

# The impact of statin-ezetimibe combination therapy versus statin monotherapy on coronary plaque regression in patients with acute coronary syndrome: a meta-analysis

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## Abstract

**Objective:** To investigate the effects of statin monotherapy and statin-ezetimibe combination therapy on coronary plaque regression in acute coronary syndrome patients.

**Methods:** The systematic review was conducted from July to September 2022 and comprised search on PubMed, ScienceDirect and Cochrane databases to identify studies from January 2010 to July 2022 assessing the effects of statin-ezetimibe combination therapy versus statin monotherapy on coronary plaque regression in patients with acute coronary syndrome. The outcomes of interest were total atheroma volume, plaque volume, and percent atheroma volume assessed by intravascular ultrasound. Meta-analyses were performed on the studies, and mean differences with 95% confidence interval were estimated using Review Manager v5.4.

**Results:** Of the 730 studies identified, 12(1.64%) were shortlisted, and, of them, 5(41.7%) were analysed in detail. There were a total of 557 patients with a mean follow-up of  $9 \pm 2.43$  months. The difference between baseline and follow-up showed significant lowering in total atheroma volume, plaque volume, and percent atheroma volume ( $p < 0.05$ ) in the patients who were receiving statin-ezetimibe combination therapy.

**Conclusion:** Adding ezetimibe to statin medication was found to be significantly more successful in reducing coronary plaque than statin monotherapy.

**Key Words:** Ezetimibe, Plaque, Atherosclerotic, Hydroxy, Coronary, Ultrasonography, Interventional. (JPMA 74: S-23; 2024) DOI: <https://doi.org/10.47391/JPMA.S6-ACSA-05>

## Introduction

Major adverse cardiovascular events can occur in people with acute coronary syndrome (ACS) if their low-density lipoprotein (LDL) cholesterol levels are high. However, statin-assisted LDL reduction can lower LDL and enhance clinical outcomes. Several randomised clinical investigations have proven this.<sup>1-3</sup> Additionally, research has indicated that compared to moderate lipid-lowering medication, intensive lipid-lowering therapy considerably lowers the risk of coronary events.<sup>4-5</sup> Numerous studies using intravascular ultrasonography (IVUS) have amply illustrated the advantages of statin therapy, which has been strongly linked to the regression of coronary plaque.<sup>6-8</sup>

IVUS is a diagnostic technique that analyses blood vessels in three-dimension (3D) images and offer details regarding lesion features, such as the degree of calcification and the presence of lipid-rich plaques.<sup>9,10</sup> For the stability of brittle plaque and improvement of long-

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term clinical outcomes in ACS patients, statin treatment has been recommended.<sup>11,12</sup> According to research, statins may reduce total atheroma volume (TAV), plaque volume (PV) and percent atheroma volume (PAV).<sup>13-16</sup>

There is presently insufficient proof that using high-dose statin therapy along with non-statin drugs, like ezetimibe, can more effectively lower the risks, particularly in the case of coronary plaque regression. The current systematic review was planned to compare the effects of statin monotherapy with statin-ezetimibe combination therapy on coronary plaque regression in individuals with ACS.

## Materials and Methods

The systematic review was conducted from July to September 2022 and comprised search on PubMed, ScienceDirect and Cochrane databases to identify studies from January 2010 to July 2022 assessing the effects of statin-ezetimibe combination therapy versus statin monotherapy on coronary plaque regression in patients with acute coronary syndrome. The systematic review and meta-analysis protocol was registered with the International prospective register of systematic reviews PROSPERO link: <https://www.crd.york.ac.uk/prospero/#searchadvanced>

(CRD42022372515), and the review was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist.<sup>17</sup>

Data search covered prospective and retrospective observational studies assessing the effects of statin monotherapy and statin-ezetimibe combo treatment on the reversal or regression of coronary plaque in ACS patients. The key search terms included "statin", "ezetimibe" and "plaque".

After removing duplicate entries, a researcher independently reviewed titles and abstracts, followed by full-text review. The studies that compared the results of statin-ezetimibe combination therapy with statin monotherapy in the treatment of coronary plaque regression in patients with ACS, and published in the English language were included. The final selection was done with consensus among the researchers.

The outcomes of interest was coronary plaque regression measured through TAV, PV and PAV using IVUS.

Baseline parameters and IVUS data of the studies selected were retrieved And included sample size, age, gender,

comorbidities (hypertension, diabetes mellitus [DM], smoking status, dyslipidaemia), and follow-up duration. Newcastle-Ottawa Scale (NOS) for observational studies was used for quality assessment of the included studies.<sup>17</sup> The quality of investigation was rated as poor (5 points), moderate (5-7 points), or good (>7 points). This was done with consensus among the researchers.

