The efficacy and safety of statin in combination with ezetimibe compared with double-dose statin in patients with high cardiovascular risk: A meta-analysis

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ABSTRACT

Currently, statins are the first-line therapies for dyslipidemia and atherosclerotic cardiovascular disease, however, their hypolipidemic effects have not been satisfactory. We performed a meta-analysis to compare lipid-lowering efficacy and safety of ezetimibe and statin combination therapy with double-dose statin monotherapy in patients with high cardiovascular risk. Fourteen studies involving 3105 participants were included in the final analysis; 1558 (50.18%) participants received ezetimibe and statin combination therapy and 1547 (49.82%) received double-dose statin monotherapy. Eight studies reported the percentages of changes in several lipid parameters from baseline to endpoint in both groups. Lipid parameters changed more significantly in patients coadministered with ezetimibe and statin (low-density lipoprotein cholesterol [LDL-C]: MD = -9.39, 95% CI -13.36 to -5.42; non-high-density lipoprotein cholesterol [non-HDL-C]: MD = -10.36, 95% CI -14.23 to -6.50; total cholesterol [TC]: MD = -8.11, 95% CI -10.95 to -5.26; and triglyceride [TG]: MD = -5.96, 95% CI -9.12 to -2.80), with moderate to high heterogeneity among the studies. Two out of fourteen studies investigated several different statins. Our subgroup analysis showed that, compared with double-dose atorvastatin monotherapy, ezetimibe and atorvastatin combination therapy significantly decreased LDL-C, non-HDL-C, TC, and TG levels by 14.16%, 14.01%, 11.06%, and 5.96%, respectively ($p < 0.001$). No significant difference was found in the incidence of laboratory-related adverse events (AEs) between statin combination therapy and monotherapy. Overall, ezetimibe and statin combination therapy significantly decreased LDL-C, non-HDL-C, and TC levels in patients with high cardiovascular risk, among which ezetimibe combined with atorvastatin had the best therapeutic effect. Compared with ezetimibe and statin combination therapy, double-dose statin monotherapy did not increase the risk of AEs.

KEYWORDS: Efficacy; safety; statin; ezetimibe; combination therapy

INTRODUCTION

Cardiovascular disease is one of the main causes of mortality around the world [1]. Among diverse etiological factors, dyslipidemia is the most important reversible risk factor for cardiovascular diseases [2]. Previous studies showed that serum cholesterol levels were directly correlated with coronary heart disease (CHD)-related mortality [3-5]. A meta-analysis of individual data obtained from 174,000 participants in 27 randomized trials showed that every 1.0 mmol/L reduction of low-density lipoprotein cholesterol (LDL-C) level resulted in a 12% reduction in vascular mortality [6]. Thus, developing effective and safe therapies for treating dyslipidemia is crucial for the prevention and treatment of cardiovascular diseases.

In general, hypolipidemic drugs are classified into the following categories: hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), niacin, cholic acid chelating agents, ezetimibe, and PCSK9 monoclonal antibody. Notably, statins are the first-line therapeutic approach for dyslipidemia and atherosclerotic cardiovascular disease (ASCVD) [7]. Unfortunately, the recommended LDL-C levels cannot be reached in partial patients receiving statin monotherapy. Thus, the current clinical hypolipidemic guidelines recommend powerful lipid-lowering drugs, such as statins at high doses, for treating patients with ultrahigh risk of ASCVD [7-9]. However, high doses of statins may cause side effects in patients, especially in the elderly. Some clinical trials showed that the risks of adverse events (AEs), such as myopathy and liver injury, generally increased with increasing doses of statins [10]. It remains controversial whether high doses of statins are good for treating patients with high cardiovascular risk.

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In the current study, the primary efficacy endpoint was the percentage of change in lipid parameters. Moreover, the safety of two treatment strategies was assessed by reviewing adverse experiences and laboratory values. According to the 2018 Cholesterol Clinical Practice Guidelines, a high cardiovascular risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple other high-risk conditions [11].

A meta-analysis is an effective statistical tool for overcoming the limitations of individual studies with different sample sizes. Thus, we performed a meta-analysis to compare lipid-lowering efficacy and safety between ezetimibe and statin combination therapy and double-dose statin monotherapy in patients with high cardiovascular risk.

MATERIALS AND METHODS

Search strategy

The meta-analysis was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [12]. In December 2018, two of the authors searched six databases independently, including PubMed, Cochrane Central, EMBASE, Medline, CNKI, and Wanfang. The search terms, deliberately generic, included ("Ezetimibe" OR "Ezetrol" OR "SCH-58235" OR "SCH58235" OR "Zetia") AND ("Hydroxymethylglutaryl-CoA Reductase Inhibitors" OR "HMG-CoA Statins" OR "HMG-CoA Reductase Inhibitors" OR "Hydroxymethylglutaryl-CoA Inhibitors" OR "Statins" OR "Hydroxymethylglutaryl-Coenzyme A Inhibitors").

Inclusion criteria

1. Comparisons of the efficacy or safety of double-dose statin monotherapy vs. statin and ezetimibe combination therapy;
2. Reports on the percentages of changes in lipid parameters from baseline to endpoint, including LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglyceride (TG);
3. Information on clinical AEs;
4. Randomized control trials.

Exclusion criteria

1. Abstracts, letters, case reports, reviews, or nonclinical studies;
2. Studies with insufficient data to estimate standard deviation (SD) and 95% confidence interval (CI);
3. Studies that contained duplicate data or repeated analyses;
4. Studies that excluded original data to calculate the percentages of changes in lipid parameters.

Data extraction and quality assessment

All candidate articles were independently evaluated and extracted by two authors (Yunyun Zhu and Shaoyi Lin). Extracted data were further verified by a senior author, and any discrepancies were resolved by a consensus agreement. Data items to be collected were determined before the literature search. The risk of bias in each individual trial was assessed using the Cochrane Collaboration's tool (Figure S1 and S2).

Statistical analysis

The meta-analysis was performed using Review Manager Version 5.3. (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) and Stata SE12.0 Software (StataCorp LLC, Texas, USA). Summary estimates were represented as mean difference (MD) and 95% CI. Continuous variables were reported as mean and SD, with nonparametric data transformed to mean (SD) as previously described [13]. Cochran's Q test and Higgins I^2 statistic were performed to assess the heterogeneity of included trials. Heterogeneity was considered significant when $p < 0.10$ or I^2 value $> 50\%$, where a random-effect model was applied. Otherwise, a fixed-effect model was applied. Subgroup analysis and sensitivity analysis were performed to explore the sources of heterogeneity. For all analyses, two-sided $p < 0.05$ was considered statistically significant. The quality of outcome was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation system. Publication bias was assessed visually by funnel plots and statistically by Egger's test.

