

# Comparison of Efficacy and Safety of Statin-ezetimibe Combination Therapy With Statin Monotherapy in Patients With Diabetes: A Meta-analysis of Randomised Controlled Studies

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## Original investigation

**Keywords:** Diabetic dyslipidaemia, Statin, Ezetimibe, Combination therapy

**Posted Date:** June 16th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-605068/v1>

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**Version of Record:** A version of this preprint was published at American Journal of Cardiovascular Drugs on December 20th, 2021. See the published version at <https://doi.org/10.1007/s40256-021-00516-3>.

# Abstract

**Background and aims:** Diabetic dyslipidaemia is characterised by very high levels of triglycerides, low high-density lipoprotein (HDL), and slightly elevated low-density lipoprotein (LDL) cholesterol. Additionally, the potentially increased risk of morbidity and mortality following atherosclerotic cardiovascular diseases should be considered in the treatment of dyslipidaemia in patients with diabetes.

**Methods:** We performed a meta-analysis of the published data to compare the effects of statin-ezetimibe combination therapy and statin monotherapy on lipid and glucose parameters in patients with diabetes. Additionally, the safety based on the reported adverse events was compared between the two groups.

**Results:** Seventeen articles were included in this meta-analysis. In the efficacy assessment, the combination treatment afforded a significantly greater reduction in LDL cholesterol than did statin monotherapy (standard difference in means = 0.894; 95% confidence interval 0.598–1.191). A significantly greater improvement effect was observed in the levels of HDL cholesterol, total cholesterol, triglyceride, and apolipoprotein B, but not apolipoprotein A1, with combination therapy than with statin monotherapy. Additionally, combination therapy reduced the fasting blood glucose levels more significantly than did statin monotherapy. In terms of safety, there were no significant differences in treatment-related adverse events between the two treatments.

**Conclusions:** Statin-ezetimibe combination therapy appears to enhance LDL cholesterol and other lipid levels without an increased risk of adverse events, compared with statin monotherapy. The present meta-analysis presents valid evidence for appropriate drug regimens to treat dyslipidaemia in patients with diabetes.

## Background

Dyslipidaemia, along with insulin resistance, obesity, and hypertension, is a metabolic syndrome-related factor that causes atherosclerosis and increases the risk of cardiovascular diseases (CVD) and stroke [1]. There are several subtypes of dyslipidaemia, including hypercholesterolaemia, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, and diabetic dyslipidaemia. Dyslipidaemia in diabetic patients is characterised by very high triglycerides and low HDL cholesterol levels and by slightly elevated low-density lipoprotein (LDL) cholesterol levels [2]. There is concern that patients with diabetes are at a higher risk of morbidity and mortality following atherosclerotic cardiovascular disease. Thus, the differences in lipid properties and potentially increased risk should be considered in the treatment of dyslipidaemia in patients with diabetes.

The primary target in patients with diabetes is to reduce LDL cholesterol to prevent atherosclerotic CVD, as in most patients with dyslipidaemia [3, 4]. Thus, statins are considered the first-line treatment for lipid abnormalities in patients with diabetes. There is much clinical trial evidence, obtained primarily from studies investigating statins, that lowering lipid levels will reduce vascular events and mortality in patients with type 2 diabetes [5, 6]. Although statins are the most relevant treatment modality, combination therapy may be considered in many patients with type 2 diabetes who do not reach the recommended goal of LDL cholesterol [7]. A combination with other lipid-lowering therapies, such as fibrates, niacin, bile acid resins, or ezetimibe, may assist in attaining the optimal lipid levels.

Ezetimibe reduces LDL cholesterol level by approximately 18% by inhibiting the intestinal uptake of dietary and biliary cholesterol; this reduction may be greater in combination with statin therapy because of the complementary mechanisms of action [8, 9]. A meta-analysis found that, in high-risk patients with acute coronary syndrome, statin-ezetimibe combination therapy reduced the CVD risk more than did statin monotherapy [10]. Therefore, combination therapy with ezetimibe and statins is the preferred approach for managing lipid or lipoprotein abnormalities. However, consensus via a systematic review or meta-analysis has not yet been reported for studies comparing the lipid-lowering effects of statin monotherapy versus combination therapy with ezetimibe in patients with diabetes. The safety issues associated with combination therapies also remain controversial.

