ¹⁶	6	239/230	Rosuvastatin 40 + ezetimibe 10/rosuvastatin 40	63.1 ± 10.2/63.5 ± 10.6	41.4/44.3	34.4/39.6	86.6/87.0	
Davidson et al ¹⁷	12	73/74	Atorvastatin 40 + fenofibrate 145/atorvastatin 40	54.9 ± 10.74/56.3 ± 9.88	45.2/52.7			
Tsujita et al ¹⁸	36-48	100/102	Atorvastatin ^d + ezetimibe 10/atorvastatin	66.0 ± 10.0/67.0 ± 10.0	22.0/22.0	29.0/30.0	75.0/66.0	
Muhlestein et al ¹⁹	12	100/100	Simvastatin 20 + fenofibrate 160/simvastatin 20	58.8/61.4	42.0/41.0	100.0/100.0	77.0/69.0	
Taylor et al ²⁰	48	87/80	Simvastatin 20 + niacin 1000-1500/simvastatin20	67.0 ± 10.0/68.0 ± 10.0	10.3/7.5	27.6/27.5	73.6/76.3	
AIM-HIGH Investigators et al ²¹	144	1718/1696	Niacin 1500 + simvastatin40/simvastatin40	63.7 ± 8.8/63.7 ± 8.7	14.7/14.8	34.2/33.6	72.8/70.1	
Kastelein et al ²²	96	357/363	Simvastatin 80 + ezetimibe 10/simvastatin 80	46.1 ± 9.0/45.7 ± 10.0	47.5/50.7	2.2/1.4	18.8/14.0	

^aPitavastatin 4 mg/d, rosuvastatin 10 mg/d, atorvastatin 20 mg/d, pravastatin 40 mg/d, lovastatin 40 mg/d, simvastatin 40 mg/d, or fluvastatin 80 mg/d.

^bWeeks 1-4, 1000/40 mg/d. Weeks 5-12, 2000/40 mg/d.

^cRosuvastatin 5 mg for 8 wks, then 10 mg for 8 additional weeks.

^dAtorvastatin was increased by titration within the usual dose range with a treatment goal of LDL-C < 70 mg/dL on the basis of published lipoprotein management guidelines.

goal of therapy and a target non-HDL-C < 130 mg/dL as the secondary goal of therapy if elevated TG was coexisting.⁶ There are four studies^{11,12,15,16} comparing the percent of attaining LDL-C goals between two groups (Figure 1) and three studies^{11,15,16} comparing the percent of attaining LDL-C and non-HDL-C level goals in the meantime (Figure 2). The percent of attaining goals with combination therapy was bigger than that of monotherapy in LDL ($z = 2.93, P = 0.003$), as was that in LDL-C and non-HDL-C in the meantime ($z = 4.87, P = 0.000$). Begg's test and Egger's test both show no publication bias in LDL-C (Begg's test: $Pr > |z| = 0.734 > 0.05$; Egger's test: $Pr > |t| = 0.545 > 0.05$; 95% CI: -8.056724 to 11.30788) or non-HDL-C (Begg's Test: $Pr > |z| = 0.296 > 0.05$; Egger's test: $Pr > |t| = 0.247 > 0.05$; 95% CI: -21.23999 to 31.37664).

Foody et al²³ found that combination ezetimibe/statin therapy improves goal attainment and reduces the use of high-potency or high-dose statins in high risk of cardiovascular disease. This is also testified in this article.

3.2.2 | Change of lipid level

The final LDL-C level reduced more significantly from baseline in the combination group than in the statin monotherapy group (Figure 3). Data collected from 10 studies^{11-15,17,18,20-22} show a greater change

level in combination therapy ($z = 2.80, P = 0.005$). The final HDL-C level in the combination group increased *more* from baseline than that in statin monotherapy (Figure 4). Data collected from 10 studies^{11-15,17,18,20-22} show a greater change level in combination therapy ($z = 17.62, P = 0.000$). The final TG level in the combination group reduced less from baseline than that in statin monotherapy (Figure 5). Data collected from six studies^{11,12,14,15,17,20} show a greater change level in combination therapy ($z = 3.41, P = 0.001$).