RESULTS

Search results

A total of 2493 initial citations were retrieved through electronic searches, among which 45 studies were identified as potential candidates after screening. Further, 107 studies that involved non-ezetimibe intervention (n = 17), non-double-dose statin intervention (n = 33), or different primary endpoints (n = 57) were excluded from our study. The details of the study selection process are shown in Figure 1.

Fourteen studies [14-27] involving 3105 participants were included for final quantitative analysis, among which 1558 (50.18%) participants received ezetimibe and statin combination therapy and 1547 (49.82%) received double-dose statin monotherapy. The average age of participants was 68.2 years with 30.9%–78.9% males. The follow-up duration in these studies ranged from 42 days to 365 days. All research subjects were high-risk population for cardiovascular diseases based on their medical histories of cardiovascular diseases (i.e., CHD) or related diseases (i.e., diabetes, hypertension, etc.). Among the fourteen studies, two studies investigated multiple statins of different types. The statins used in the study by Nakamura

et al. [18] included atorvastatin, pravastatin, rosuvastatin, and pitavastatin, and the statins used in the study by Yu et al. [27] included simvastatin, atorvastatin, and pravastatin. Additional baseline and patient characteristics are listed in Table 1.

The Primary efficacy variable – the percentages of changes in lipid parameters from baseline to endpoint

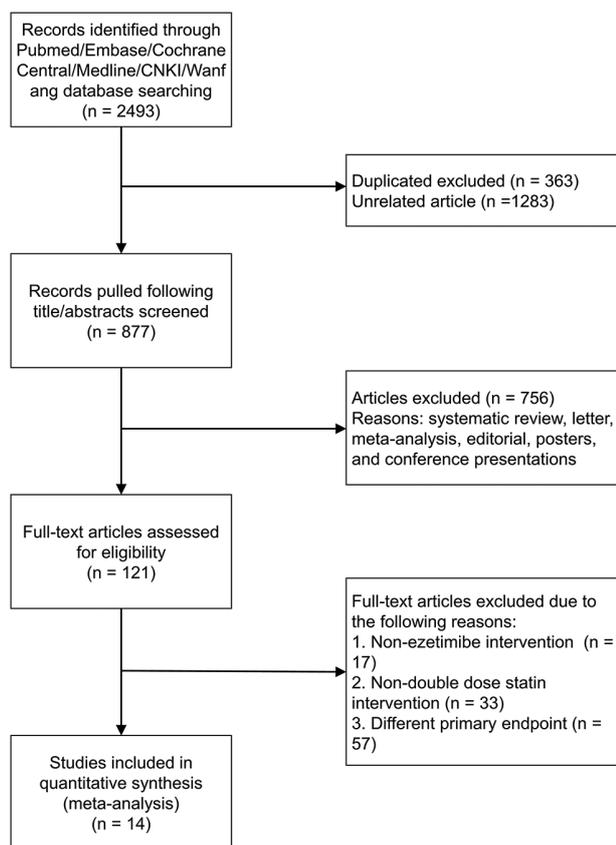A total of eight studies reported data about the percentages of changes in lipid parameters from baseline to endpoint, including LDL-C, HDL-C, non-HDL-C, TC, and TG, in both 10-mg ezetimibe plus statin group and double-dose statin group.

Combination of ezetimibe and statin was correlated with a greater percentage of LDL-C change from baseline (MD = -9.39, 95% CI -13.36 to -5.42). However, there was greater heterogeneity among the studies ($I^2 = 75\%$, $p < 0.001$) (Figure 2A). Then, statins were classified into subgroups for a subgroup analysis (Figure 2B). In rosuvastatin subgroup, the point estimation of MD (95% CI) was -3.30 (-7.45, 0.86) ($p = 0.12$), suggesting that there was no statistical significance between rosuvastatin in combination with ezetimibe and double-dose rosuvastatin. The results obtained with Q-test and I^2-test showed that there was no heterogeneity among the studies in rosuvastatin subgroup ($I^2 = 0\%$, $p = 0.59$). Compared with double-dose atorvastatin treatment, LDL-C levels after ezetimibe plus atorvastatin treatment decreased by 14.16%, with a statistically significant difference (MD = -14.16, 95% CI -16.01 to -12.31; $p < 0.001$), and no heterogeneity was observed between the studies ($I^2 = 0.00\%$, $p = 0.90$). While no significant differences in the lipid-lowering efficacies were observed between the two subgroups (rosuvastatin vs. atorvastatin; $p = 0.12$), high heterogeneity ($I^2 = 55\%$) was observed, suggesting multiple statin subgroups were the main source of heterogeneity.

The results for non-HDL-C and TC were similar to the results for LDL-C. The changes in non-HDL-C and TC from baseline were more significant in patients receiving ezetimibe and statin combination therapy vs. double-dose statin monotherapy (non-HDL-C: MD = -10.36, 95% CI -14.23 to -6.50, $p < 0.001$; TC: MD = -8.11, 95% CI -10.95 to -5.26, $p < 0.001$) (Figures 3A and 4A). However, there was greater heterogeneity among the studies (non-HDL-C: $I^2 = 75\%$, TC: $I^2 = 73\%$). Compared with double-dose atorvastatin subgroup, non-HDL-C and TC levels declined by 14.01% ($p < 0.001$) and

FIGURE 1. Flow chart of the selection process.

TABLE 1. The main characteristics of studies included in the meta-analysis

Study	Year	Country	Study type	n	Age (mean)	Male (%)	Statin	Follow-up (days)	CHD (%)	T2MD (%)	HTN (%)
Yang *et al.* [26]	2017	Korea	RCT	155	64	60.6	Rosuvastatin	56	26.7	41.9	67.3
Ran *et al.* [20]	2017	China	RCT	83	60.5	74.4	Rosuvastatin	84	71.2	25.6	48
Nicholls *et al.* [19]	2017	Australia	RCT	135	63.4	66.1	Atorvastatin	75	53	50.5	NR
Liu *et al.* [17]	2017	China	RCT	230	84.1	51.7	Atorvastatin	365	100	38.3	70
Farnier *et al.* [15]	2016	USA	RCT	197	61	61.3	Rosuvastatin	168	58	41.3	72.5
Sakamoto *et al.* [23]	2015	Japan	RCT	107	62.2	57.8	Atorvastatin	84	12.8	100	NR
Yu *et al.* [27]	2012	China	RCT	63	58	55.6	Multiple statins	56	28.6	47.6	58.7
Sasaki *et al.* [24]	2012	Japan	RCT	191	67.6	30.9	Pravastatin	84	12.6	39.3	69.6
Nakamura *et al.* [18]	2012	Japan	RCT	57	62.5	78.9	Multiple statins	180	75.4	35.1	61.4
Bays *et al.* [14]	2011	Multi-country	RCT	440	61.2	61.8	Rosuvastatin	42	100	NR	NR
Rotella *et al.* [22]	2010	USA	RCT	213	62.9	60.8	Simvastatin	42	44.7	43.7	57.3
Reckless *et al.* [21]	2008	Multi-country	RCT	424	63	60.6	Simvastatin	98	26.7	26.9	69.8
Gaudiani *et al.* [16]	2005	USA	RCT	214	58.1	57.5	Simvastatin	168	NR	100	NR
Stein *et al.* [25]	2004	Multi-country	RCT	596	52.3	53.1	Atorvastatin	98	30.6	6.8	37.4