The Mantel-Haenszel fixed-effects models using mean difference (MD) as the effect measure and the corresponding 95% confidence interval (CI) were used to pool the data. The Higgins I<sup>2</sup> statistic was used to gauge statistical heterogeneity between the groups, with I<sup>2</sup>=0 indicating no heterogeneity, and I<sup>2</sup> >50% indicating substantial heterogeneity. Funnel plot asymmetry was used to identify publication bias. For all analyses, Review Manager 5.4.1 was employed. Two-sided p<0.05 was considered statistically significant.

## Results

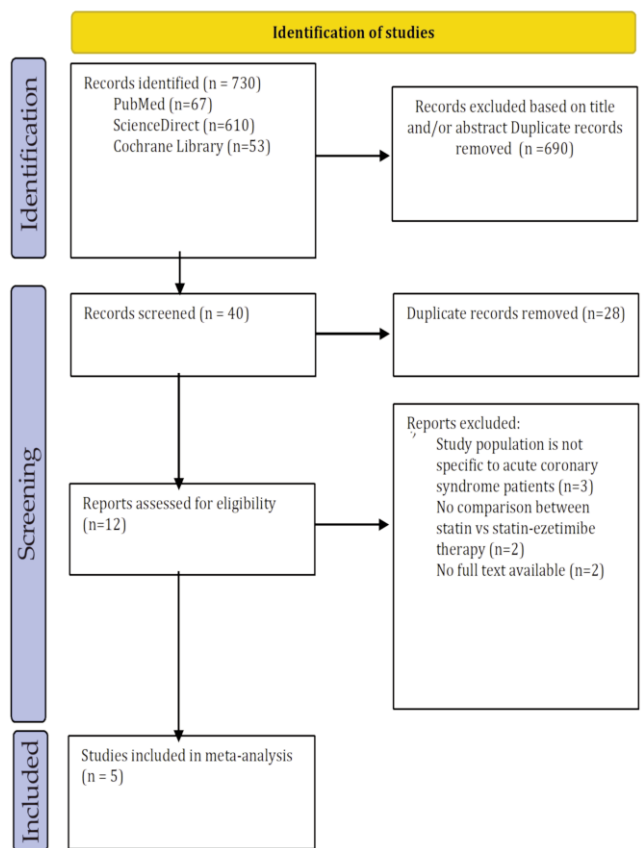
Of the 730 studies identified, 12(1.64%) were shortlisted for full-text review, and, of them, 5(41.7%) were analysed in detail<sup>18-22</sup> (Figure 1). There were a total of 557; patients, 280(50.3%) receiving statin monotherapy and 277(49.7%)

**Table-1:** Main characteristics of the studies reviewed.

Study, year / Country	Patients	Mean Age (years)	Male (%)	Hypertension (%)	DM (%)	Smoking (%)	Dyslipidaemia (%)	Follow-up (month)
	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe	Statin/Statin + Ezetimibe
Hougaard, 2016 <sup>18</sup> / Denmark	44/43	57.2/55.3	81.8/90.7	18.2/16.3	2.3/2.3	52.3/58.1	68.2/74.4	12 (±3,5)
Nakajima, 2014 <sup>19</sup> / Japan	45/50	60.7/63.7	84.4/80	68.9/70	40/32	68.9/64	NA/NA	6 (±0,8)
Lee, 2016 <sup>20</sup> / South Korea	36/34	59.3/60.9	75/79.4	58.3/50	25/32.4	50/44.1	NA/NA	3(±0,3)
Tsujita, 2015 <sup>21</sup> / Japan	102/100	67/66	78/78	66/75	26/25	32/20	69/72	12(±4,1)
Hibi, 2018 <sup>22</sup> / Japan	53/50	63/63	77/82	64/46	21/20	38/44	NA/NA	12(±2,3)

**Table-2:** Newcastle-Ottawa Scale (NOS) scores of the studies reviewed.

Item	Hougaard 2016	Nakajima 2014	Lee 2016	Tsujita 2015	Hibi 2018
<b>Selection</b>					
Exposed truly representative of average Selection					
Exposed truly representative of average Selection of non-exposed from the same community		X	X	X	X
Exposure ascertained by secure record or interview	X	X	X	X	X
Demonstration of outcome of interest not present at the start of the study	X	X	X		X
<b>Comparability</b>					
Study controls for other variables	X	X	X	X	X
<b>Outcome</b>					
Follow up long enough for outcome to occur	X	X	X	X	X
Complete follow up of all subjects accounted for	X	X	X	X	X
Subject lost to follow up unlikely to introduce bias	X		X	X	
<b>Score</b>	7	6	7	6	6



**Figure-1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

receiving statin-ezetimibe combination therapy. The mean follow-up period of the studies was  $9 \pm 2.43$  months (Table 1).