This study aimed to perform a meta-analysis to evaluate the efficacy of statin-ezetimibe combination therapy with that of statin monotherapy in patients with type 2 diabetes. The glucose-related changes and safety were also evaluated.

## Methods

### Search strategy and study selections

We searched for published articles comparing the lipid-lowering effects and safety of statins and ezetimibe in patients with diabetes and dyslipidaemia. We searched online databases, including MEDLINE (OVID and PubMed), Embase, and the Cochrane Library. The search terms were combinations of the following PubMed MeSH terms and related text terms: *statins*, *hydroxymethylglutaryl-CoA reductase inhibitors*, *3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors*, and *ezetimibe*. The bibliographies of the retrieved articles and relevant reviews were searched to identify additional eligible studies. We did not impose any publication limitations and the search was completed on 30 March 2021.

Two authors independently reviewed and selected the studies for inclusion in the systematic review. We included studies that (1) were randomised clinical trials; (2) administered ezetimibe plus statin vs. statin only in patients with diabetes; (3) included measurements of lipid concentrations; and (4) described the safety or toxicity data. Any disagreement regarding the inclusion of an article for evaluation was resolved by discussion. If a trial was described in more than one report, we extracted the data from the most complete account and used the other publications only to clarify those data.

The study protocol for this meta-analysis was registered in the International Prospective Register for Systematic Reviews (PROSPERO) CRD42021244578 on 10 May 2021.

### Data extraction and quality assessment

Detailed reviews of the full-text articles were performed independently by two authors. The following data were extracted from each study: the first author's surname, year of publication, country in which the work was performed, number of participants, patient characteristics (sex and age), treatment given (regimen and period), changes in serum lipid concentrations, and adverse events. The methodological quality of each trial was evaluated by two authors using the Jadad scale [11]. The Jadad scale evaluates randomised controlled trials using five indicators: an adequate description of how randomisation was achieved, the appropriateness of the

randomisation method, an adequate account of how the investigators were double-blinded, the appropriateness of the double-blinding method chosen, and details on patient withdrawal and dropout. A score greater than three was considered to reflect high-quality work. Any disagreements between the two authors were resolved through discussion.

## Data synthesis and analyses

In terms of evaluation of efficacy, the primary endpoints of the analysis were changes in the lipid concentrations, including changes in LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides, apolipoprotein (Apo) A1, and Apo B levels for meta-analysis. Each mean change with a 95% confidence interval (CI) was calculated to assess the lipid-lowering effects of statin monotherapy or combination therapy with ezetimibe. Odds ratios (ORs) and 95% CIs were also calculated to assess the percentage of patients who attained the targeted goal of LDL cholesterol. The secondary endpoints were changes in the fasting blood glucose and glycosylated haemoglobin (HbA1c) levels. Each mean change with a 95% CI was calculated to assess the effects of both treatments on diabetes.

To evaluate the treatment safety, we counted the number of patients who experienced treatment-related adverse events in each group and compared these values between treatments. The relative risk (RR) values and 95% CIs were calculated to compare the frequencies of adverse events associated with the use of statin monotherapy or combination therapy with ezetimibe. Similarly, the RR and 95% CIs for treatment discontinuation due to treatment-related adverse events were calculated. Liver-related toxicities were evaluated by comparing the frequencies of elevated alanine aminotransferase (ALT) levels.

The study heterogeneity was assessed using the  $\chi^2$  test (employing Q statistics) and quantified by calculating the  $I^2$  values [12]. A fixed-effects model (Mantel–Haenszel method) or a random-effects model (DerSimonian–Laird method) was applied in the calculations based on the result of the heterogeneity test in each analysis [13, 14]. Sensitivity analyses were performed by excluding the contribution of each study to the meta-analysis data. The potential existence of publication bias was examined using Begg’s and Egger’s tests [15, 16].

All statistical analyses were performed using Comprehensive Meta-analysis Software version 2 (CMA 26526; Biostat, Englewood, NJ, USA). All statistical tests were two-sided and a value of  $P < 0.05$  was considered to indicate statistical significance.