CHD: Coronary heart disease; T2MD: Type 2 diabetes mellitus; HTN: Hypertension; RCT: Randomized controlled trial; NR: No reference
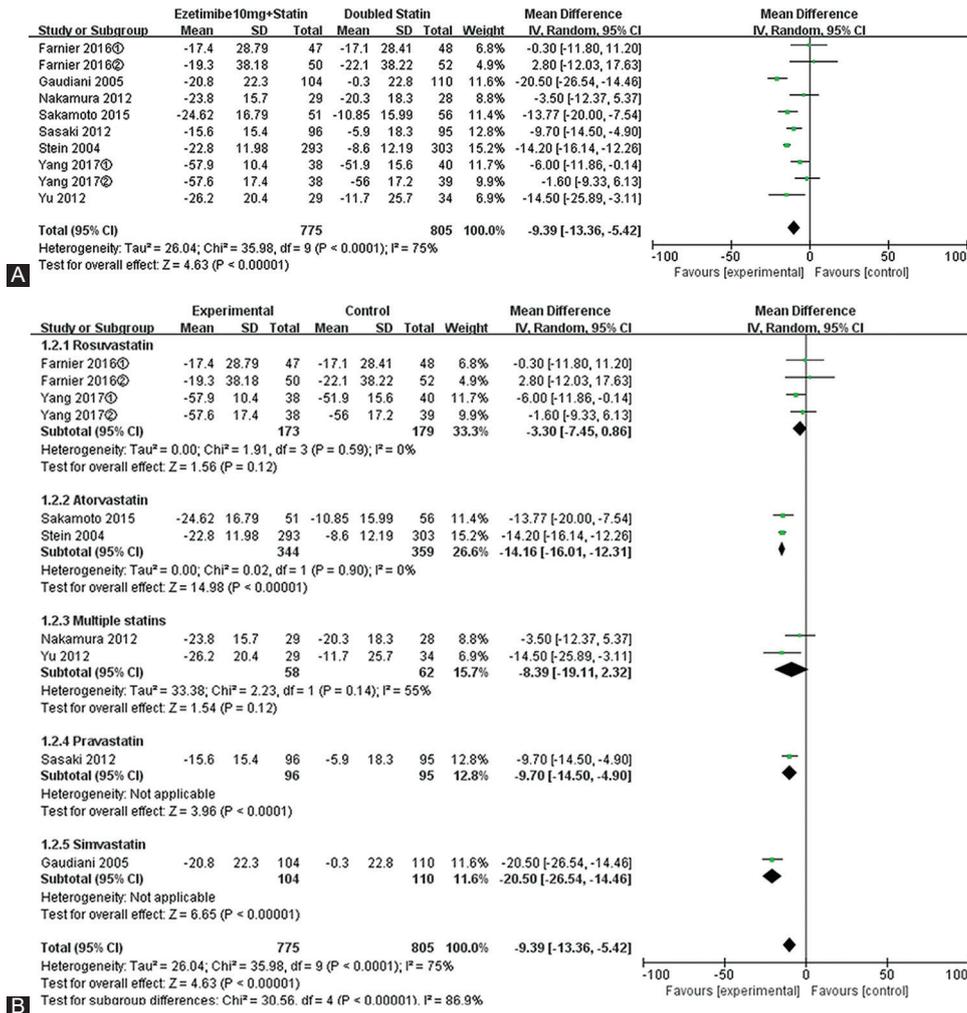
FIGURE 2. Forest plot of the percentages of changes in low-density lipoprotein cholesterol (LDL-C) (A). Forest plot of subgroup meta-analysis by the type of statin for LDL-C (B).

11.06% ($p < 0.001$), respectively, in ezetimibe plus atorvastatin group, with statistically significant differences (non-HDL-C: 95% CI -15.85 to -12.18; TC: 95% CI -12.61 to -9.50) (Figures 3B and 4B), and there was no heterogeneity between the studies ($I^2 = 0\%$). There was significant heterogeneity in rosuvastatin subgroup ($I^2 = 61\%$), suggesting that rosuvastatin subgroup was the main source of heterogeneity for TC.

For TG levels, as shown in Figure 5A, the point estimation and 95% CI of MD were -5.96 (95% CI -9.12 to -2.80, $p = 0.0002$) and z-value was 3.70, which indicated that compared with double-dose statin monotherapy, the combination therapy significantly decreased TG levels, by 5.96%. The results obtained from Q-test and I^2-test showed that there was moderate heterogeneity for TG ($I^2 = 42\%$, $p = 0.08$). Notably, the results from atorvastatin subgroup showed a statistical significance (MD = -5.74, 95% CI -10.28 to -1.19, z = 2.47, $p = 0.01$) and lower heterogeneity between atorvastatin in combination with ezetimibe and double-dose atorvastatin ($I^2 = 0\%$, $p = 0.59$, Figure 5B). However, there was great heterogeneity in rosuvastatin subgroup ($I^2 = 42\%$), indicating that rosuvastatin subgroup was the single source of heterogeneity for TG.

In terms of the percentages of changes in HDL, the point estimation of combined MD was 0.49 (95% CI -0.73 to 1.72), suggesting that there was no statistical significance. Also, there was no heterogeneity between the studies ($I^2 = 0\%$, Figure 6A).

Safety and tolerability assessment

Indicators of AEs include: elevated levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), i.e., more than threefold of the upper limit of normal [ULN] for two successive measurements; elevated levels of transaminases, i.e., more than threefold of the ULN during the final laboratory examination (considered as "presumed consecutive"); or elevated creatine phosphokinase (CPK) levels, i.e., more than tenfold of the ULN. In this study, there was no significant difference in the incidence of laboratory-related AEs between the two therapies ($I^2 = 0\%$, $p = 0.91$, RR = 0.63, 95% CI 0.31 to 1.26, z = 1.31, $p = 0.19$) (Figure 6B).