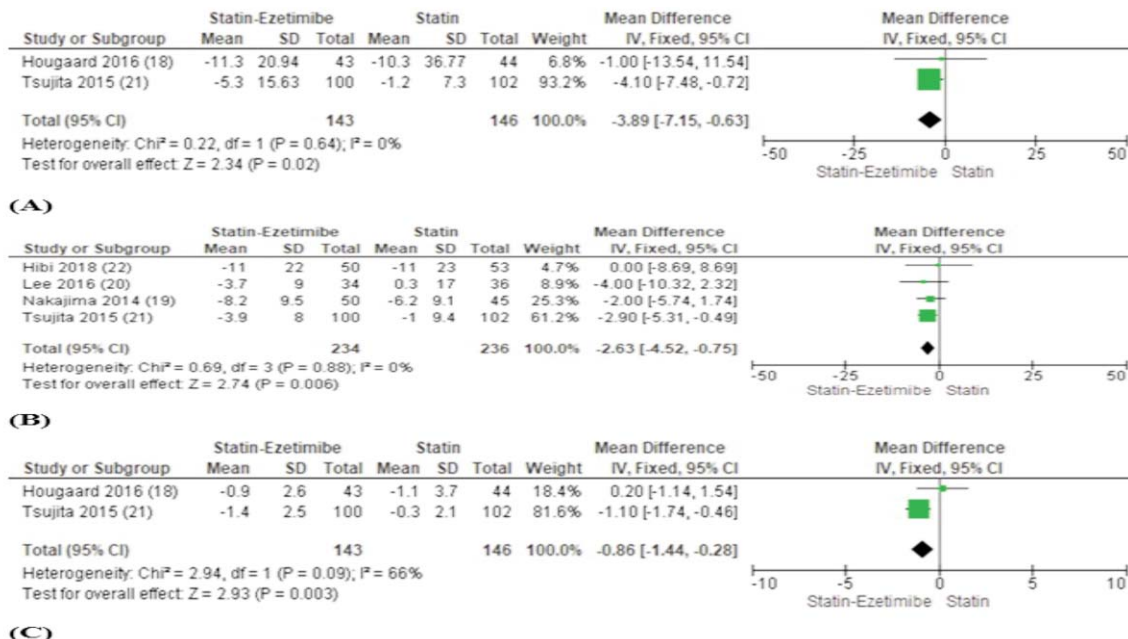
The overall risk of bias in observational was moderate (Table 2).

After the follow-up, there was significant lowering of TAV ( $p=0.02$ ; MD  $-3.89\text{mm}^3$ , 95% CI:  $-7.15--0.63$ ,  $I^2=0\%$ ), PV ( $p=0.006$ ; MD  $-2.63\text{mm}^3$ , 95%CI:  $-4.52--0.75$ ,  $I^2=0\%$ ) and PAV ( $p=0.003$ ; MD  $-0.86\%$ , 95%CI:  $-1.44--0.28$ ,  $I^2=66\%$ ) (Figures 2-3) in those taking combined statin-ezetimibe medication compared to those on statin monotherapy.