LDL-C response is typically dependent on baseline LDL-C and inversely related to baseline TG. Many studies proved that the reduction of LDL-C was remarkable with combination therapy.²⁴⁻²⁶

3.2.3 | Adverse events

Four trials^{13-15,17} reported the incidence of drug-related adverse events (Figure 6) and four trials^{13,14,16,17} reported the incidence of myalgia (Figure 7). Compared with statin monotherapy, there was no difference with statin combination therapy in the incidence of drug-related adverse events ($z = 0.79, P = 0.427$; Begg's test $Pr > |z| = 1.000$). There was also no difference between statin combination therapy and statin monotherapy in the incidence of myalgia ($z = 1.34, P = 0.181$). Combination therapy does not reduce the incidence of adverse events.

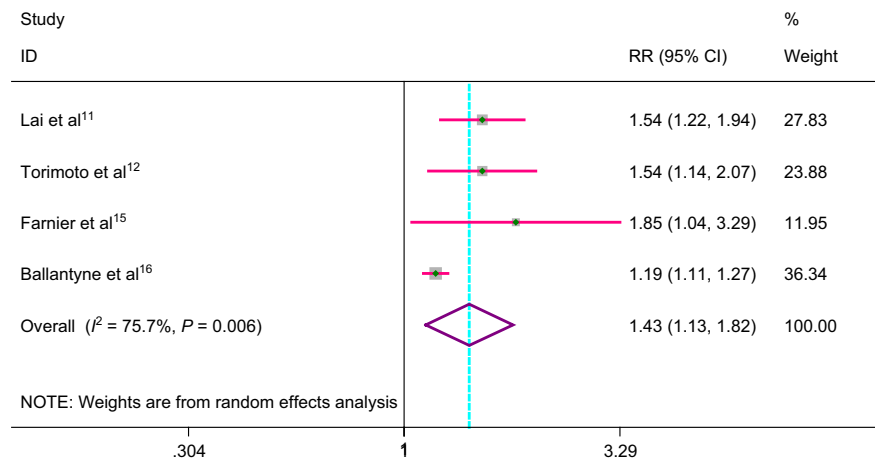


FIGURE 1 Attaining goals rate of LDL-C between combination and monotherapy

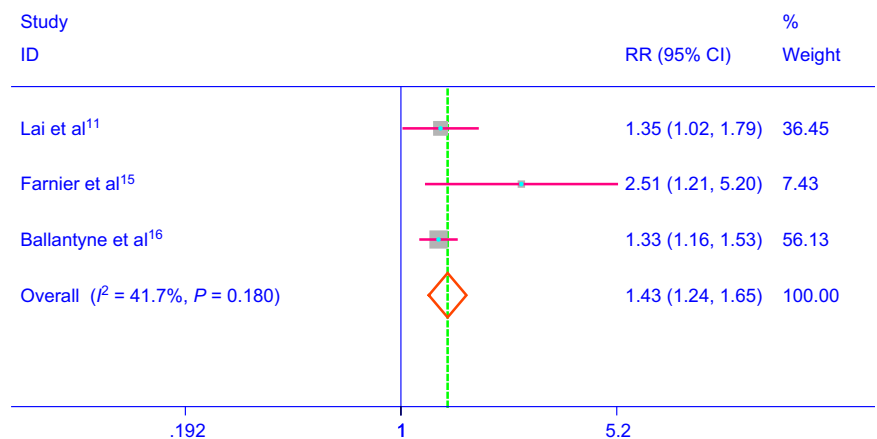


FIGURE 2 Attaining goals rate of LDL-C and HDL-C

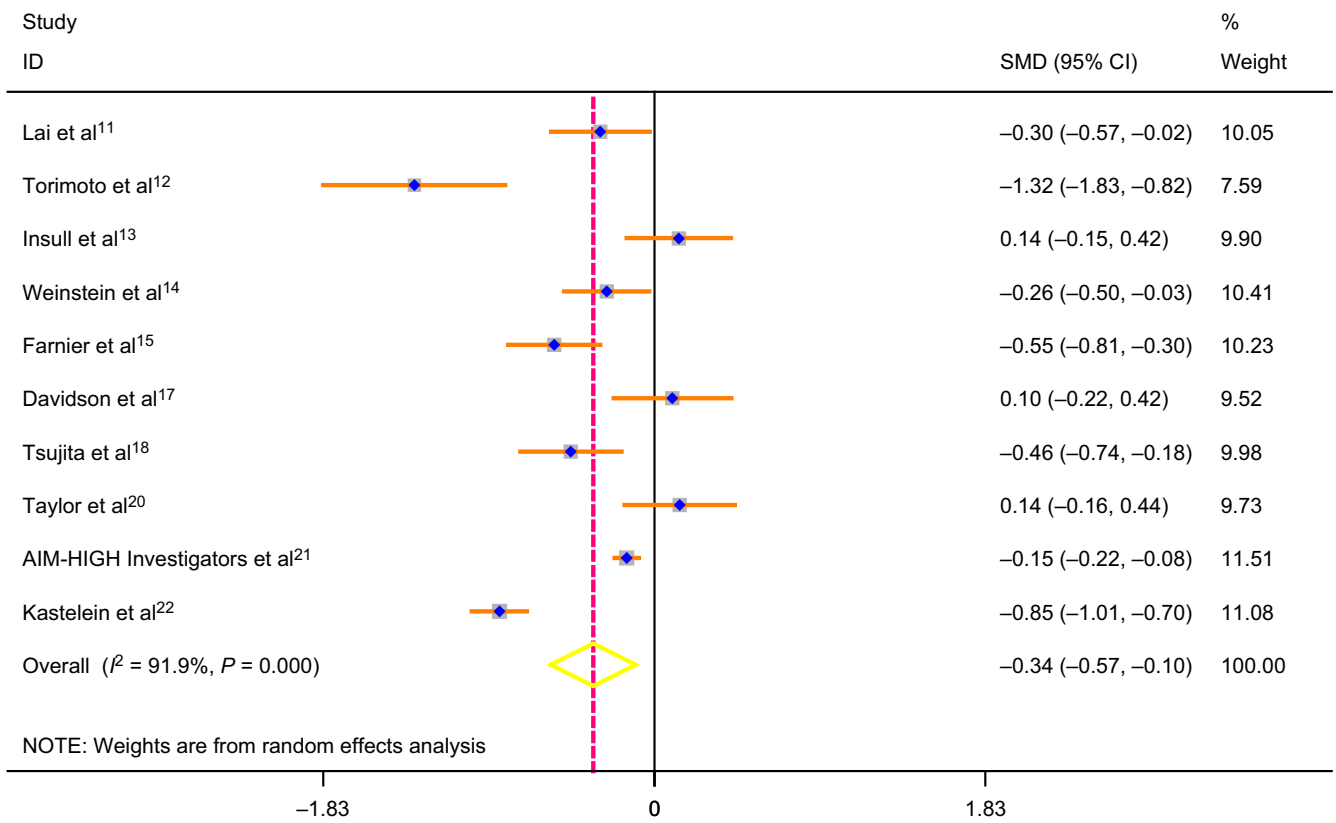


FIGURE 3 The changed level of LDL-C

