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Review

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Efficacy and Safety of Moderate-Intensity Statin and Ezetimibe Combination Therapy Versus High-Intensity Statin Monotherapy in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Statins represent the first-line therapy for cholesterol management. However, for patients prone to statin side effects, unable to tolerate higher doses, or requiring additional low-density lipoprotein cholesterol (LDL-C) reduction, ezetimibe alone or in combination with statins is recommended. This meta-analysis aimed to evaluate the safety and efficacy of combining low- or moderate-intensity statins with ezetimibe compared to high-intensity statin monotherapy, yielding reliable evidence to guide clinical decision-making and personalize treatment strategies. PubMed, Embase, and Scopus were systematically searched from inception until May 2023. All randomized controlled trials (RCTs) comparing a high-intensity statin with a low/moderate-intensity statin with ezetimibe were included. The outcomes of interest comprised changes in concentrations of lipids—LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TGs)—and apolipoprotein (Apo) A1, Apo B, and high-sensitivity C-reactive protein (hs-CRP), along with major adverse cardiovascular events (MACE). All data were analyzed using Review Manager version 5.4. *p*-values less than 0.05 were considered to indicate statistical significance. Overall, 20 RCTs, with 5,412 participants, were included. A low/moderate-intensity statin combined with ezetimibe yielded a significantly greater reduction in LDL-C levels than high-intensity statin monotherapy (mean difference [MD], −6.59; 95% confidence interval [CI], −10.95, −2.24; p=0.003; I^2=84%). No significant differences were observed between combination and high-intensity statin monotherapy regarding TC, TG, or HDL-C levels. However, hs-CRP levels were significantly higher with combination therapy (MD, 0.32; 95% CI, 0.01, 0.64; p=0.04; I^2=0%). Combination therapy involving a low/moderate-intensity statin with ezetimibe was significantly associated with lower LDL-C levels than high-intensity statin monotherapy. No significant differences were observed for TC, TGs, HDL-C, alanine transaminase, or MACE. However, creatine phosphokinase levels significantly increased with monotherapy.

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Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Author Contributions
Conceptualization: Yasmin F, Moeed A, Umar M, Alraies MC; Data curation: Yasmin F, Moeed A, Umar M, Alraies MC; Investigation: Yasmin F, Moeed A, Umar M, Alraies MC; Methodology: Yasmin F, Moeed A, Umar M, Alraies MC; Project administration: Yasmin F, Moeed A, Umar M, Zaidi F, Khan MS, Alraies MC; Resources: Yasmin F, Moeed A, Umar M, Alraies MC; Supervision: Yasmin F, Moeed A, Umar M, Alraies MC; Validation: Yasmin F, Moeed A, Umar M; Visualization: Yasmin F, Moeed A, Umar M; Writing - original draft: Yasmin F, Moeed A, Umar M; Writing - review & editing: Zaidi F, Khan MS.

Keywords: Statins; Ezetimibe; Cardiovascular disease; Hydroxymethylglutaryl-CoA reductase inhibitors

INTRODUCTION

Statins are widely recognized as first-line therapies for managing dyslipidemia and reducing the risk of atherosclerotic cardiovascular (CV) events. These drugs lower cholesterol levels by inhibiting hydroxy-3-methylglutaryl-coenzyme A reductase, typically by 50% or more, thus preventing the formation of atherosclerotic plaques. Even in the most advanced stages of the disease, such as critical limb ischemia, statin therapy has been shown to improve 1-year mortality rates, reduce major adverse CV events, and increase amputation-free survival.[1-4]

Statins are categorized by their intensity, which reflects the degree to which they reduce low-density lipoprotein cholesterol (LDL-C) levels. High-intensity, moderate-intensity, and low-intensity statins are used clinically to reduce LDL-C levels by at least 50%, 30% to 50%, and less than 30%, respectively.[5-8] High-intensity statins are prescribed for patients at substantial risk of CV events and those with markedly elevated LDL-C levels.[9] Although statin therapy is generally well-tolerated and effective, it can occasionally cause mild muscle pain[10] or weakness and, in rare instances, rhabdomyolysis. Statins may also lead to mild elevations in liver enzymes.[11] Thus, regular monitoring of liver function is advised, especially during the initial months of treatment. Statins can also interact with certain medications, such as some antibiotics, antifungal drugs, and CV medications, affecting their metabolism. Less common side effects of statin therapy include gastrointestinal symptoms, memory or cognitive changes, and an increased risk of developing diabetes in some individuals. Given these potential side effects, it is crucial to maintain vigilant monitoring in clinical practice. Strategies such as administering low-dose therapies or employing alternative treatments, like combining recombinant therapy with medications such as ezetimibe, are important to achieve optimal outcomes in the management of dyslipidemia.

Statins are typically considered the first-line therapy for cholesterol management. However, when statin therapy alone or lifestyle modification proves insufficient for managing cholesterol levels, ezetimibe monotherapy is often the preferred alternative.[12,13] Ezetimibe can be administered either in combination with statins or as monotherapy to lower cholesterol levels by inhibiting the absorption of cholesterol.[12] Ezetimibe combination therapy is particularly beneficial for individuals who are susceptible to the side effects of statins, cannot tolerate higher doses of statins, or require additional LDL-C reduction. Clinical trials, such as the IMPROVE-IT trial, have evaluated the efficacy of ezetimibe and simvastatin combination therapy versus simvastatin alone in patients who have experienced acute coronary syndrome.[14] The study revealed that combination therapy led to a further reduction in LDL-C levels, resulting in a statistically significant decrease in CV events, including CV death, myocardial infarction, and stroke. Another trial, the Study of Heart and Renal Protection, investigated the effects of ezetimibe and simvastatin combination therapy in patients with chronic kidney disease. This trial demonstrated that the combination therapy significantly reduced major atherosclerotic events compared to placebo.[15] Furthermore, the Cholesterol Treatment Trialists' Collaboration, a large-scale meta-analysis, has shown that adding ezetimibe to statin therapy consistently improves CV outcomes compared to statin monotherapy, while also markedly lowering LDL-C levels.[16]