Publication bias

For TG, HDL-C, and laboratory-related AEs, the Egger's test showed no statistically significant publication bias
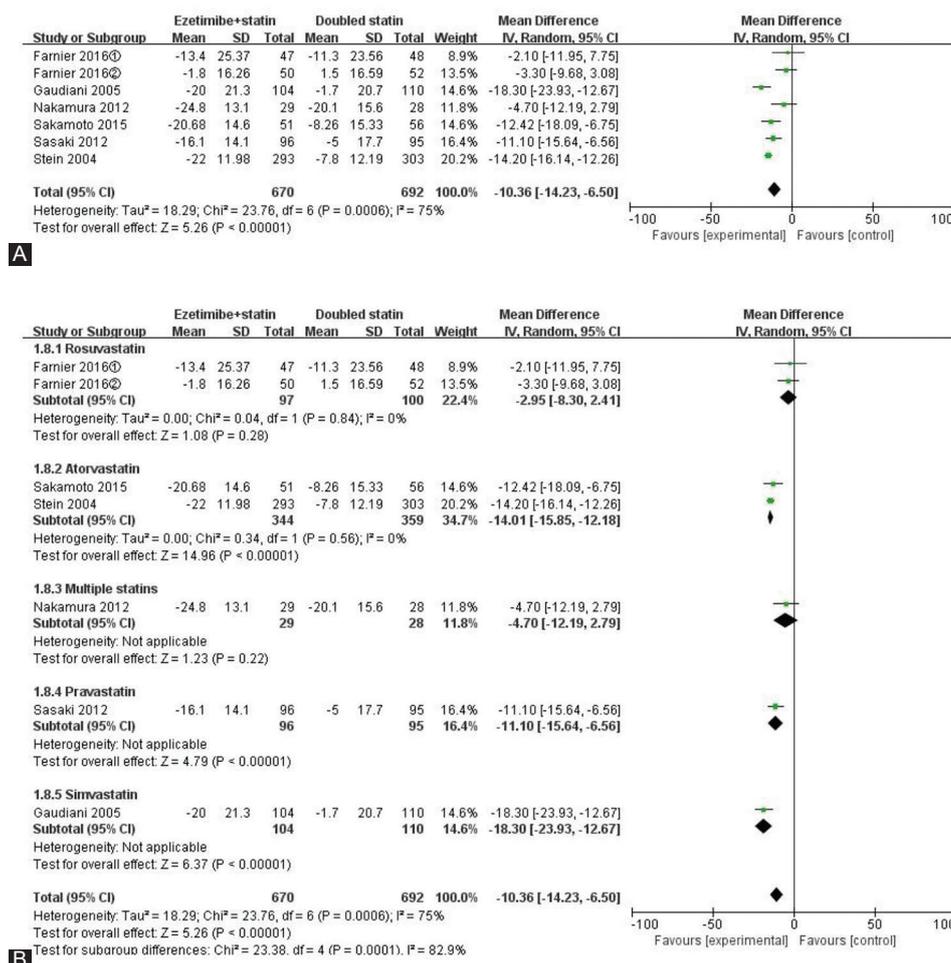
FIGURE 3. Forest plot of the percentages of changes in non-high-density lipoprotein cholesterol (non-HDL-C) (A). Forest plot of subgroup meta-analysis by the type of statin for non-HDL-C (B).

($p > 0.05$), while the funnel plots were symmetrically distributed, suggesting that publication bias could not be excluded (Figure S3-S5). For TC, LDL-C, and non-HDL-C the Egger's test showed statistically significant publication bias ($p < 0.05$), and the funnel plots were unsymmetrically distributed, suggesting that there was publication bias (Figure S6-S8).

DISCUSSION

Multiple studies have investigated the lipid-lowering efficacy and safety of ezetimibe and statin combination therapy and double-dose statin monotherapy in patients with high cardiovascular risk, however, the results of those studies are inconsistent and inconclusive (Table S1). In this study, we reviewed the relevant published studies and performed a meta-analysis to estimate the value of two distinct statin-based therapies. We analyzed the outcomes of 3105 patients from fourteen individual studies. Our results indicated that the efficacy of 10-mg ezetimibe and statin combination therapy to reduce LDL-C, non-HDL-C, TC, and TG levels was significantly better than the efficacy of double-dose statin monotherapy in patients with hypercholesterolemia with high risk of cardiovascular

diseases. Notably, the subgroup analyses showed that, compared with double-dose atorvastatin monotherapy, ezetimibe and atorvastatin combination therapy caused significant reductions in the levels of LDL-C, non-HDL-C, TC, and TG, with no heterogeneity between the studies.

Our results are consistent with the results of previous studies comparing ezetimibe and atorvastatin combination therapy with atorvastatin monotherapy, which showed that statin administration alone could not properly control the LDL-C levels of patients with moderate to high cardiovascular risk [28,29]. Compared with 40-mg atorvastatin therapy, coadministration of 10-mg ezetimibe with 20-mg atorvastatin resulted in more significant decreases in LDL-C levels in hypercholesterolemic patients at moderately high risk for CHD [28]. In hypercholesterolemia patients with high risk of CHD, 10-mg ezetimibe combined with 40-mg atorvastatin had a more potent effect than 80-mg atorvastatin in lowering LDL-C levels and could even reduce LDL-C levels to less than 70 mg/dL [29]. In our analysis, compared with 40-mg atorvastatin monotherapy, atorvastatin and ezetimibe combination therapy caused a higher decrease in non-HDL-C and TC levels. All these results suggest that
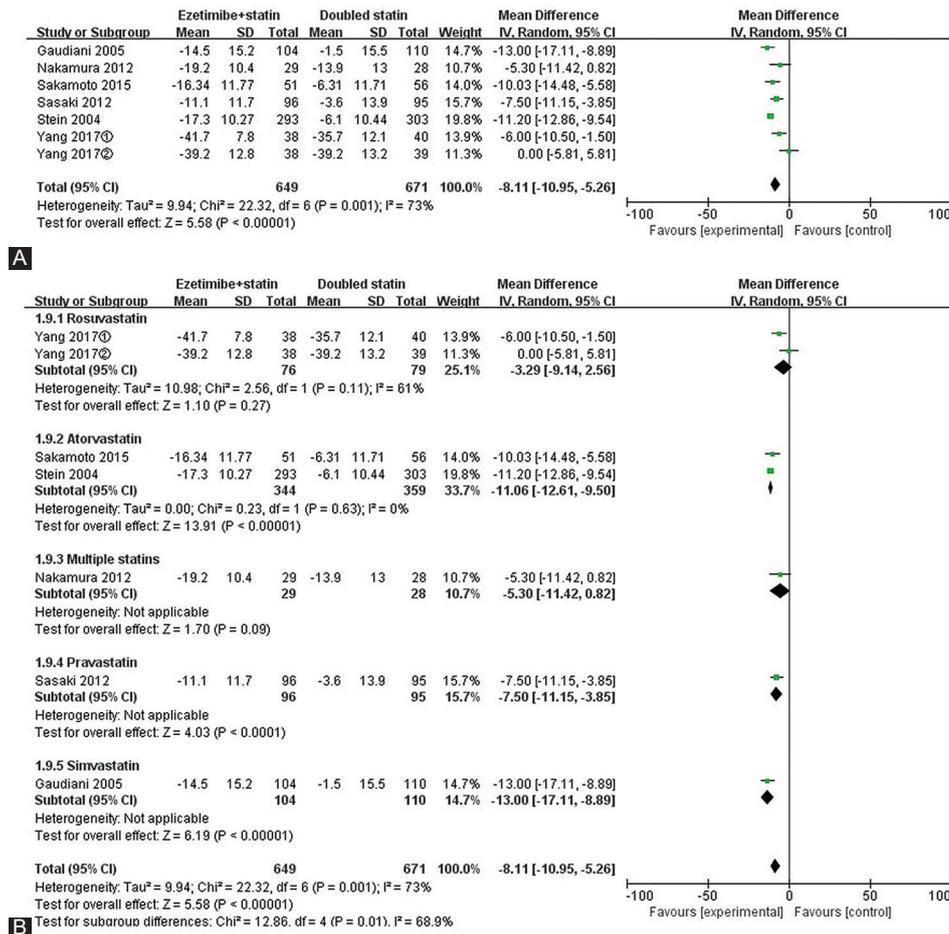
FIGURE 4. Forest plot of the percentages of changes in total cholesterol (TC) (A). Forest plot of subgroup meta-analysis by the type of statin for TC (B).