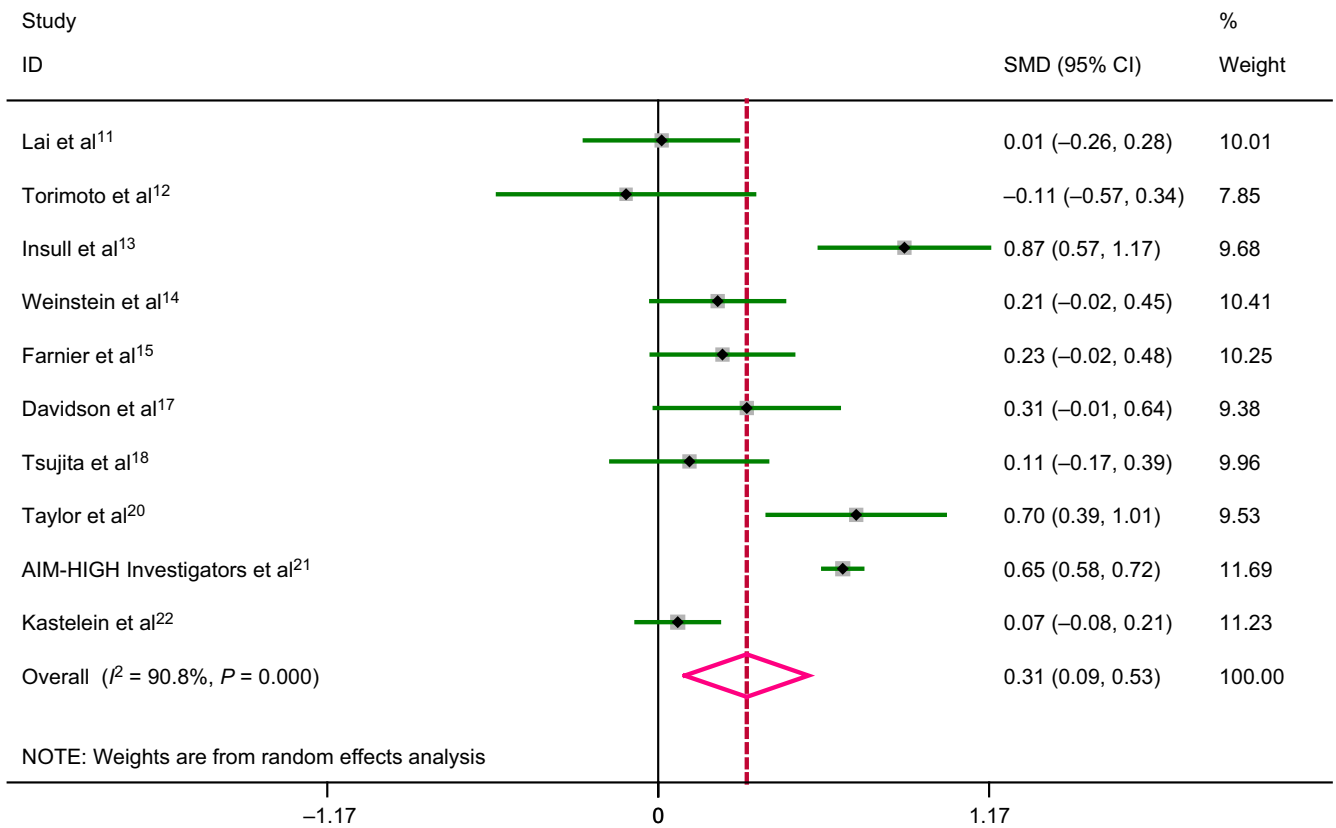


FIGURE 4 The changed level of HDL-C

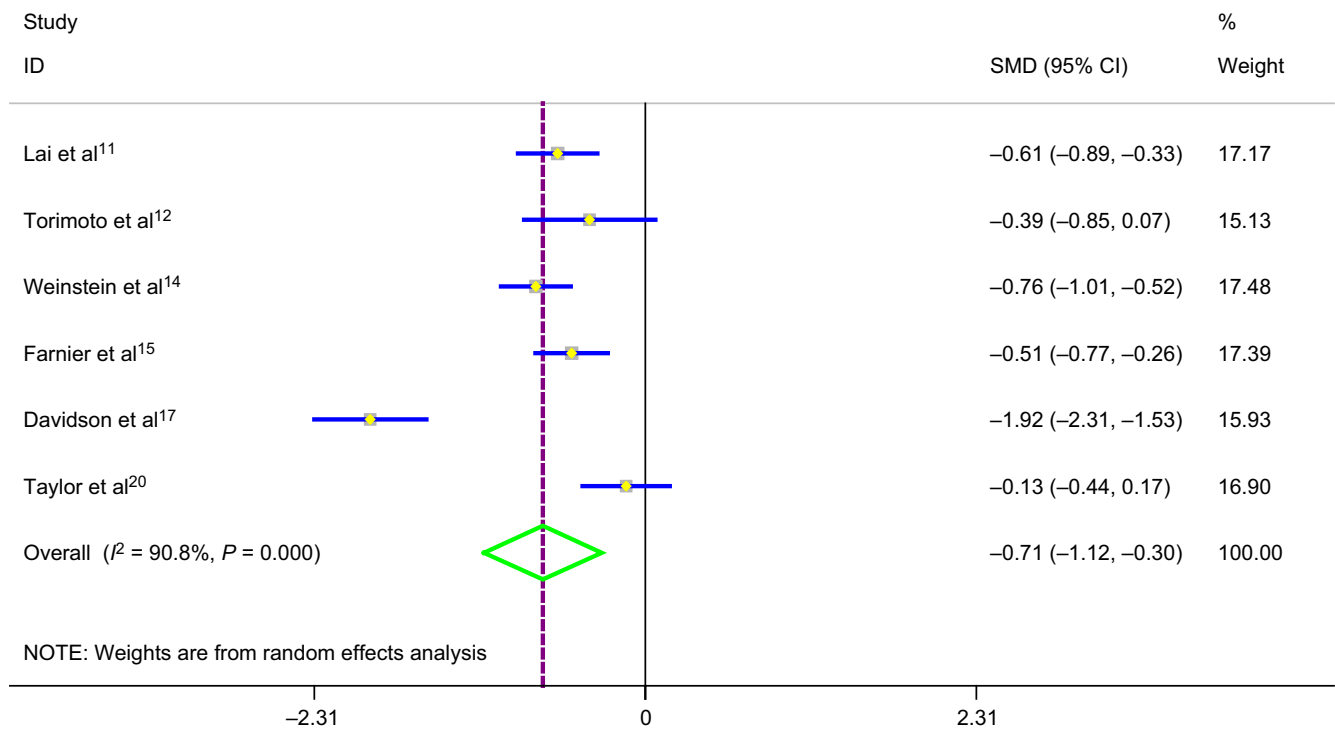


FIGURE 5 The changed level of TG

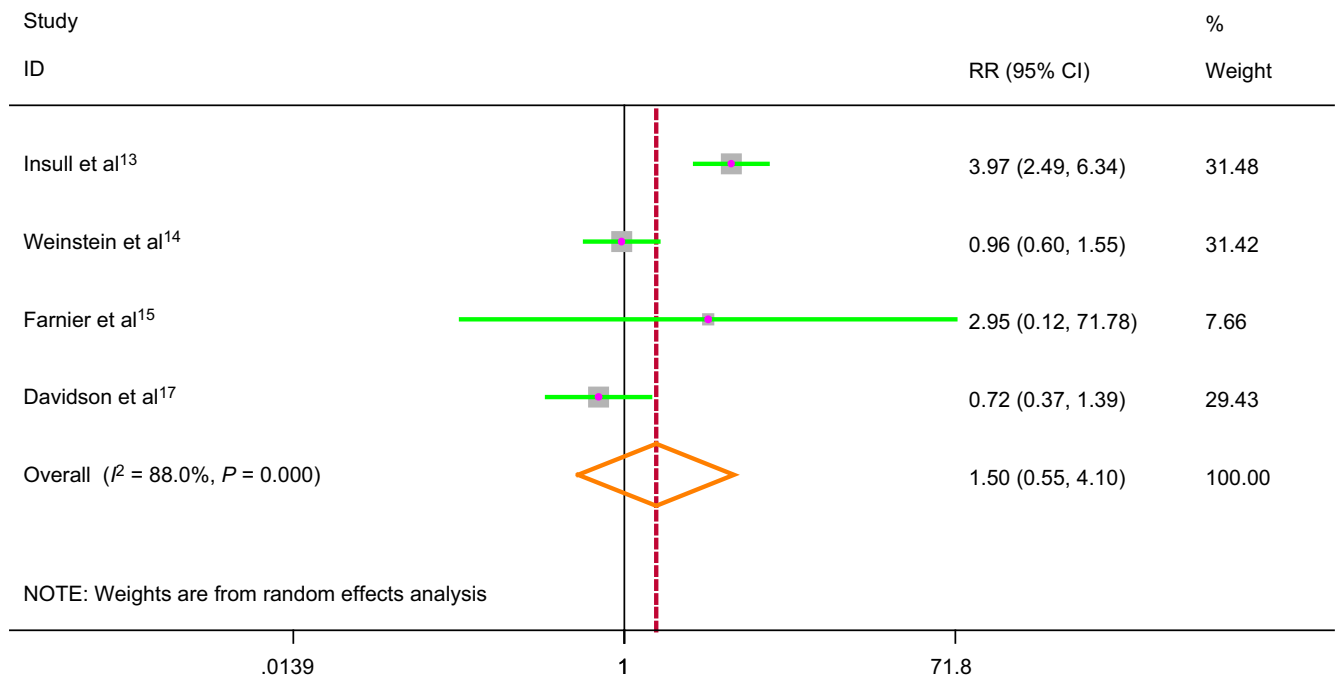


FIGURE 6 Drug-related adverse events

Neither Begg's test nor Egger's test show a publication bias (Egger's test $Pr > |t| = 0.954$, 95% CI: -341.665 to 345.6016) in the incidence of drug-related adverse events or in the incidence of myalgia (Begg's test $Pr > |z| = 1.000$, $Pr > |t| = 0.403$, 95% CI: -35.44793 to 28.58507).

4 | DISCUSSION

Residual cardiovascular risk persists despite of the achievement of target LDL-C levels with statin monotherapy for some high-risk cardiovascular patients. It is well accepted that residual cardiovascular