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Despite the recognized safety, efficacy, and key implications of recombinant treatment plans, a knowledge gap remains due to inconsistent reporting in the existing literature. This meta-analysis aims to assess the comparative safety and efficacy of low- or moderate-intensity statin and ezetimibe combination therapy versus high-intensity statin monotherapy. The goal is to confirm the reliability of the evidence, which will assist in guiding clinical decisions, personalizing treatment strategies, and shaping healthcare policies and guidelines.

METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[17] Cochrane,[18] and Assessing the Methodological Quality of Systematic Reviews-2 guidelines.[19] Institutional review board approval was not necessary for this study because the data utilized were publicly available.

1. Data sources and search strategy

A literature search was conducted of the PubMed, Embase, and Scopus databases, from inception through May 2023. Online resources such as www.clinicaltrials.gov and the China National Knowledge Infrastructure database were also searched to identify any grey literature. Two independent reviewers (FY and AM) conducted the literature search, abstract, and full-text review. Discrepancies in study selection were resolved by a third reviewer (SFZ). The reference lists of retrieved trials, reviews, editorials, and previous meta-analyses were manually screened to identify additional relevant articles. No restrictions were placed regarding time, language, year of publication, or country/institution of publication. The comprehensive literature search utilized the following keywords and their corresponding MeSH terms: "statins" OR "hydroxymethylglutaryl-CoA reductase inhibitors" OR "3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors" AND "ezetimibe." The detailed search strategy for each database is provided in **Supplementary Table 1**.

2. Study selection

All articles initially retrieved from the systematic search of the electronic databases were transferred to Endnote Reference Library (version X7.5; Clarivate Analytics, Philadelphia, PA, USA), in which duplicates were identified and removed. Two independent reviewers (FY and AM) then screened the remaining articles, initially by title and abstract, followed by a full-text evaluation. Any discrepancies between the reviewers were resolved through discussion with a third reviewer (SFZ). Articles were ultimately selected based on the following eligibility criteria: (a) the study was a randomized clinical trial; (b) it compared the administration of high-intensity statin versus low- or moderate-intensity statin with ezetimibe; (c) it included lipid parameters; and (d) it provided safety data. The outcomes of interest included changes in lipid concentrations, including LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TGs), as well as apolipoprotein (Apo) A1, Apo B, and high-sensitivity C-reactive protein (hs-CRP). To assess safety, we examined differences in the treatment-induced elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine phosphokinase (CK). Additionally, we compared major adverse cardiovascular events (MACE) between the two groups.

3. Data extraction and quality assessment

Two independent reviewers (FY and AM) extracted data from the selected articles. The following information was extracted from each study: (a) study name and year, (b) study

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design, (c) location of the study, (d) study duration, (e) number of patients in each group, (f) general patient characteristics (age, gender, body mass index, and comorbidities), and (g) all outcomes of interest. The same two independent reviewers (FY and AM) also conducted a quality assessment to evaluate the validity and reliability of the included studies. The methodological quality of the included randomized controlled trials (RCTs) was assessed using the Oxford scoring Jadad scale.[20] A Jadad score of 3 or higher indicates high quality according to the Oxford scale, which assesses bias across five domains: randomization, double-blind study design, appropriateness of the randomization scheme, appropriateness of the blinding scheme, and description of withdrawals.

4. Statistical analysis

This meta-analysis was conducted using Review Manager (RevMan) version 5.4 (Cochrane Collaboration). A random effects meta-analysis and the inverse variance method were used to calculate weighted mean differences (MDs) and their corresponding 95% confidence intervals (CIs) for continuous outcomes. The pooled results are presented as forest plots. To assess heterogeneity, the Higgins I^2 value was used.[21] An I^2 value of 25% to 50% was considered indicative of mild heterogeneity, 50% to 75% moderate heterogeneity, and >75% severe heterogeneity. Funnel plots were used to evaluate potential publication bias in outcomes, following Cochrane guidelines.[18] Outcomes with visible asymmetry on the funnel plot were further examined using Egger regression and the Begg test to confirm the risk of publication bias.[22] In all analyses, *p*-values of less than 0.05 were considered to indicate statistical significance.

RESULTS

A total of 6,860 articles were identified following the initial search. After deduplication and screening titles and abstracts, 187 articles were identified for full-text review. Articles were subsequently excluded if they involved incorrect statin dosages or were retrospective or prospective cohort studies. Ultimately, 20 articles were included in the quantitative synthesis. **Fig. 1** illustrates the study selection process. The 20 studies[23-42] included in this meta-analysis encompassed 5,412 patients, with a mean age of 60.5±12.1 years. Regarding quality assessment, most RCTs were deemed to be of high quality, with 11 trials scoring 3 or higher on the Jadad scale. Rosuvastatin was the high-dose statin used in eight studies, atorvastatin in seven, and simvastatin in five. Among the 20 clinical trials, four were crossover, 13 were parallel-group, two were double-blind, and one was open-label. The study characteristics are detailed in **Table 1**.