the lipid-lowering efficacy of ezetimibe plus statin therapy is more potent.

We did not observe a significant difference between double-dose rosuvastatin monotherapy and ezetimibe and rosuvastatin combination therapy in lowering the levels of LDL-C, non-HDL-C, TC, and TG. However, it should be noted that an increase in the basal dose of rosuvastatin in combination therapy could impair the efficacy of this therapy, causing only a mild decrease in LDL-C levels. Moreover, our results are inconsistent with the ACTE study in which 10-mg ezetimibe in combination with stable starting doses of rosuvastatin decreased LDL-C more significantly in patients with hypercholesterolemia compared with rosuvastatin uptitration, which caused a 21% reduction in LDL-C levels from the baseline [13]. The inconsistent results could be associated with the different dosages of rosuvastatin between the studies. The dosage applied in the ACTE study was 5 mg or 10 mg, while the dosage of rosuvastatin in the studies included in this meta-analysis ranged from 5 mg to 40 mg.

When comparing the overall curative effects between ezetimibe and statin combination therapy and double-dose statin monotherapy, we found that the percentages of changes in HDL-C levels were not significantly different.

Notably, our meta-analysis showed no significant difference in the laboratory AEs between double-dose statin-treated patients and ezetimibe-statin-treated patients. ALT, AST, and CPK are sensitive biomarkers for consecutive hepatocyte or muscle cell injury. Compared with ezetimibe and statin combination therapy, there was no significant difference in the levels of these indicators in patients receiving double-dose statin monotherapy. Randomized trials generally involve limited numbers of cases, which poses a limitation on obtaining a realistic overview of patients with poly-medications and comorbidities. Myalgia generally occurs in 5% to 10% of patients and the incidence of severe rhabdomyolysis is <0.07% in clinical practice [30]. In addition, due to the different durations of therapies in the included studies (the duration ranged from 42 days to 365 days), we could not draw a solid conclusion about the tolerability of regimens. Studies involving longer treatment durations are needed for collecting more specific data on drug safety.

The main focus of the current therapeutic guidelines is to reach the recommended LDL-C levels and to ensure drug safety. In our meta-analysis, ezetimibe and statin combination therapy significantly lowered LDL-C, non-HDL-C, and TC levels, especially when ezetimibe was administered
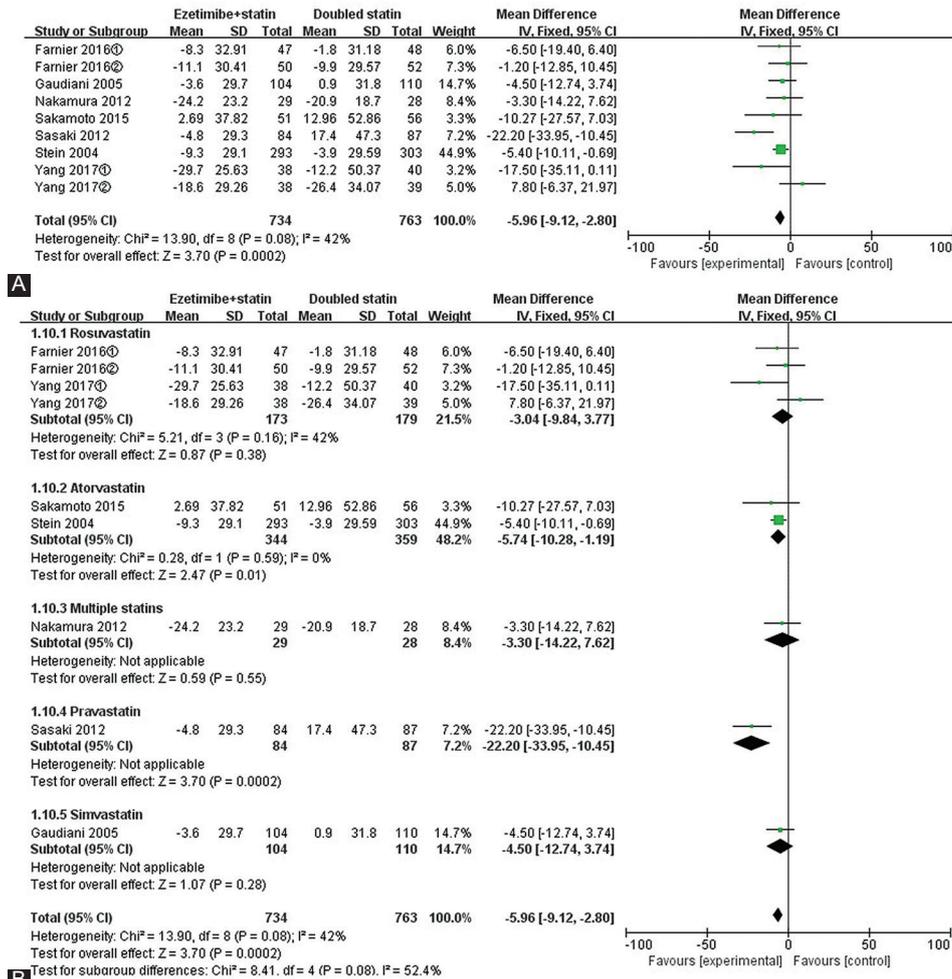
FIGURE 5. Forest plot of the percentages of changes in triglyceride (TG) (A). Forest plot of subgroup meta-analysis by the type of statin for TG (B).
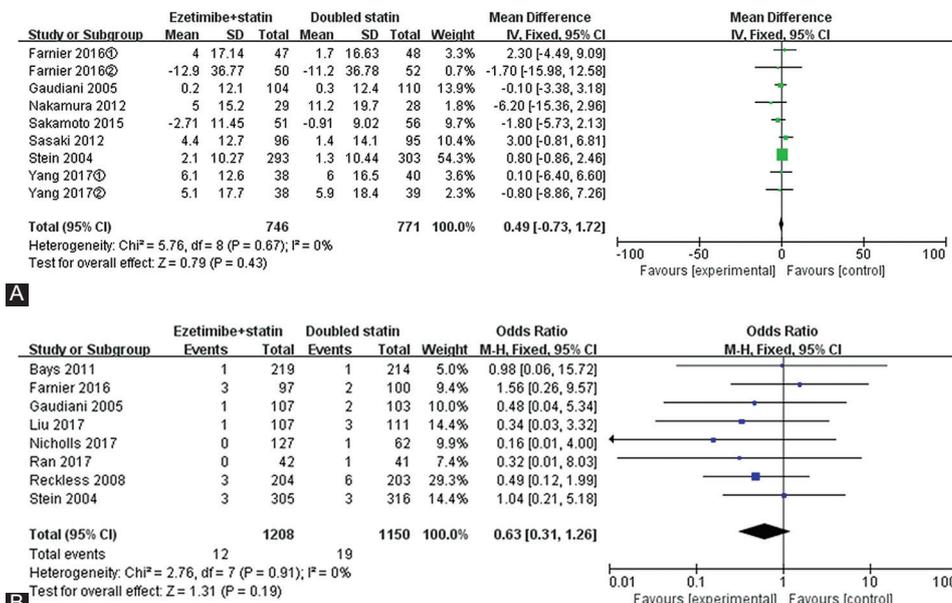

