RESEARCH PAPER

Comparative efficacy of Statin Monotherapy, Statin–Ezetimibe Dual Therapy, and Statin–Ezetimibe–Bempedoic Acid Triple Therapy in patients with Acute Coronary Syndrome: A Prospective comparative study

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ABSTRACT

Background: Patients with acute coronary syndrome (ACS) remain at very high risk for recurrent cardiovascular events despite contemporary therapy. Current guidelines recommend aggressive low-density lipoprotein cholesterol (LDL-C) reduction following ACS. Although statins remain the cornerstone of lipid-lowering therapy, many patients fail to achieve recommended LDL-C targets with statin monotherapy. Ezetimibe and bempedoic acid provide additional LDL-C lowering through complementary mechanisms and may improve target attainment in high-risk patients.

Objectives: To compare the efficacy of statin monotherapy, statin plus ezetimibe therapy, and statin plus ezetimibe plus bempedoic acid therapy in reducing LDL-C levels and achieving guideline-recommended LDL-C targets among patients with ACS.

Methods: This prospective comparative study was conducted in 300 patients with ACS between July 2024 and March 2026. Eligible patients with elevated LDL-C levels and no prior lipid-lowering therapy were allocated into three treatment groups: statin monotherapy (n=100), statin plus ezetimibe (n=100), and statin plus ezetimibe plus bempedoic acid (n=100). LDL-C levels were assessed at baseline, 1 month, and 3 months. The primary outcome was percentage reduction in LDL-C levels. Secondary outcomes included absolute LDL-C reduction and achievement of LDL-C target <55 mg/dL.

Results: All treatment groups demonstrated significant reductions in LDL-C levels during follow-up. At 3 months, mean LDL-C levels decreased to 53.0 ± 16.6 mg/dL in the statin monotherapy group, 44.8 ± 14.2 mg/dL in the statin plus ezetimibe group, and 36.6 ± 16.1 mg/dL in the triple therapy group. Percentage LDL-C reductions were 52.0%, 60.6%, and 75.7%, respectively. LDL-C target attainment (<55 mg/dL) at 3 months was achieved in 64.2% of patients receiving statin monotherapy, 80.7% receiving statin plus ezetimibe, and 90.9% receiving triple therapy. Intergroup differences were statistically significant (ANOVA F=23.43, p<0.001).

Conclusion: Triple therapy consisting of a statin, ezetimibe, and bempedoic acid achieved significantly greater LDL-C reduction and superior LDL-C target attainment compared with statin monotherapy or statin–ezetimibe dual therapy in patients with ACS. Early intensive combination lipid-lowering therapy may represent an effective strategy for achieving guideline-recommended LDL-C goals in very high-risk patients.

Keywords: Acute coronary syndrome; LDL cholesterol; Statins; Ezetimibe; Bempedoic acid; Combination lipid-lowering therapy...

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INTRODUCTION

Acute coronary syndrome (ACS) remains a major cause of morbidity and mortality worldwide despite significant

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advances in revascularization techniques, antithrombotic therapy, and secondary prevention strategies. Cardiovascular disease continues to account for a substantial proportion of global deaths, and patients surviving an ACS event remain at high risk for recurrent myocardial infarction, stroke, repeat revascularization, heart failure, and cardiovascular mortality[1-3]. Consequently, optimization of modifiable cardiovascular risk factors has become a cornerstone of contemporary ACS management.

Among the various cardiovascular risk factors, low-density lipoprotein cholesterol (LDL-C) plays a central role in the initiation, progression, and clinical manifestations of atherosclerotic cardiovascular disease (ASCVD). Extensive evidence from epidemiological studies, genetic investigations, Mendelian randomization analyses, and randomized clinical trials has established a causal relationship between LDL-C exposure and cardiovascular risk[4]. Elevated LDL-C promotes cholesterol deposition within the arterial wall, triggering endothelial dysfunction, inflammation, plaque formation, and ultimately plaque rupture leading to acute coronary events[1,5].

Based on this evidence, contemporary lipid management guidelines emphasize aggressive LDL-C lowering in patients with ACS. The 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines classify ACS patients as very high-risk and recommend at least a 50% reduction in LDL-C from baseline together with achievement of LDL-C levels below 55 mg/dL[6]. Similarly, the 2018 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines advocate initiation of high-intensity statin therapy in all eligible ACS patients and recommend escalation to combination lipid-lowering therapy when LDL-C targets are not achieved[7].