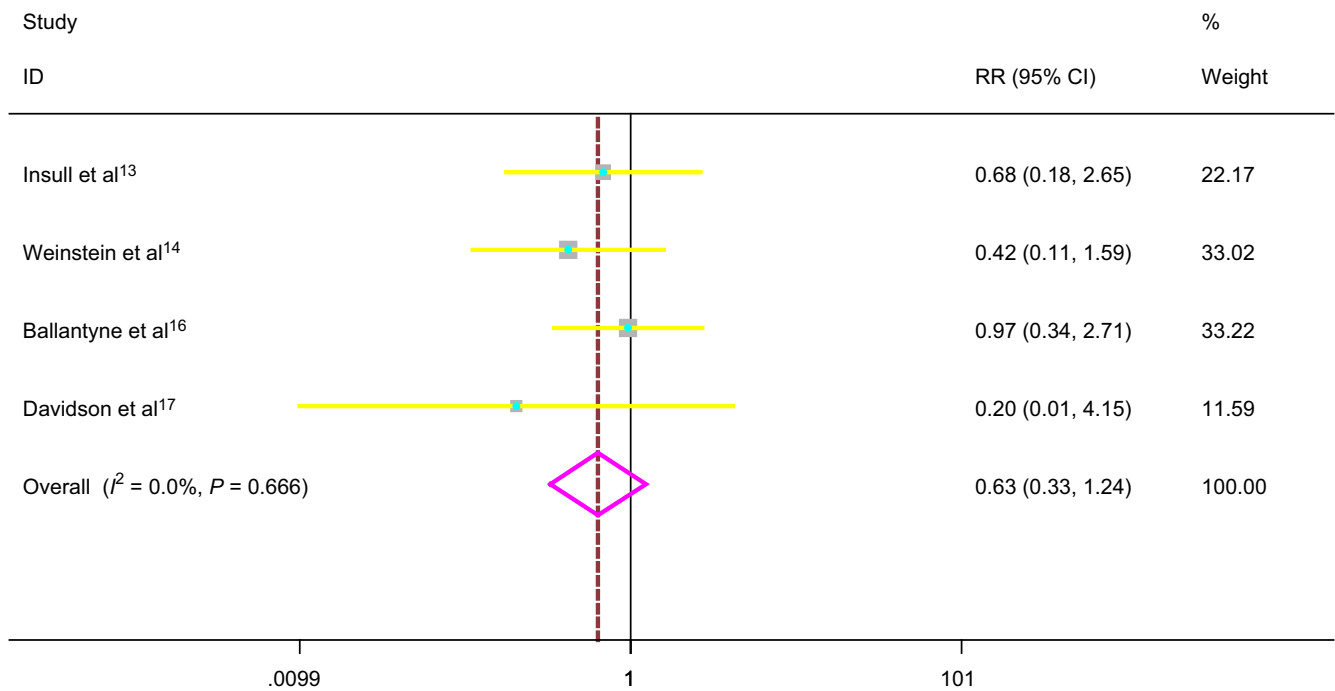


FIGURE 7 Incidence of myalgia

risk is partially due to low HDL-C and high TG. Therefore, raising HDL-C and lowering TG represent an important strategy for reducing residual cardiovascular risk in patients already treated with statins. There are other people who cannot tolerate a high dose of statin. With the increase of statin dosage, the incident of adverse events reportedly increases;²⁷ thus, a drug to effectively replace statin is needed.

Ezetimibe primarily reduces LDL-C levels (19%), with more modest reductions in TG (8%) and increases in HDL-C (3%) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.²⁸ Niacin primarily increases HDL-C levels (15%-35%), and to a lesser extent reduces triglycerides (20%-50%), with moderate LDL-C-lowering effects (5%-25%).^{29,30} Omega-3 fatty acids are effective agents for lowering TG. The GISSI-Prevenzione trial showed that dietary supplementation with omega-3 fatty acids reduced mortality by 20% in survivors of myocardial infarction.³¹ The percent reductions in LDL-C level in ezetimibe/rosuvastatin combination groups were more than 50% from baseline.²⁷

The addition of niacin, omega-3 fatty acids, or fibrates to statin therapy has produced their expected additive lipid effects but has failed to achieve a clinical benefit. Adding ezetimibe to statin therapy can further lower LDL-C safely and translate into a clinical benefit in patients at high risk of cardiovascular events.³²

Adding fenofibric acid had a modest, incremental, favorable effect on LDL-C, non-HDL-C, total cholesterol, and hypersensitive C-reactive protein between moderate- and low-dose combination therapy, and the effect on TG and HDL-C was similar whether fenofibric acid was combined with a moderate- or low-dose statin. This was expected as only the statin dose was increased. Higher-

dose combination therapy does not provide additional benefits on TG and HDL-C.³³

There is no need to increase the dose of statin if statin monotherapy fails to attain the treatment goals, and a moderate dose should suffice. High-dose statin generates the same effect with the moderate dose, but increases the incidence of adverse events. Additional appropriate lipid-modified drug combination therapy can be used according to the patient's blood lipid level. Combination therapy can lower LDL-C and TG and increase HDL-C more effectively, but will not reduce the risk of adverse cardiovascular events. Thus, in a clinical context, this treatment must be selected carefully.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

C.W., F.W., and S.C. designed the study; C.W. and F.W. carried out the cell experiments; Q.C., Z.L., and L.H. provided the facilities for experiments and made suggestions on the performance of experiments. All authors have read and approved the final manuscript.

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