1. Meta-analysis of lipid parameters and hs-CRP

A total of 20 studies, encompassing 5,412 participants, measured LDL-C levels. Combination therapy, consisting of low- to moderate-intensity statin and ezetimibe, yielded a significantly greater reduction in LDL-C levels than high-intensity statin monotherapy (MD, −6.59; 95% CI, −10.95, −2.24; p=0.003; I^2=84%) (**Fig. 2**). The combination therapy significantly reduced LDL-C levels for secondary cardiovascular disease prevention vs. primary prevention upon subgroup analysis (MD, −9.61; 95% CI, −11.97, −7.25; p<0.00001; I^2=4%) (**Supplementary Fig. 1**). Fifteen studies evaluated changes in TC levels, finding no significant difference between the combination therapy and monotherapy groups (MD, 1.75; 95% CI, −6.49, 9.99; p=0.68; I^2=52%) (**Fig. 3**). Similarly, the groups exhibited no significant difference in TG levels (MD, 4.68; 95% CI, −4.97, 14.32; p=0.34; I^2=0%) (**Fig. 4**). Changes in HDL-C levels also did not differ significantly (MD, −0.49; 95% CI, −2.23, 1.24; p=0.58; I^2=0%) (**Fig. 5**). However,

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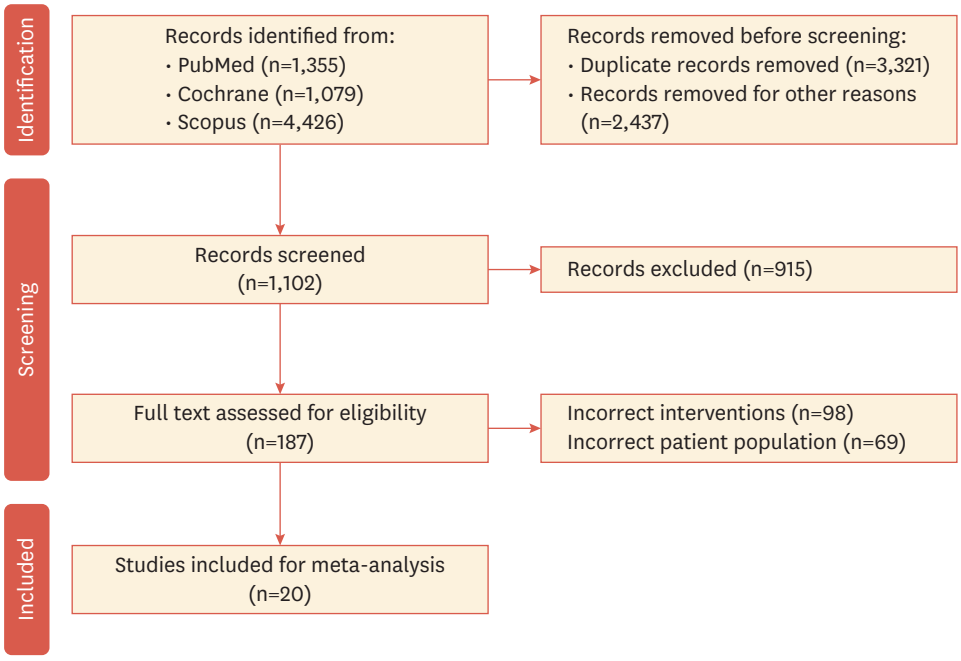

Fig. 1. PRISMA flowchart.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

changes in hs-CRP levels were significantly higher in the combination therapy group compared to the high-intensity statin monotherapy group (MD, 0.32; 95% CI, 0.01, 0.64; p=0.04; I^2=0%) (**Fig. 6**).

2. Meta-analysis of intervention safety

Regarding liver toxicity, no significant difference was observed in ALT levels (MD, 0.78; 95% CI, −0.73, 2.29; p=0.31; I^2=0%) (**Fig. 7A**). However, AST levels were significantly more elevated in the group receiving combination therapy (MD, 6.23; 95% CI, 0.65, 11.80; p=0.03; I^2=95%) (**Fig. 7B**). Regarding muscle-related toxicity, high-intensity statin monotherapy was associated with a significantly greater increase in CK levels (MD, −31.95; 95% CI, −50.69, −13.21; p=0.0008; I^2=72%) (**Fig. 8A**). No significant difference in MACE was noted between groups (risk ratio, 0.91; 95% CI, 0.74, 1.12; p=0.36; I^2=0%) (**Fig. 8B**).

3. Publication bias

The initial step involved generating funnel plots to assess the risk of publication bias. For outcomes displaying asymmetry, the Egger regression test was employed to confirm the presence of publication bias. The Egger test indicated significant publication bias for TC and TG, with two-tailed p-values of 0.021 and 0.033, respectively. The funnel plots can be found in the supplementary material (**Supplementary Figs. 2-4**).

DISCUSSION

This analysis indicates that combination therapy consisting of a low- to moderate-intensity statin with ezetimibe is significantly associated with lower LDL-C levels compared to high-intensity statin monotherapy. No significant differences were observed for TC, TGs, HDL-C, ALT, or MACE. However, AST and CK levels were significantly higher with monotherapy.