High-intensity statins remain the foundation of lipid-lowering therapy following ACS. Landmark trials such as MIRACL and PROVE-IT TIMI-22 demonstrated that early intensive statin therapy significantly reduces recurrent ischemic events and improves cardiovascular outcomes in patients with ACS[8,9]. However, despite widespread statin use, a considerable proportion of patients fail to achieve recommended LDL-C targets. Data from contemporary registries such as EUROASPIRE V and the DA VINCI study have highlighted substantial gaps in LDL-C target attainment among high-risk cardiovascular patients receiving routine lipid-lowering therapy[10,11].

More recently, bempedoic acid has emerged as a novel oral lipid-lowering agent for patients requiring additional LDL-C reduction. Bempedoic acid inhibits adenosine triphosphate citrate lyase, an enzyme involved in hepatic cholesterol biosynthesis upstream of HMG-CoA reductase[12]. Because of its distinct mechanism of action, bempedoic acid produces additive LDL-C lowering when combined with statins and ezetimibe.

The need for effective lipid-lowering strategies is particularly relevant in India. South Asians exhibit a disproportionately high burden of premature coronary artery disease, diabetes mellitus, metabolic syndrome, and atherogenic dyslipidemia characterized by elevated triglycerides, reduced high-density lipoprotein cholesterol, and increased prevalence of small dense LDL particles[13-15]. Although substantial evidence supports the individual efficacy of statins, ezetimibe, and bempedoic acid, prospective comparative data evaluating statin monotherapy, statin–ezetimibe dual therapy, and statin–ezetimibe–bempedoic acid triple therapy in patients with ACS remain limited, particularly in the Indian population. Therefore, the present study was undertaken to compare the efficacy of statin monotherapy, statin plus ezetimibe therapy, and statin plus ezetimibe plus bempedoic acid therapy in achieving LDL-C reduction and guideline-recommended LDL-C targets among patients with acute coronary syndrome.

MATERIALS AND METHODS

This single-center prospective comparative study was conducted in the Department of Cardiology at a tertiary care teaching hospital in India. The study was conducted between July 1, 2024 and March 31, 2026. Patients presenting to the outpatient department, inpatient department, coronary care unit, or emergency services with a diagnosis of ACS were screened for eligibility. ACS included ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina.

Patients with elevated low-density lipoprotein cholesterol (LDL-C) levels who fulfilled the eligibility criteria and provided written informed consent were enrolled consecutively.

Inclusion criteria:

Age ≥18 years.

Diagnosis of acute coronary syndrome (STEMI, NSTEMI, or unstable angina).

Elevated LDL-C levels at baseline evaluation.

No prior exposure to lipid-lowering therapy.

Willingness to provide written informed consent.

Exclusion criteria:

Known myopathy or myositis.

Previous intolerance or hypersensitivity to lipid-lowering therapy.

Current treatment with statins or other lipid-lowering agents before enrollment.

Severe systemic illness likely to interfere with study participation or follow-up.

Refusal or inability to provide informed consent.

A total of 300 eligible patients were included in the study. Consecutive sampling was employed until the desired sample size was achieved.

Patients were allocated into three treatment groups comprising 100 patients each:

Group A: Statin monotherapy (n = 100)

Group B: Statin plus ezetimibe therapy (n = 100)

Group C: Statin plus ezetimibe plus bempedoic acid therapy (n = 100)

Treatment selection and dosage adjustments were made according to prevailing clinical guidelines and treating physician discretion.

Data collection procedure:

The diagnosis of ACS was established based on clinical presentation, electrocardiographic findings, cardiac biomarker levels, and standard diagnostic criteria.

At baseline, demographic and clinical characteristics were recorded, including age, sex, cardiovascular risk factors, diabetes mellitus, hypertension, and ACS subtype. Baseline laboratory investigations were performed before initiation of lipid-lowering therapy.

Patients subsequently received one of the three lipid-lowering treatment strategies. All participants received counselling regarding medication adherence, dietary modification, lifestyle changes, and the importance of follow-up.