FIGURE 6. The percentages of changes in high-density lipoprotein cholesterol (HDL-C) (A) and the rate of adverse events associated with statin therapies (B).

in combination with atorvastatin. Moreover, the application of double-dose statin monotherapy did not increase the risk of ALT, AST, and CPK elevation, compared with ezetimibe and statin combination therapy. The results suggested that

ezetimibe and statin combination therapy could be more effective than double-dose statin monotherapy when the classical treatments fail to reduce LDL-C levels. However, more clinical trials are required for specifying the incidence of major cardiac AEs between two groups, i.e., ezetimibe plus statin therapy and double-dose statin monotherapy.

Limitations

There are several limitations to our study. First, significant heterogeneity was observed among the studies due to the different types of HMG-CoA reductase inhibitors used in each trial. The type of HMG-CoA reductase inhibitors was the only significant variable defined by meta-regression. In addition, the dosages of statins varied significantly among these studies, which partially affected the endpoints. Third, this meta-analysis was based on published data. In the future, more real-world data need to be included to draw a more comprehensive conclusion. Finally, although a large proportion of raw data was obtained from original authors in this study, a small portion of related data was incomplete.

CONCLUSION

Overall, this meta-analysis indicated that compared with double-dose statin monotherapy, ezetimibe and statin combination therapies, especially ezetimibe and atorvastatin combination therapy, showed higher efficacies in lowering LDL-C, non-HDL-C, TC, and TG levels in patients with high cardiovascular risk. In addition, the safety of ezetimibe and statin combination therapy vs. double-dose statin therapy was no significantly different.

ACKNOWLEDGMENTS

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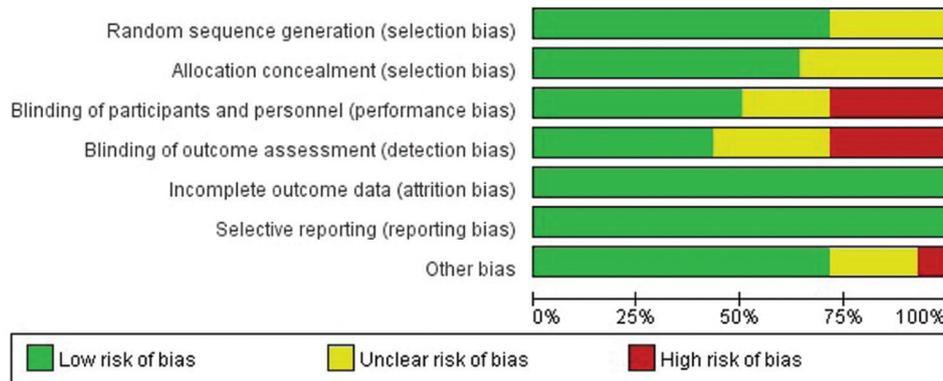
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SUPPLEMENTAL DATA

FIGURE S1. Risk of bias graph. Review of authors' judgments about each item presented as percentages across all included studies.

TABLE S1. The results of the studies included in the meta-analysis in terms of therapy efficacy and safety

Studies	Efficacy		Safety			
	In favor of double-dose	In favor of combination	In favor of double-dose	In favor of combination	No difference	No conclusion
Stein *et al.* (2004) [25]		✓			✓	
Gaudiani *et al.* (2005) [16]		✓	✓			
Reckless *et al.* (2008) [21]		✓	✓			
Rotella *et al.* (2010) [22]		✓				✓
Bays *et al.* (2011) [14]		✓			✓	
Yu *et al.* (2012) [27]		✓				✓
Nakamura *et al.* (2012) [18]		✓				✓
Sasaki *et al.* (2012) [24]		✓				✓
Sakamoto *et al.* (2015) [23]		✓				✓
Farnier *et al.* (2016) [15]	✓			✓		
Ran *et al.* (2017) [20]		✓	✓			
Nicholls *et al.* (2017) [19]		✓	✓			
Liu *et al.* (2017) [17]		✓	✓			
Yang *et al.* (2017) [26]	✓	✓	✓	✓	✓	✓