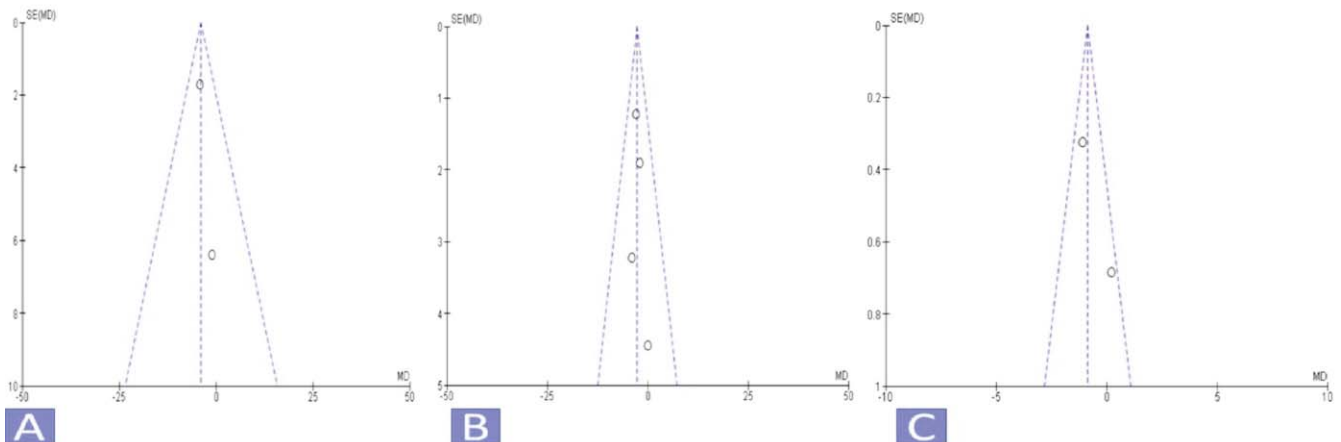
**Discussion**

In ACS patients, statin-ezetimibe combination treatment effectively lowered PV, TAV and PAV as measured by IVUS. Statins lower cholesterol, and also stabilise atherosclerotic plaque, lessen oxidative stress, enhance endothelial function, lessen vascular inflammation, and hasten blood vessel repair after stent insertion.<sup>23</sup> Prior grayscale IVUS studies showed a relationship between statin usage and reversal of coronary artery atherosclerotic plaque.<sup>6-8</sup> Ezetimibe is a non-statin medication that prevents the gut from absorbing cholesterol and reduces the amount of cholesterol absorbed by 54% to 65%.<sup>24</sup>

Ezetimibe-statin combination reduces LDL levels by approximately 18% more than statin monotherapy



**Figure-2:** Forest plot showing total atheroma volume (TAV) (A), plaque volume (PV) (B) and percent atheroma volume (PAV) (C) in acute coronary syndrome (ACS) patients on statin-ezetimibe therapy compared to those on statin monotherapy.



**Figure-3:** Funnel plot showing total atheroma volume (TAV) (A), plaque volume (PV) (B) and percent atheroma volume (PAV) in acute coronary syndrome (ACS) patients on statin-ezetimibe therapy compared to those on statin monotherapy.

because it prevents both cholesterol absorption and production in the intestinal tract.<sup>25</sup> In a study, ezetimibe was added to high-dose statin therapy, and cardiovascular events were significantly reduced.<sup>26</sup> The finding suggests that non-statin drugs that lower lipids may also prevent atherosclerosis.<sup>5</sup> According to a study, using ezetimibe in addition to a statin for 12 months caused a substantial 25% larger relative decrease in LDL and plaque regression than taking a statin alone.<sup>18</sup> Similar results were reported by Nakajima, et al.<sup>19</sup>

In a recent multicentre, randomised, controlled trial, patients who had percutaneous coronary intervention (PCI) were evaluated between the effects of ezetimibe with atorvastatin and atorvastatin monotherapy. It showed that there was a considerably lower PAV (-1.4%), a significantly lower PV (-3.9mm<sup>3</sup>), and a significantly lower TAV (-5.3mm<sup>3</sup>) throughout the follow-up period of 9–12 months.<sup>20</sup> The current review also found similar reductions.

The association between lower LDL levels and regressed coronary plaque was also supported by a trial in which participants with plaque regression had significantly lower LDL values than those with plaque progression.<sup>20</sup> The inhibition of the compensatory augmentation of cholesterol absorption was another plausible element that contributed to the therapeutic effect of dual lipid lowering. When mortality rose, the cholestanol-to-cholesterol ratio, a measure of cholesterol absorption, rose as well in a study.<sup>25</sup>

By demonstrating the inhibitory effect of ezetimibe in conjunction with statin-induced accelerated cholesterol absorption markers, the current review demonstrated a strong correlation between the reversal of coronary

plaque and the suppression of indicators of cholesterol absorption. The use of ezetimibe and fluvastatin to stabilise plaque was also supported by an earlier optical coherence tomography analysis which found a smaller fibrous cap that protected lipid-rich plaque in those receiving fluvastatin monotherapy rather than dual cholesterol-lowering therapy.<sup>25</sup>

The current systematic review has limitations as each study used different types of statins with different doses, and had different follow-up periods. This could have affected the final outcome.

## Conclusion

When combined with statin medication, ezetimibe significantly reduced PV, TAV and PAV compared to statin monotherapy as assessed by IVUS.

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