Follow-up assessments were performed at 1 month and 3 months after initiation of therapy. At each follow-up visit, clinical evaluation and repeat lipid profile testing were performed.

Patients who failed to attend scheduled follow-up visits despite contact attempts were considered lost to follow-up and were excluded from follow-up analyses.

Data were collected using a structured and predesigned case record form. The following variables were recorded, demographic characteristics, clinical history and cardiovascular risk factors, physical examination findings, laboratory investigations, treatment details and follow-up lipid parameters. Electrocardiography and transthoracic echocardiography were performed as part of routine clinical evaluation in all patients.

The study protocol was approved by the Institutional Ethics Committee prior to initiation of patient recruitment. Written informed consent was obtained from all participants before enrollment. Patient confidentiality and anonymity were maintained throughout the study.

Statistical Analysis:

Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA).

Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Normality of data distribution was assessed prior to statistical analysis.

Comparisons of continuous variables between groups were performed using Student's unpaired t-test and one-way analysis of variance (ANOVA), as appropriate. Following significant ANOVA results, post-hoc pairwise comparisons were performed using Bonferroni correction. Categorical variables were analyzed using the chi-square test, Fisher's exact test, or test of proportions as appropriate. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Baseline characteristics of study participants

Characteristic	Statin Monotherapy (n=100)	Statin + Ezetimibe (n=100)	Statin + Ezetimibe + Bempedoic Acid (n=100)	Total (N=300)
Age Group, n (%)				
25–34 years	1 (1.0)	1 (1.0)	3 (3.0)	5 (1.7)
35–44 years	7 (7.0)	4 (4.0)	9 (9.0)	20 (6.7)
45–54 years	25 (25.0)	22 (22.0)	23 (23.0)	70 (23.3)
55–64 years	30 (30.0)	37 (37.0)	32 (32.0)	99 (33.0)
65–74 years	27 (27.0)	27 (27.0)	28 (28.0)	82 (27.3)
75–84 years	8 (8.0)	9 (9.0)	3 (3.0)	20 (6.7)
≥85 years	2 (2.0)	0	2 (2.0)	4 (1.3)
Sex, n (%)				
Male	70 (70.0)	74 (74.0)	68 (68.0)	212 (70.7)
Female	30 (30.0)	26 (26.0)	32 (32.0)	88 (29.3)
Co-morbidities, n (%)				
Diabetes mellitus	46 (46.0)	43 (43.0)	44 (44.0)	133 (44.3)
Hypertension	39 (39.0)	50 (50.0)	45 (45.0)	134 (44.7)
Diabetes + Hypertension	15 (15.0)	23 (23.0)	21 (21.0)	59 (19.7)

Thyroid disorder	0	1 (1.0)	3 (3.0)	4 (1.3)

The study included 300 patients with acute coronary syndrome, distributed equally among the three treatment groups. The majority of participants were aged 55–64 years (33.0%), followed by 65–74 years (27.3%) and 45–54 years (23.3%). Male participants predominated across all treatment groups, comprising 70.7% of the overall study population. Diabetes mellitus and hypertension were common comorbidities, affecting 44.3% and 44.7% of participants, respectively, whereas thyroid disorders were uncommon (1.3%).

Table 2: LDL-C levels and percentage reduction during follow-up

Treatment Group	Baseline LDL-C (mg/dL) Mean ± SD	1-Month LDL-C Mean ± SD	LDL-C Reduction (%)	3-Month LDL-C Mean ± SD	LDL-C Reduction (%)
Statin monotherapy	110.9 ± 21.7	62.8 ± 21.8	43.4	53.0 ± 16.6	52.0
Statin + Ezetimibe	113.6 ± 27.1	56.7 ± 26.9	50.1	44.8 ± 14.2	60.6
Statin + Ezetimibe + Bempedoic Acid	150.9 ± 45.8	46.6 ± 24.0	69.1	36.6 ± 16.1	75.7

All treatment groups demonstrated substantial reductions in LDL-C levels during follow-up. At 1 month, the percentage reduction in LDL-C was 43.4% in the statin monotherapy group, 50.1% in the statin plus ezetimibe group, and 69.1% in the triple therapy group. Further reductions were observed at 3 months, with LDL-C reductions reaching 52.0%, 60.6%, and 75.7%, respectively. The greatest reduction in LDL-C levels was consistently observed among patients receiving statin, ezetimibe, and bempedoic acid combination therapy.