# Results

## Study quality and characteristics

In total, 1911 articles were identified by the literature search. After the removal of duplicates, the titles and abstracts of 963 articles were screened. Of these, 656 non-relevant articles were excluded, and the full texts of the remaining 307 articles were assessed in terms of eligibility. A further 290 articles were excluded through full-text review, and the data from the remaining 17 articles were included in this meta-analysis (available in the supplementary figure). Using the Jadad system, three studies were classified as low-quality (a score of 2 or less) and 14 studies as high-quality (scores of 3 or greater) (Table 1).

## Effect on lipid parameters

Nine studies measured the changes in LDL cholesterol level in 342 patients treated with statin monotherapy and 333 patients treated with a statin plus ezetimibe. The combination treatment resulted in a significantly greater reduction in LDL cholesterol level than did statin monotherapy (Figure 1A). Eight studies assessed the changes in HDL cholesterol level in 262 patients treated with statin monotherapy and 260 patients treated with a statin plus ezetimibe. Combination therapy resulted also in greater improvement of HDL cholesterol level than did statin monotherapy (Figure 1B). The combination treatment resulted in significant decreases in the levels of total cholesterol, triglyceride, and Apo B compared to statin monotherapy, except for Apo A1 (Figure 1C–1F). The patients receiving combination therapy had a significantly higher percentage of patients reaching their targeted LDL cholesterol level than those receiving statin monotherapy (OR = 0.478; 95% CI 0.318–0.718). As a qualitative assessment of the lipid parameters not included in the meta-analysis, the non-HDL cholesterol and Apo A1/Apo B ratio in each study are presented in Table 2.

## Effect on glucose parameters

Seven studies measured the changes in HbA1c levels in 321 patients treated with statin monotherapy and 321 patients treated with statin plus ezetimibe; there was no significant difference identified (Figure 2A). Five studies measured the changes in fasting blood glucose levels in 253 patients treated with statin monotherapy and 246 patients treated with a statin plus ezetimibe, and found that combination treatment significantly reduced fasting blood glucose levels compared with statin monotherapy (Figure 2B). However, a re-analysis using the random-effects model did not reveal any significant difference between the two treatments.

## Effect on adverse events

Eight studies were included in the safety assessment of adverse events. Six studies were assessed for treatment-related adverse events; these studies included 1,898 patients treated with a statin alone and 1,823 patients treated with a statin plus ezetimibe. There was no significant difference between the two treatments (RR = 0.774; 95% CI 0.550–1.090). Eight studies were assessed for discontinuations due to treatment-related adverse events, and the results also revealed no significant difference (RR = 0.963; 95% CI 0.455–2.036). Only three included studies assessed ALT elevation, with no significant difference identified between the two treatments (RR = 0.907; 95% CI 0.165–4.983).

## Sensitivity analyses and publication bias

Sensitivity analysis was performed by recalculating all the findings after the data from each study included in the meta-analysis were omitted in turn. The findings were not significantly altered throughout this process (data available upon request). We also evaluated the publication bias. The results of Begg's rank-correlation test and Egger's regression test are shown in Table 3.

## Discussion

We performed a meta-analysis to evaluate the efficacy and safety of statin monotherapy and combination therapy with statin and ezetimibe in patients with diabetes. First, we found that changes in lipid concentrations differed significantly between the two drug regimens. Combination therapy with statin and ezetimibe improved the lipid parameters more than statin monotherapy, with the exception of Apo A1. Second, treatment with a combination of statin and ezetimibe was associated with a significant increase in fasting blood glucose levels. Third, in terms of safety, there was no significant difference between the two interventions in treatment-related adverse events and discontinuations due to treatment-related adverse events.

LDL cholesterol is clinically the most important measurement in dyslipidaemia because it is closely related to atherosclerotic CVD or death [34, 35]. Based on the present meta-analysis, statin-ezetimibe combination therapy has a better effect on lowering LDL cholesterol level in patients with diabetes than does statin monotherapy. In addition, similar results were identified for other the lipid profiles, except for that of Apo A1. This might be explained by the complementary mechanism of ezetimibe to the statin; while ezetimibe inhibits cholesterol absorption, statins inhibit cholesterol synthesis. This indicates that lipid management with combination therapy can be considered preferable for the prevention of CVD or stroke in patients with diabetes.