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Table 1. General characteristics of the included studies

Study	Design	Participants	Duration (mon)	Intervention drug and dosage (mg)	Sample size	Age (yr)	Male (%)	Diabetes (%)	HTN (%)	Smoker (%)	Jadad score
Kim et al.[23] (2022)	Open-label	Atherosclerotic cardiovascular disease	12	R* 20	1,886	64±10	75	37	68	16	3
				R10 + E† 10	1,894	64±10	75	37	66	17	
Qian et al.[24] (2022)	Double-blind	Uncontrolled hypercholesterolemia	3	A‡ 40	140	60.6±10.3	94 (67.1)	NR	66.4	NR	3
				A20 + E10	137	59.4±9.3	103 (75.2)		66.4		
Oh et al.[25] (2020)	Open-label, parallel	Acute coronary syndrome	6	R20	25	59.2±9.7	92.0	20.2	28.0	36.0	3
				R5 + E10	25	59.6±9.9	84.0	16.7	45.8	37.5	
Liu et al.[26] (2018)	Parallel	Coronary heart disease	2	A30	60	60±8.5	61.7	NA	58.3	46.7	2
				A20 + E10	60	60±8.7	66.7		55.0	48.3	
Wu et al.[27] (2018)	Open-label, parallel	Atherosclerotic cardiovascular disease	3	A40	50	57±8	72.0	NA	NA	NA	2
				A20 + E10	48	56±11	72.9				
Ran et al.[28] (2017)	Open-label, parallel	Non-ST elevation acute coronary syndrome	3	R20	41	60.5±10.0	73.2	26.8	48.8	53.7	3
				R10 + E10	42	60.4±8.2	76.2	26.2	50.0	54.8	
Yang et al.[29] (2017)	Double-blind, placebo-controlled	High cardiovascular risk	3	R20	39	62.7±9.6	66.7	56.4	61.9	17.9	3
				R10 + E10	38	64.8±8.2	55.3	36.8	71.1	18.4	
						62.1±9.5	65.0	42.5	60.5	10.0	
Japaridze et al.[34] (2016)	Open-label, parallel	Acute coronary syndrome	4	A40-80	146	62.62±11.03	53.1	1.4	NA	NA	2
				A20-40 + E10	146	62.21±11.36	54.1	4.8			
Pytel et al.[30] (2017)	Parallel	Coronary artery disease	6	R20	21	62±71	NA	NA	NA	NA	2
				A10 + E10	20						
Pytel et al.[31] (2016)	Parallel	Coronary artery disease	6	A40	6	63±7	NA	NA	NA	NA	2
				A10 + E10	9						
Villegas-Rivera et al.[32] (2015)	Double-blind, parallel	Type 2 diabetes	4	R20	25	54.0±10.5	48	100	NA	48	5
				S§ 20 + E10	25	55.0±12.0	40	100		32	
Deharo et al.[33] (2014)	Open-label, parallel	Acute coronary syndrome	1	R20	64	59.4±11.22	91	16	NA	45	2
				S40 + E10	64	58.4±10.9	86	26		55	
Moreira et al.[35] (2014)	Open-label, parallel	Dyslipidemia	3	R80	57	NA	NA	NA	NA	NA	2
				S40 + E10	55						
Westerink et al.[36] (2013)	Double-blind, crossover	Obesity with metabolic syndrome	1.5	S80	93	57±9	59	NA	NA	NA	3
				S10 + E10							
Araujo et al.[37] (2010)	Crossover	Hypercholesterolemia	1	S80	12	NA	NA	NA	NA	NA	2
				S10 + E10	11						
Hajer et al.[38] (2008)	Double-blind, crossover	Obesity with metabolic syndrome	1.5	S80	15	54±7	100	NA	NA	NA	3
				S10 + E10							
Ostad et al.[39] (2009)	Double-blind, parallel	Coronary artery disease	2	A80	24	66±9	79	25	88	17	3
				A10 + E10	25	64±10	76	16	68	32	
Olijhoek et al.[40] (2008)	Double-blind, crossover	Metabolic syndrome	1.5	S80	19	54±7	NA	NA	NA	NA	3
				S10 + E10							
Settergren et al.[41] (2008)	Double-blind, parallel	Type 2 diabetes or coronary artery disease	1.5	S80	20	70	75	85	NA	20	5
				S10 + E10	19	74	58	100		21	
Piorkowski et al.[42] (2007)	Parallel	Coronary artery disease	1	A40	25	61.4±1.8	76.9	15.4	NA	69.2	2
				A10 + E10	26	62.0±2.1	88.0	28.0		64.0	

Values are presented as mean ± standard deviation or number (%).
HTN, hypertension; NR, no response; NA, not applicable.
*Rosuvastatin; †Ezetimibe; ‡Atorvastatin; §Simvastatin.

Since LDL-C is significantly associated with an increased risk of CV diseases and mortality, reducing plasma levels is the primary goal in the management of dyslipidemia.[43,44] Our analysis suggests that combining ezetimibe with a low- to moderate-intensity statin can yield beneficial outcomes in lowering LDL-C, compared to using a high-intensity statin alone . This finding aligns with a previous meta-analysis by Ah et al.,[45] which included 1,539 patients and demonstrated a significant reduction in LDL-C levels with combination therapy versus monotherapy (standard error, 0.307; 95% CI, 0.153, 0.462).[45] Ezetimibe alone has been shown to decrease LDL-C levels by 13% to 20%, and when combined with a statin, it provides incremental lipid-lowering effects through a complementary mechanism of action.[46] Our