Table 3: Comparison of mean LDL-C levels among treatment groups

Follow-up	Statin Monotherapy Mean ± SD	Statin + Ezetimibe Mean ± SD	Triple Therapy Mean ± SD	F-value	p-value
1 Month (n=300)	62.78 ± 21.8	58.06 ± 22.2	46.60 ± 24.0	13.51	<0.001
3 Months (n=252)	53.07 ± 16.61	44.83 ± 14.19	36.60 ± 16.10	23.43	<0.001

Comparison of mean LDL-C levels revealed significant differences among treatment groups at both follow-up visits. At 1-month, mean LDL-C levels were lowest in the triple therapy group (46.60 ± 24.0 mg/dL), followed by the dual therapy group (58.06 ± 22.2 mg/dL) and the statin monotherapy group (62.78 ± 21.8 mg/dL). Similar findings were observed at 3 months, with the triple therapy group maintaining the lowest LDL-C levels (36.60 ± 16.10 mg/dL). One-way ANOVA demonstrated statistically significant intergroup differences at both 1 month ($F = 13.51$, $p < 0.001$) and 3 months ($F = 23.43$, $p < 0.001$), indicating superior lipid-lowering efficacy of triple therapy.

Table 4: Post Hoc Bonferroni comparison of LDL-C levels

Comparison	Mean Difference at 1 Month (mg/dL)	p-value	Mean Difference at 3 Months (mg/dL)	p-value
Statin vs Statin + Ezetimibe	4.72	0.43	8.24	0.003
Statin vs Triple Therapy	16.22	<0.001	16.47	<0.001
Statin + Ezetimibe vs Triple Therapy	11.50	0.001	8.23	0.020

Post hoc Bonferroni analysis demonstrated that triple therapy achieved significantly lower LDL-C levels than both statin monotherapy and statin plus ezetimibe therapy at 1 month and 3 months. At 1month, significant differences were observed between statin monotherapy and triple therapy ($p < 0.001$) and between dual therapy and triple therapy ($p = 0.001$), whereas the difference between statin monotherapy and dual therapy was not statistically significant ($p = 0.43$). At 3 months, all

pairwise comparisons reached statistical significance, with the largest mean difference observed between statin monotherapy and triple therapy (16.47 mg/dL, $p < 0.001$).

Table 5: Achievement of LDL-C target (<55 mg/dL) during follow-up

Treatment Group	1 Month n (%)	3 Months n/N (%)
Statin monotherapy	36 (36.0)	52/81 (64.2)
Statin + Ezetimibe	53 (53.0)	67/83 (80.7)
Statin + Ezetimibe + Bempedoic Acid	72 (72.0)	80/88 (90.9)

Achievement of the guideline-recommended LDL-C target (<55 mg/dL) improved progressively across all treatment groups during follow-up. At 1 month, target attainment was achieved in 36.0% of patients receiving statin monotherapy, 53.0% receiving statin plus ezetimibe therapy, and 72.0% receiving triple therapy. By 3 months, target attainment increased to 64.2%, 80.7%, and 90.9%, respectively. The highest rates of LDL-C target achievement were consistently observed in the triple therapy group, demonstrating its superior effectiveness in achieving recommended lipid goals among patients with acute coronary syndrome.

DISCUSSION

Baseline characteristics

In the present study, the majority of patients belonged to the 55–64-year age group (33.0%), followed by the 65–74-year age group (27.3%). Patients aged 45–54 years constituted 23.3% of the study population. These findings are consistent with previous Indian ACS registries demonstrating that coronary artery disease predominantly affects middle-aged and elderly individuals. The CREATE registry reported a mean age of 57.5 years among Indian ACS patients, while the Kerala ACS Registry documented a mean age of approximately 60 years among hospitalized ACS patients. The age distribution observed in the present study therefore reflects the typical demographic profile of ACS patients in India[16,17].