Our result echoes the conclusion of a previous meta-analysis that statin-ezetimibe combination therapy is more effective than statin monotherapy in reducing the incidence of CVD, with no significant difference between diabetic and non-diabetic individuals [36]. A post hoc analysis has also reported that combination therapy provided a significantly better improvement in lipid concentrations than did statin monotherapy, with a similar safety profile in patients with and without diabetes [37]. Interestingly, greater reductions in LDL cholesterol, total cholesterol, and non-HDL cholesterol levels were found in patients with diabetes than in those without diabetes in this analysis. In this regard, it has been reported that mRNA expression of Niemann Pick C1-like 1 protein, the specific target of ezetimibe, is increased in both animal models and patients with type 2 diabetes [38–40]. This indicates that the response to ezetimibe increases in diabetic conditions. However, this should be clarified through further research.

Qualitative assessment of other lipid parameters was performed owing to the restrictions of inconsistent data types or missing data for meta-analysis (Table 2). Eight studies evaluated non-HDL cholesterol; apart from one study that did not report p-values, all others reported greater reductions in non-HDL cholesterol with combination therapy [17–19, 21, 29, 32, 33]. Three studies evaluating the Apo B/Apo A1 ratio reported a significant increase after the combination treatment [18, 19, 27]. Overall, the results of our qualitative assessment indicated that statin-ezetimibe combination therapy was generally more effective in regulating lipid concentration than was statin monotherapy; this echoes the results of our meta-analysis results.

Another notable point is the effect of the statin-ezetimibe combination on glycaemic control in this meta-analysis. Although a few studies with considerable heterogeneity were included, there remained a significant difference in the fasting blood glucose levels between the two groups (Figure 2B). Similarly, another meta-analysis reported that ezetimibe plus low-dose statin therapy for more than three months may be beneficial to counterbalance the adverse effects of blood glucose attributed to high-dose statin therapy [41]. Unfortunately, several systematic reviews and meta-analyses have suggested that statins can impair glucose metabolism [42–44]. Impairments in glucose metabolism are of greater concern in patients with diabetes. Thus, the

combined regimen of statin and ezetimibe may be strongly recommended to treat dyslipidaemia, although further studies are required to confirm the influence of ezetimibe on glucose metabolism.

There were limitations to our meta-analysis. First, our analysis was based on previous reports, which were not necessarily complete or accurate, and we were unable to analyse data, including gender, age, duration, or other factors. Second, the results based on our overall statistical analysis could differ from the evaluations of safety or efficacy in individual patients. Despite these limitations, this is a clinically useful meta-analysis of the safety and efficacy of statin monotherapy with that of statin-ezetimibe combination therapy in patients with diabetes, as we derived accurate estimates of the clinical efficacies of the two types of treatment, and our data have greater statistical power than do the data subsets of the reports included in the meta-analysis.

## **Conclusion**

Statin-ezetimibe combination therapy for LDL cholesterol and other lipid levels without an increased risk of adverse events, when compared with statin monotherapy. We suggest that combination therapy has an additional, albeit limited, benefit in blood glucose management. On this basis, our meta-analysis provides valid evidence for drug selection to treat dyslipidaemia in patients with diabetes.

## **Abbreviations**

ALT: alanine aminotransferase; CI: confidence interval; CVD: cardiovascular diseases; HbA1c: glycosylated haemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ORs: odds ratios; RR: relative risk.

## **Declarations**

### **Authors' contributions**

Shin KH and Choi HD conducted the search, collected the data, performed the analysis and wrote the manuscript.

### **Acknowledgements**

Not applicable.

### **Competing interests**

The authors declare that they have no competing interests.

### **Availability of data and materials**

All data generated or analysed during this study are included in this published article and its Additional information files.

### **Consent for publication**

Not applicable.

## Ethics of approval and consent to participate

Not applicable.

## Funding

This research was supported by a 2020 Yeungnam University Research Grant.