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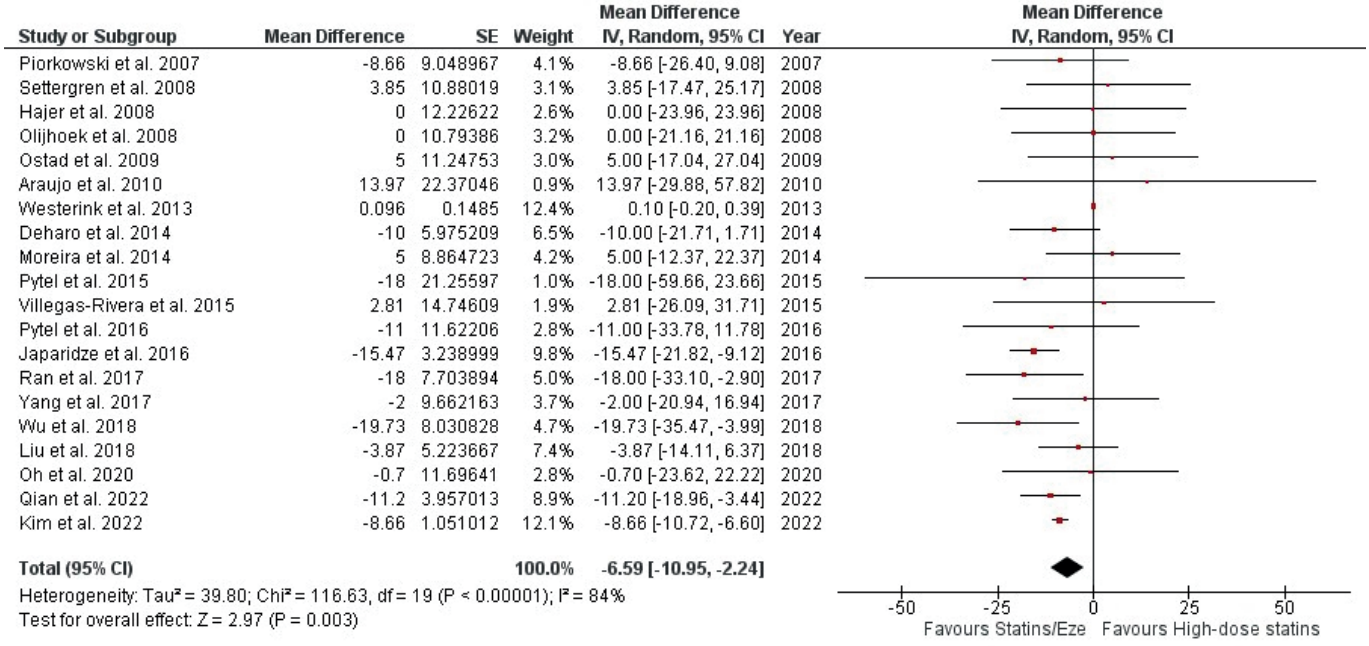

Fig. 2. Forest plot of changes in LDL-C levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe; LDL-C, low-density lipoprotein cholesterol.

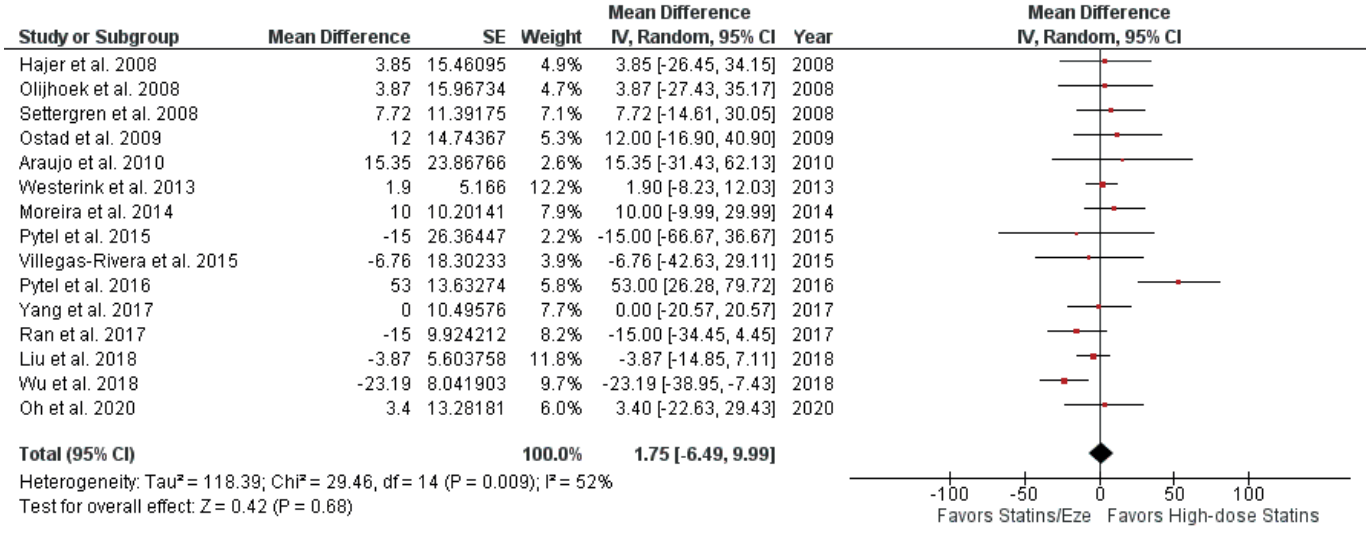

Fig. 3. Forest plot of changes in total cholesterol levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe.

meta-analysis revealed no significant differences in TC, TG, or HDL-C levels. However, the meta-analysis by Ah et al.[45] did report significantly lower levels of TC and TG with ezetimibe combination therapy compared to monotherapy.