FIGURE S2. Risk of bias summary. Review of authors' judgments about each risk of bias item for each included study.
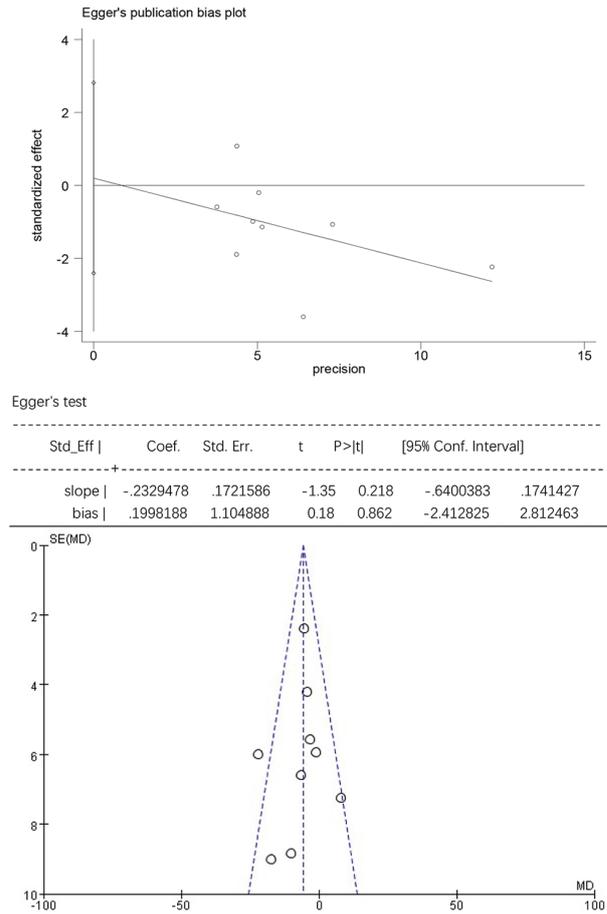

FIGURE S3. The Egger's publication bias plot and funnel plot for triglyceride (TG).

Egger's publication bias plot

Egger's test

```
-----------------------------------------------------------------
   Std_Eff |   Coef.    Std. Err.     t     P>|t|   [95% Conf. Interval]
-----------+-----------------------------------------------------
    slope |  .1963932   .106074     1.85    0.107   -.0544321   .4472184
     bias | -1.12756    .6876775   -1.64    0.145   -2.753659   .498539
-----------------------------------------------------------------
```
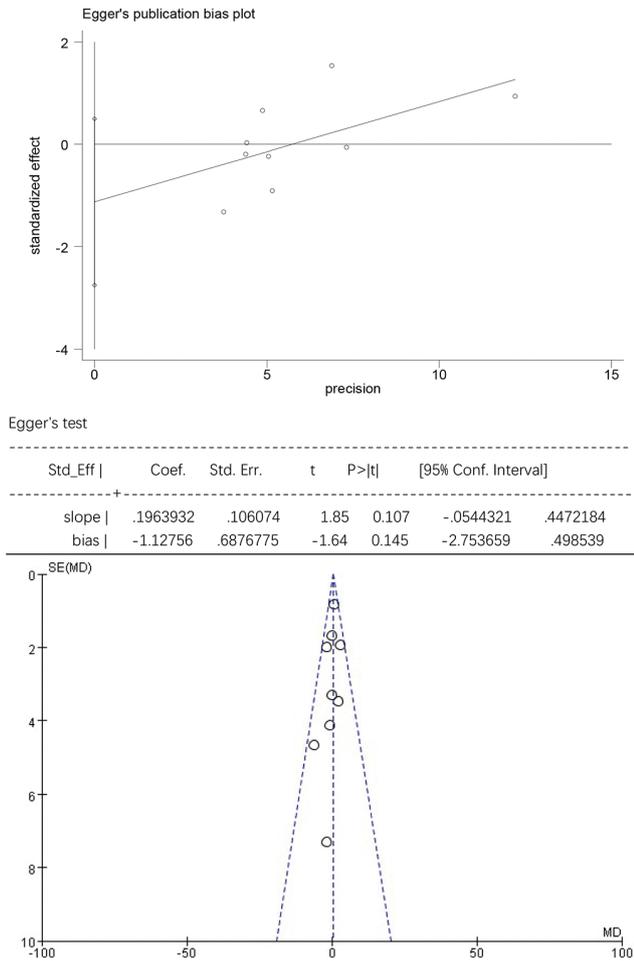
FIGURE S4. The Egger's publication bias plot and funnel plot for high-density lipoprotein cholesterol (HDL-C).

Egger's publication bias plot

Begg's Test

```
adj. Kendall's Score (P-Q) =       -8
      Std. Dev. of Score =       8.08
      Number of Studies =          8
                       z =      -0.99
              Pr > |z| =       0.322
                       z =       0.87 (continuity corrected)
              Pr > |z| =       0.386 (continuity corrected)
```

Egger's test

```
-----------------------------------------------------------------
   Std_Eff |   Coef.    Std. Err.     t     P>|t|   [95% Conf. Interval]
-----------+-----------------------------------------------------
    slope |  .4345017   .7662315    0.57    0.591   -1.440399   2.309403
     bias | -.8794097   .7410516   -1.19    0.280   -2.692698   .9338782
-----------------------------------------------------------------
```

FIGURE S5. The Egger's publication bias plot and funnel plot for adverse events (AE).

Egger's publication bias plot

Egger's test

```
Std_Eff |    Coef.    Std. Err.      t      P>|t|     [95% Conf. Interval]
---------+----------------------------------------------------------------
  slope | -1.428952   .2065815    -6.92    0.001    -1.959987   -.8979172
   bias |  4.30671    1.354486     3.18    0.025     .8248933    7.788526
```