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## Tables

**TABLE 1** General characteristics of included studies

Study	Study Design	Population	Patient <sup>a</sup>		Treatments	Jadad score
			Total (% male)	Ages <sup>b</sup>		
Simons, 2004 [17]	Randomized double-blind placebo-controlled study	DM or metabolic syndrome	ES: 92 (62.0) S: 99 (60.0)	64 63	Ongoing statin with ezetimibe or placebo for 8 weeks	3
Gaudiani, 2005 [18]	Randomized double-blind multicenter study	LDL-C > 100 mg/dl and TG < 600 mg/dl with type 2 DM	ES: 104 (59.8) S: 110 (55.5)	57.8 58.3	Simvastatin 40 mg or ezetimibe + simvastatin 20 mg daily for 6 weeks	3
Denke, 2006 [19]	Randomized double-blind placebo-controlled multicenter study	DM, metabolic syndrome without diabetes, or neither disorder who had LDL-C levels exceeding NCEP-ATP III goals	ES: 768 (49.7) S: 396 (46.8)	61.7 ± 11.1 60.9 ± 11.4	Ongoing statin with ezetimibe or placebo for 6 weeks	3
Goldberg, 2006 [20]	Randomized double-blind multicenter study	Type 2 DM	494 (44.7)	59.3 ± 10.2	Atorvastatin 10, 20 or 40 mg, ezetimibe + simvastatin 10 mg, or ezetimibe + simvastatin 40 mg daily for 6 weeks	4
Constance, 2007 [21]	Randomized double-blind active-controlled study	Type 2 DM	ES: 220 (50.9); 222 (50.5) S: 219 (49.3)	62.1 62.4 61.7	Atorvastatin 20 mg, ezetimibe + simvastatin 20 mg or ezetimibe + simvastatin 40 mg daily for 4 weeks	5
Settergren, 2008 [22]	Randomized double-blind controlled study	Type 2 DM or IGT and carotid artery disease	ES: 19 (58.0) S: 20 (75.0)	74 70	Simvastatin 80 mg or ezetimibe + simvastatin 10 mg daily for 6 weeks	5
Polis, 2009 [23]	Randomized double-blind controlled multicenter study	DM or metabolic syndrome	Study 1	60.8 ±	Atorvastatin 10, 20, 40 or 80 mg or ezetimibe +	4

			ES: 221 (47.1)	10.4 59.9 ± 9.3	atorvastatin 10-80 mg daily for 6 weeks (study 1); rosuvastatin 10, 20 or 40 mg or ezetimibe + simvastatin 10-80 mg daily for 6 weeks (study 2)	
			S: 207 (46.4)	57.7 ± 10.2		
			Study 2			
			ES: 190 (51.1)	57.8 ± 9.7		
			S: 185 (40.5)			
Bardini, 2010 [24]	Randomized double-blind, placebo-controlled multicenter study	Type 2 DM and CHD	ES: 37 (56.8)	65 ± 6.5	Simvastatin 40 mg or ezetimibe + simvastatin 20 mg daily for 6 weeks	5
			S: 50 (76.0)	64 ± 6.1		
Ruggenenti, 2010 [25]	Randomized double-blind controlled study	Type 2 DM with total cholesterol > 135 mg/dl despite lipid-lowering therapy	ES: 54 (63.0)	65.7 65.2	Simvastatin 40 mg or ezetimibe + simvastatin 40 mg daily for 6 weeks	5
			S: 54 (55.6)			
Kawagoe, 2011 [26]	Randomized controlled study	DM or IGT	ES: 12 (50.0)	64.2 ± 7.2	Fluvastatin 60 mg or ezetimibe + fluvastatin 20 mg daily for 10 weeks	2
			S: 12 (41.7)	65.1 ± 7.2		
Uemura, 2012 [27]	Randomized open-label cross-over study	Type 2 MD or IGT, and carotid artery disease	39	67.8 ± 9.7	Atorvastatin 20 mg or ezetimibe + atorvastatin 10 mg daily for 12 weeks	2
Vaverkova, 2012 [28]	Randomized double-blind active-controlled multicenter study	High cardiovascular risk with CHD, established vascular atherosclerotic disease, or type 2 DM	ES: 100 (58.0)	63.1 ± 8.6	Rosuvastatin 10 mg or ezetimibe + simvastatin 20 mg daily for 6 weeks	4
			S: 82 (54.9)	64.5 ± 9.1		
Rosen, 2013 [29]	Randomized double-blind active-controlled study	Type 1 or 2 DM and symptomatic cardiovascular disease	808 (52.2)	64.0 ± 8.5	Rosuvastatin 10 mg, doubling statin or ezetimibe + simvastatin	5