Our analysis corroborates the findings of the previous meta-analysis by Ah et al.[45] regarding the safety and adverse events of both therapies. Combination statin and ezetimibe therapy was significantly associated with a greater increase in AST levels compared to monotherapy. This contradicts the meta-analysis by Ah et al.,[45] as our analysis included more studies and a larger patient population. A possible explanation for this could be that the cumulative

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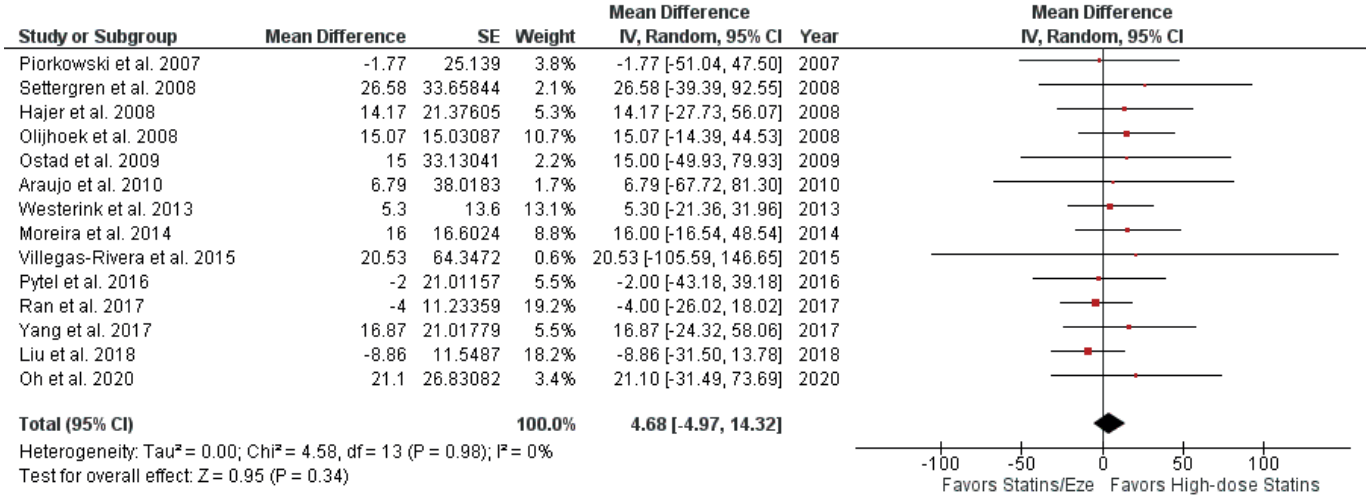

Fig. 4. Forest plot of changes in triglyceride levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe.

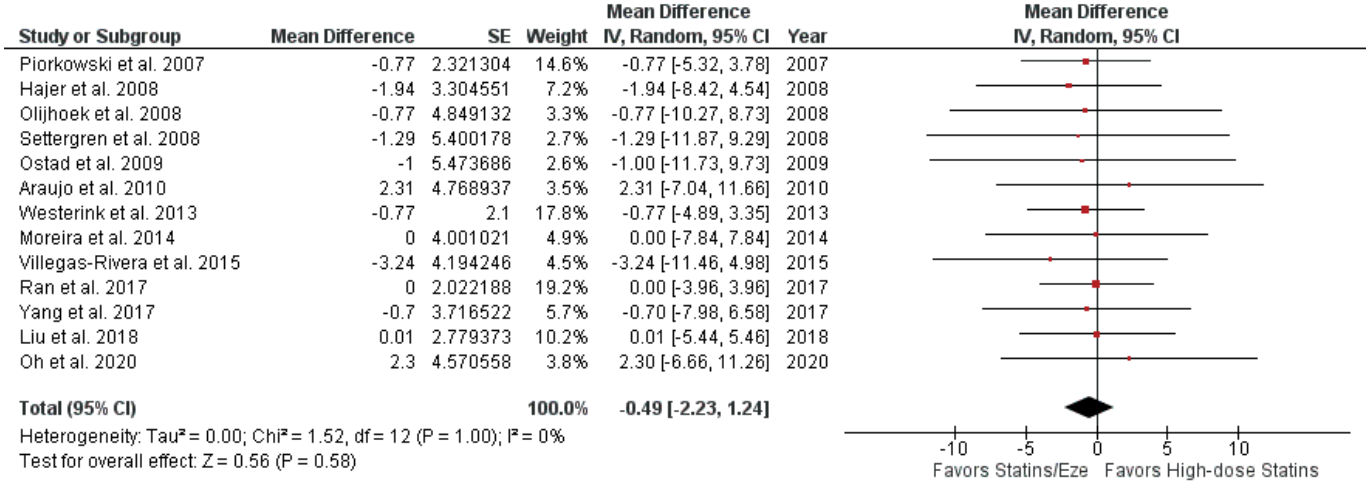

Fig. 5. Forest plot of changes in HDL-C levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe; HDL-C, high-density lipoprotein cholesterol.

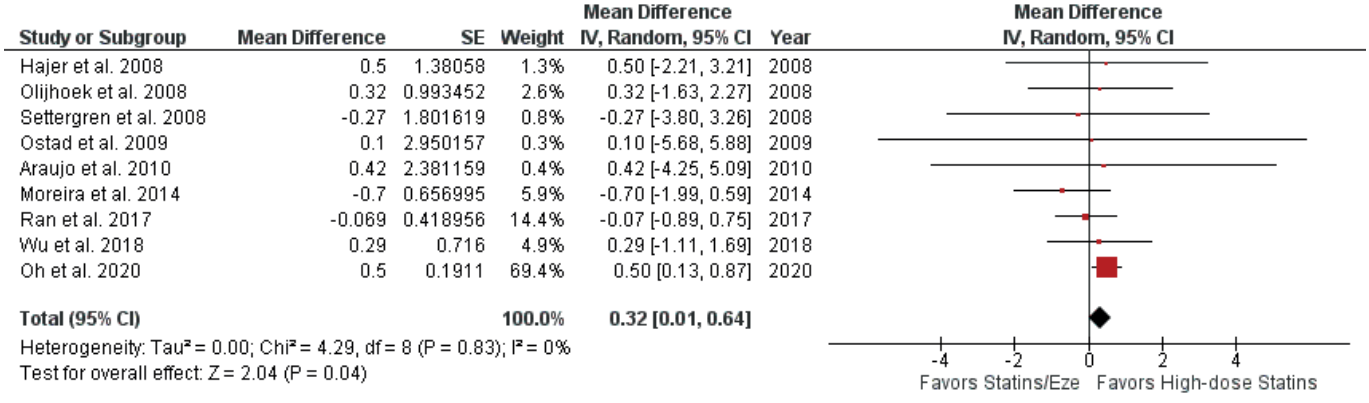

Fig. 6. Forest plot of changes in hs-CRP levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe; hs-CRP, high-sensitivity C-reactive protein.