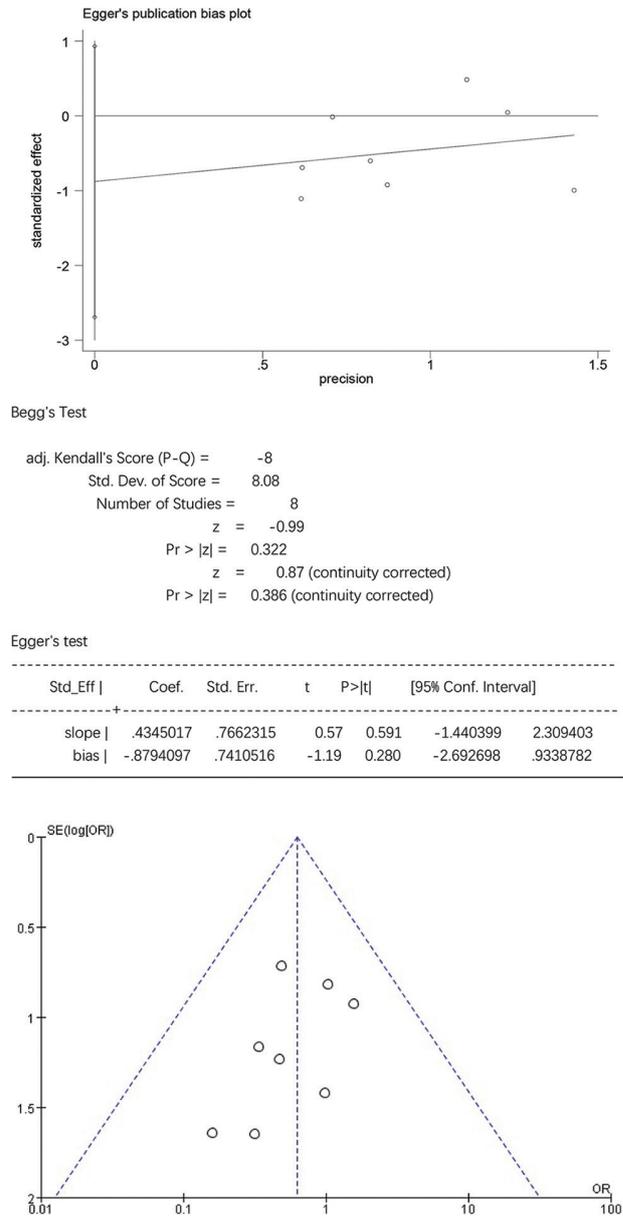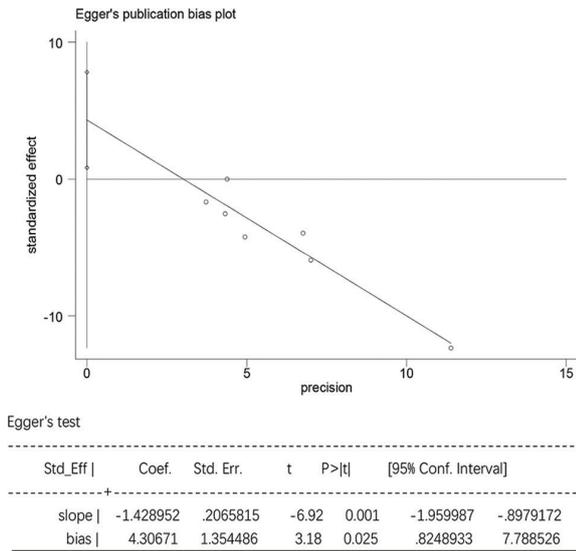**FIGURE S6.** The Egger's publication bias plot and funnel plot for total cholesterol (TC).

Egger's publication bias plot

Egger's test

```
Std_Eff |    Coef.    Std. Err.      t      P>|t|     [95% Conf. Interval]
---------+----------------------------------------------------------------
  slope | -1.659547   .2535843    -6.54    0.000    -2.244313   -1.07478
   bias |  6.050314   1.526268     3.96    0.004     2.530734    9.569894
```
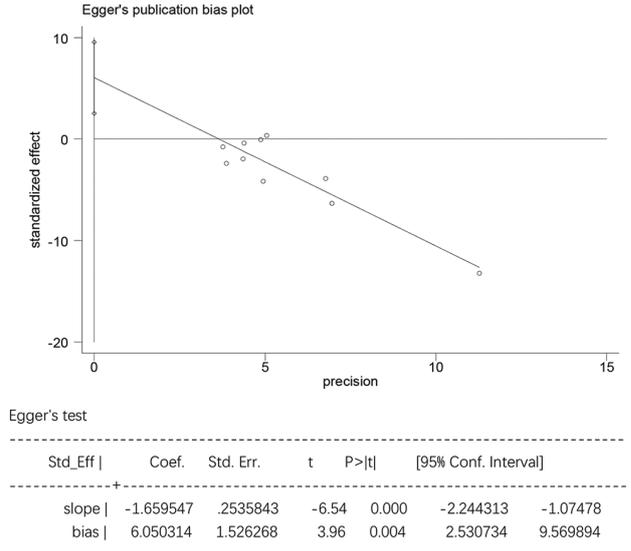
FIGURE S7. The Egger's publication bias plot and funnel plot for low-density lipoprotein cholesterol (LDL-C).

Egger's test

```
----------------------------------------------------------------------
  Std_Eff |    Coef.   Std. Err.     t     P>|t|    [95% Conf. Interval]
----------+-----------------------------------------------------------
    slope | -1.708776  .2292534   -7.45   0.001   -2.298091  -1.119461
     bias |  6.244408  1.521836    4.10   0.009    2.332405   10.15641
----------------------------------------------------------------------
```
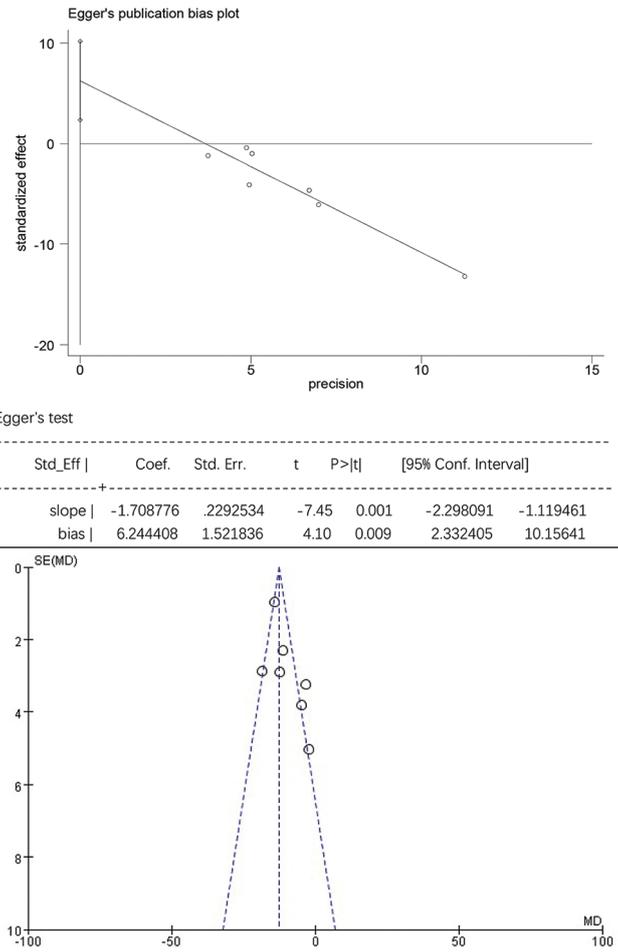

FIGURE S8. The Egger's publication bias plot and funnel plot for non-high-density lipoprotein cholesterol (non-HDL-C).