					20 mg daily for 12 weeks	
Torimoto, 2013 [30]	Randomized open-label controlled study	Type 2 DM	ES: 39 (62.0)  S: 36 (44.0)	66.3 ± 11.7  63.0 ± 13.0	Rosuvastatin 5 mg or ezetimibe + rosuvastatin 2.5 mg daily for 12 weeks	3
Villegas- Rivera, 2015 [31]	Randomized double-blind placebo-controlled study	Type 2 DM and diabetic polyneuropathy	ES: 25 (40.0)  S: 25 (48.0)	55.0 ± 12.0  54.0 ± 10.5	Rosuvastatin 20 mg or ezetimibe + rosuvastatin 20 mg daily for 16 weeks	5
Sakamoto, 2017 [32]	Randomized open- label controlled multicenter study	Type 2 DM and failed to reach target LDL-C values	ES: 53 (58.5)  S: 56 (57.1)	61.7 ± 11.1  62.6 ± 9.5	Ongoing statin (atorvastatin 10 mg, pitavastatin 1 mg) with ezetimibe or doubling statin (atorvastatin 20 mg, pitavastatin 2 mg) for 12 weeks	3
El- Tamalawy, 2018 [33]	Randomized controlled study	Type 2 DM or IGT and atherosclerosis	ES: 20 (55.0)  S: 20 (70.0)	61.0 ± 7.1  62.0 ± 6.9	Doubling atorvastatin or ezetimibe + atorvastatin 40 mg daily for 3 months	2

Abbreviations: DM, diabetic mellitus; ES, ezetimibe plus stain; S, statin; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; IGT, impaired glucose tolerance; CHD, coronary heart disease

<sup>a</sup> Data of DM patients are presented.

<sup>b</sup> Values are presented mean or mean ± standard deviation.

**TABLE 2** Qualitative assessments of other lipid parameters

	Statin alone			Ezetimibe plus statin			<i>P</i> value <sup>a</sup>
	Baseline	End of treatment	% Change	Baseline	End of treatment	% Change	
<i>Non-HDL cholesterol (mg/dL)</i>							
Simons, 2004 [17]	153		-1.4	150	122.8	-25.2	<0.001
Gaudiani, 2005 [18]	118.5		-1.7	124.4		-20.0	<0.001
Denke, 2006 [19]	155.5	151.3	-3.0	155.2	117.8	-24.8	<0.001
Constance, 2007 [21]	127.1		-7.43	122.43 <sup>b</sup>		-20.9	<0.001
				125.5 <sup>c</sup>		-23.8	<0.001
Vaverkova, 2012 [28]	154.7		-7.9	156.7		-23.5	NR
Rosen, 2013 [29]	126.43 <sup>d</sup>		-6.8	129.29		-18.4	<0.001
	127.79 <sup>e</sup>		-15.1				<0.05
Sakamoto, 2017 [32]	164		-8.3	155		-0.7	<0.0001
El-Tamalawy, 2018 [33]	227	152	-33.0	221	112	-49.3	0.002
<i>Apo B/Apo A1 ratio</i>							
Gaudiani, 2005 [18]	6.6		1.5	0.7		-12.1	<0.001
Denke, 2006 [19]	0.82	0.80	-2.9	0.83	0.66	-20.6	<0.001
Uemura, 2012 [27]	0.73	0.68	-6.85	0.73	0.57	-21.9	<0.05

HDL: high-density lipoprotein, Apo: apolipoprotein

Values are presented as mean for baseline and end point values.

<sup>a</sup> % change difference between the two groups.

<sup>b</sup> Treated group with ezetimibe and simvastatin 10 mg.

<sup>c</sup> Treated group with ezetimibe and simvastatin 40 mg.

<sup>d</sup> Treated group with doubling statin dose.

<sup>e</sup> Treated group with rosuvastatin 10 mg.

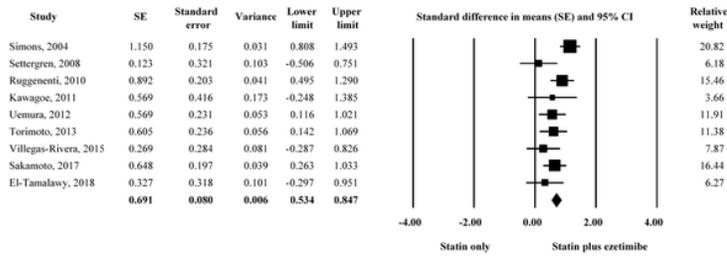
**TABLE 3** Test of heterogeneity and publication bias