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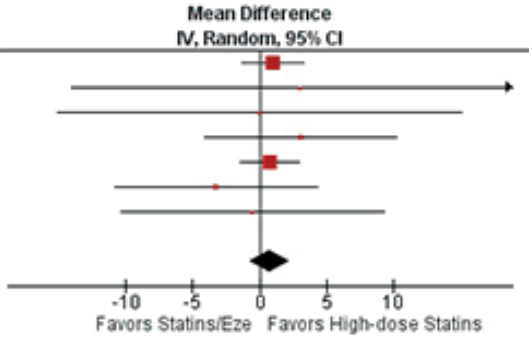
A

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Year
Piorkowski et al. 2007	1	1.19446	41.5%	1.00 [-1.34, 3.34]	2007
Hajer et al. 2008	3	8.698659	0.8%	3.00 [-14.05, 20.05]	2008
Olijhoek et al. 2008	0	7.694838	1.0%	0.00 [-15.08, 15.08]	2008
Deharo et al. 2014	3.1	3.679907	4.4%	3.10 [-4.11, 10.31]	2014
Villegas-Rivera et al. 2015	0.75	1.133111	46.1%	0.75 [-1.47, 2.97]	2015
Ran et al. 2017	-3.253	3.884249	3.9%	-3.25 [-10.87, 4.36]	2017
Wu et al. 2018	-0.54	5.009431	2.4%	-0.54 [-10.36, 9.28]	2018
Total (95% CI)			**100.0%**	**0.78 [-0.73, 2.29]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 6 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



B

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Year
Piorkowski et al. 2007	-1.6	0.660356	19.2%	-1.60 [-2.89, -0.31]	2007
Hajer et al. 2008	0	4.472136	13.1%	0.00 [-8.77, 8.77]	2008
Olijhoek et al. 2008	4	4.358899	13.3%	4.00 [-4.54, 12.54]	2008
Deharo et al. 2014	76.8	8.450573	7.2%	76.80 [60.24, 93.36]	2014
Villegas-Rivera et al. 2015	3.57	0.701946	19.2%	3.57 [2.19, 4.95]	2015
Ran et al. 2017	-0.421	3.700607	14.6%	-0.42 [-7.67, 6.83]	2017
Wu et al. 2018	-0.91	4.404704	13.3%	-0.91 [-9.54, 7.72]	2018
Total (95% CI)			**100.0%**	**6.23 [0.65, 11.80]**	

Heterogeneity: Tau² = 41.58; Chi² = 110.21, df = 6 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.19 (P = 0.03)

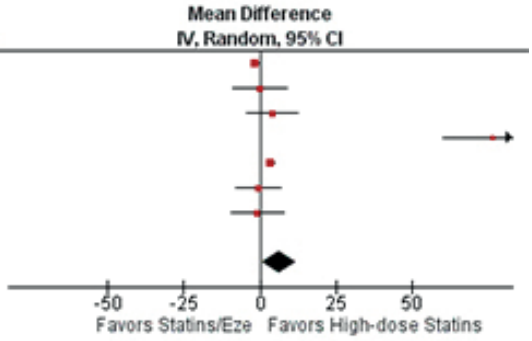
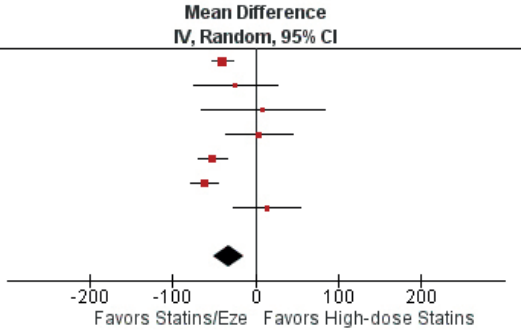


Fig. 7. Forest plot of changes in ALT and AST levels.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

A

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Random, 95% CI	Year
Piorkowski et al. 2007	-40	6.345233	22.3%	-40.00 [-52.44, -27.56]	2007
Hajer et al. 2008	-24	26.15339	8.7%	-24.00 [-75.26, 27.26]	2008
Olijhoek et al. 2008	9	38.43176	5.0%	9.00 [-66.32, 84.32]	2008
Deharo et al. 2014	4.2	20.81539	11.4%	4.20 [-36.60, 45.00]	2014
Villegas-Rivera et al. 2015	-51.89	8.598357	20.6%	-51.89 [-68.74, -35.04]	2015
Ran et al. 2017	-62.147	8.556174	20.6%	-62.15 [-78.92, -45.38]	2017
Wu et al. 2018	14.26	20.67763	11.5%	14.26 [-26.27, 54.79]	2018
Total (95% CI)			**100.0%**	**-31.95 [-50.69, -13.21]**	

Heterogeneity: Tau² = 370.00; Chi² = 21.47, df = 6 (P = 0.002); I² = 72%
Test for overall effect: Z = 3.34 (P = 0.0008)