No. of study	Test of heterogeneity				Publication bias	
	Q value	P value	$\rho$	P value (Begg's)	P value (Egger's)	
<i>Lipid parameters</i>						
LDL cholesterol	9	15.09	0.057	46.98	0.024	0.009
HDL cholesterol	8	11.57	0.116	39.47	0.451	0.201
Total cholesterol	7	13.03	0.043	53.96	0.382	0.442
Triglyceride	8	8.509	0.290	17.73	0	0.032
Apolipoprotein A1	3	0.677	0.713	0.000	0.500	0.444
Apolipoprotein B	4	2.254	0.521	0.000	0.367	0.124
LDL cholesterol goal	7	31.63	0.000	71.55	0.076	0.046
<i>Glucose parameters</i>						
HbA1c	7	0.518	0.998	0.000	0.500	0.353
Fasting blood glucose	5	8.479	0.076	52.83	0.110	0.075
<i>Adverse events</i>						
Treatment-related	8	6.618	0.470	0.000	0.193	0.0456
Discontinuation due to treatment-related	10	10.25	0.331	12.20	0.054	0.016
ALT elevation	3	1.529	0.466	0.000	0.500	0.474

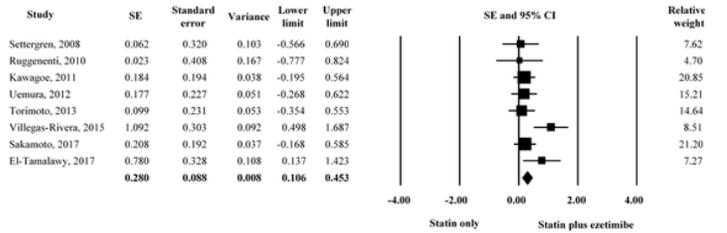
HbA1c: glycosylated haemoglobin, ALT: alanine aminotransferase.

## Figures

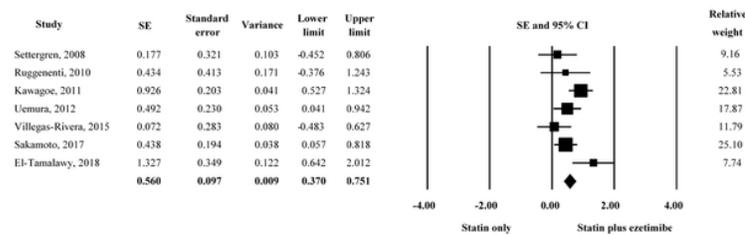
(A) LDL cholesterol



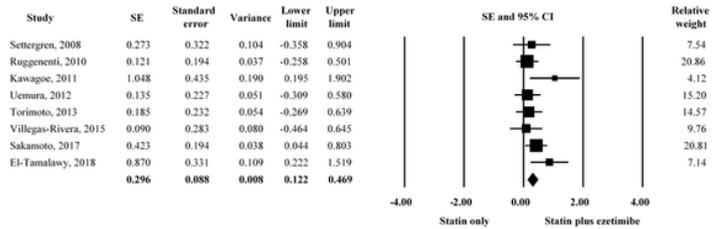
(B) HDL cholesterol



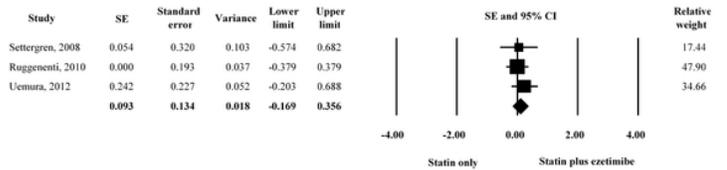
(C) Total cholesterol



(D) Triglyceride



(E) Apo A1



(F) Apo B

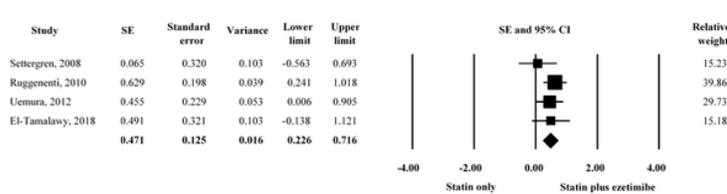
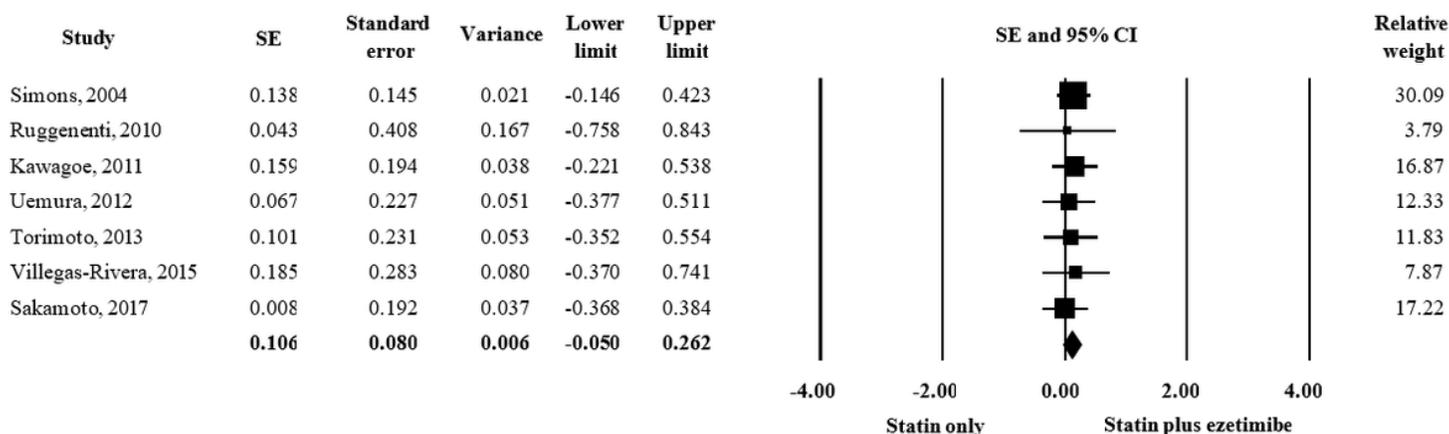


Figure 1

Forest plot of lipid parameters. Changes in LDL cholesterol (A), HDL cholesterol (B), Total cholesterol (C), Triglycerides (D) Apo A1 (E), and Apo B (F) levels, compared between statin monotherapy and combination therapy with ezetimibe LDL, low-density lipoprotein; HDL, high-density lipoprotein; Apo, apolipoprotein.

(A) HbA1c



(B) Fasting blood glucose

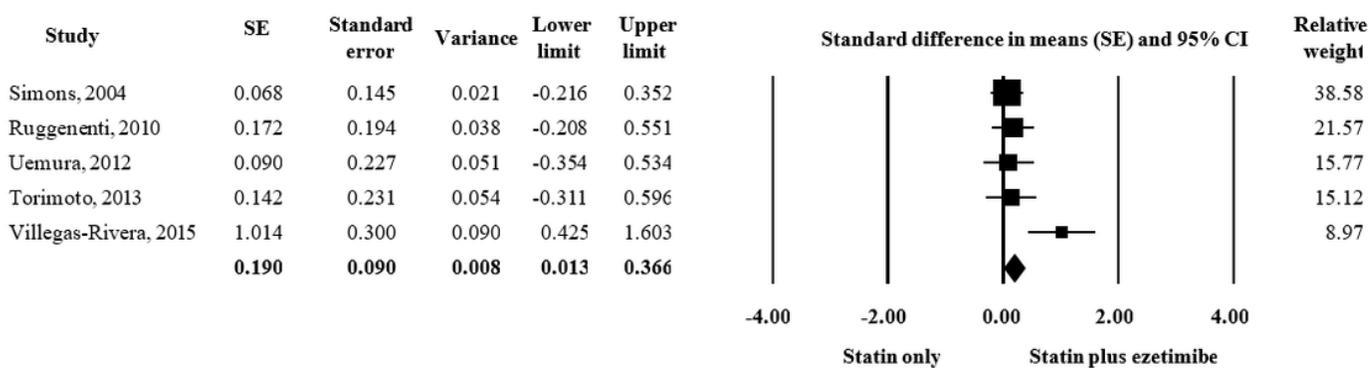


Figure 2

Forest plot of glucose parameters. Changes in HbA1c (A) and fasting blood glucose (B) levels compared between statin monotherapy and combination therapy with ezetimibe. HbA1c, glycated haemoglobin.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Fig.PRISMAprocess.docx](#)