B

Study or Subgroup	Statins/Eze Events	Statins/Eze Total	High-dose Statins Events	High-dose Statins Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ran et al. 2017	2	42	4	41	1.6%	0.49 [0.09, 2.52]	2017
Kim et al. 2022	153	1894	167	1886	98.0%	0.91 [0.74, 1.13]	2022
Qian et al. 2022	1	137	0	140	0.4%	3.07 [0.13, 74.60]	2022
Total (95% CI)		**2073**		**2067**	**100.0%**	**0.91 [0.74, 1.12]**	
Total events	156		171				

Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

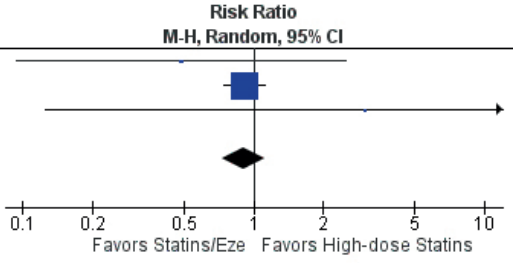


Fig. 8. Forest plot of creatine kinase levels and major adverse cardiovascular events.
SE, standard error; IV, inverse variance; CI, confidence interval; Eze, ezetimibe.

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hepatotoxic effect of statins and ezetimibe, even at lower statin doses, may exceed that of high-intensity statin monotherapy. This additive effect could account for the greater increase observed in AST levels. Furthermore, ezetimibe acts by inhibiting cholesterol absorption in the small intestine,[12] increasing reliance on the liver for cholesterol production. When used with statins, which also inhibit cholesterol synthesis, this combined action may increase the liver's metabolic workload, potentially raising AST levels as an indicator of liver stress or damage. High-intensity statin monotherapy was significantly associated with a greater increase in CK level; however, no significant difference in ALT level was observed between the two therapies. Several studies have indicated that ezetimibe is a safe and well-tolerated medication with minimal side effects.[47] During pre-marketing clinical trials, muscle pain was reported in 2% of cases with ezetimibe alone and ranged from 3.2% to 4.5% when combined with a statin. Previous research has shown a prevalence of 1.3% to 1.4% for liver damage and 0.1% to 0.2% for rhabdomyolysis, a serious condition, with combination therapy.[48] Adverse events associated with combination therapy have been linked to the use of high doses of statins.[49,50] Therefore, our analysis supports the preference for low- to moderate-intensity statins in combination with ezetimibe over high-intensity statin monotherapy in terms of safety and the risk of adverse events.

When evaluating the effect of both therapies on hs-CRP levels, our analysis corroborated the findings of Ah et al.[45]; combination therapy had a more pronounced effect than high-intensity monotherapy. Hs-CRP is an established predictor of CV risk and represents an indicator of inflammation in atherosclerosis, as supported by multiple studies.[51,52] In research conducted by Kinlay,[53] a significant positive correlation was observed between CRP and LDL-C levels, a relationship also evident in our findings. Additionally, when pooling data from three studies, no significant difference was detected in MACE between the two therapeutic approaches. Further research with longer follow-up periods is warranted to evaluate the incidence of MACE following combination therapy versus monotherapy with statins. Notably, a meta-analysis conducted by Hong et al.[54] demonstrated that ezetimibe was associated with a lower risk of MACE in patients with diabetes compared to those without the condition (p=0.012). Hence, evaluating this outcome in different patient populations would be beneficial.

In subgroup analysis based on the type of statin used for monotherapy, combination therapy significantly reduced LDL-C levels compared to monotherapy with rosuvastatin and atorvastatin. However, when comparing combination therapy to simvastatin monotherapy, no significant differences were observed. Notably, studies that used simvastatin as monotherapy administered 80 mg to participants, whereas only 10 mg was used in combination with ezetimibe. Stender et al.[55] reported that 10 mg of rosuvastatin was more effective at lowering LDL-C than 20 mg of simvastatin. Supplementary findings from the STELLAR trial showed that between 53% and 80% of patients who received rosuvastatin at doses ranging from 10 to 40 mg achieved LDL-C levels below 100 mg/dL. In comparison, the corresponding percentages for patients taking atorvastatin ranged from 18% to 70%, while for those on simvastatin, the range was a lower 8% to 53%.[56] Therefore, simvastatin at lower doses appears less potent than other statins in terms of lowering LDL-C levels. Consequently, using only 10 mg of simvastatin in combination with ezetimibe may not be as effective as monotherapy, as indicated by our subgroup analysis.

This meta-analysis, like any other, has limitations that warrant discussion. First, most of the included studies reported outcomes over short follow-up periods, underscoring the need for evaluation of these results over longer durations. Second, some variability in outcomes

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regarding safety or effectiveness is possible when considered on an individual patient basis. Despite these limitations, our results are meaningful as they present clinical evidence suggesting that a combination of low- to moderate-intensity statins with ezetimibe is a more advantageous pharmacotherapeutic option than high-intensity statin monotherapy for patients with dyslipidemia.

CONCLUSION

This comprehensive study demonstrates that combining low- to moderate-intensity statin therapy with ezetimibe yielded superior improvements in LDL-C levels compared to high-intensity statin monotherapy. Furthermore, while statin monotherapy was associated with a greater increase in CK levels, combination therapy with statin and ezetimibe was linked to a higher increase in AST levels. Thus, we recommend adopting the treatment regimen of low- to moderate-intensity statin therapy with ezetimibe rather than increasing the statin dosage.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Detailed search strategy used in each database

Supplementary Fig. 1
Changes in LDL-C levels for primary vs. secondary prevention of cardiovascular disease.

Supplementary Fig. 2
Funnel plot of LDL-C.

Supplementary Fig. 3
Funnel plot of total cholesterol.

Supplementary Fig. 4
Funnel plot of triglycerides.

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