Male predominance was observed in the present study, with males accounting for 70.7% of the study population. Similar findings have been reported in major ACS registries. In the CREATE registry, approximately 76% of ACS patients were male, while males constituted nearly 72% of participants in the Kerala ACS Registry[16,17]. The higher prevalence of ACS among men may be attributable to greater exposure to traditional cardiovascular risk factors and the relative cardioprotective effect of estrogen in premenopausal women.

Diabetes mellitus and hypertension were present in 44.3% and 44.7% of patients, respectively. These findings are comparable to observations from the INTERHEART study, which demonstrated a particularly high burden of diabetes and hypertension among South Asian populations with myocardial infarction[16]. Furthermore, South Asians have a high prevalence of metabolic syndrome, insulin resistance, and atherogenic dyslipidemia, all of which contribute to increased cardiovascular risk[17,18].

LDL-C reduction during follow-up

A major finding of the present study was the significant reduction in LDL-C levels across all treatment groups during follow-up. At 1 month, LDL-C reduction was 43.4% in the statin monotherapy group, 50.1% in the statin plus ezetimibe group, and 69.1% in the triple therapy group. At 3 months, LDL-C reduction further increased to 52.0%, 60.6%, and 75.7%, respectively.

The LDL-C reduction observed with statin monotherapy is consistent with findings from landmark statin trials. In the PROVE-IT TIMI-22 trial, intensive atorvastatin therapy reduced median LDL-C levels from approximately 106 mg/dL at baseline to 62 mg/dL during follow-up, representing a reduction of nearly 42%[19]. Similarly, the TNT trial demonstrated LDL-C levels of approximately 77 mg/dL among patients receiving atorvastatin 80 mg, corresponding to LDL-C reductions of approximately 50%. These observations support the effectiveness of intensive statin therapy in secondary prevention[19].

The additional LDL-C reduction achieved with dual therapy is supported by the IMPROVE-IT trial. Patients receiving simvastatin plus ezetimibe achieved median LDL-C levels of 53.7 mg/dL compared with 69.5 mg/dL among those receiving simvastatin alone, resulting in an additional LDL-C reduction of approximately 16 mg/dL and improved cardiovascular outcomes[20]. In the present study, addition of ezetimibe increased LDL-C reduction from 52.0% with statin monotherapy to 60.6% at 3 months, demonstrating a similar incremental benefit.

The greatest LDL-C reduction was observed with triple therapy. This finding is supported by the CLEAR Wisdom trial, in which addition of bempedoic acid to maximally tolerated statin therapy produced an additional LDL-C reduction of approximately 17.4 percentage points compared with placebo at 12 weeks[21]. Similarly, the CLEAR Outcomes trial reported a placebo-corrected LDL-C reduction of approximately 21 mg/dL at 6 months and demonstrated significant reductions in major adverse cardiovascular events[22]. The 75.7% LDL-C reduction observed in the present study likely reflects the additive effect of simultaneously inhibiting hepatic cholesterol synthesis, intestinal cholesterol absorption, and ATP citrate lyase activity[12].

Comparison of mean LDL-C levels among treatment groups

Mean LDL-C levels differed significantly among treatment groups at both follow-up visits. At 1-month, mean LDL-C

levels were 62.8 mg/dL in the statin monotherapy group, 58.1 mg/dL in the dual therapy group, and 46.6 mg/dL in the triple therapy group. At 3 months, mean LDL-C levels further decreased to 53.1 mg/dL, 44.8 mg/dL, and 36.6 mg/dL, respectively.

These findings are consistent with evidence from major lipid-lowering trials demonstrating that lower achieved LDL-C levels are associated with improved cardiovascular outcomes. In the FOURIER trial, addition of evolocumab reduced median LDL-C from 92 mg/dL to approximately 30 mg/dL, representing a 59% reduction, and significantly reduced major cardiovascular events[10]. Similarly, the ODYSSEY OUTCOMES trial achieved LDL-C levels of approximately 53 mg/dL with alirocumab therapy and demonstrated reductions in recurrent ischemic events among post-ACS patients[11].

Although PCSK9 inhibitors achieve greater LDL-C reductions than oral therapies, the present findings demonstrate that triple oral therapy can achieve LDL-C levels approaching those reported in intensive lipid-lowering studies and may therefore represent a practical alternative in resource-constrained settings.

Achievement of LDL-C target (<55 mg/dL)

Achievement of guideline-recommended LDL-C targets is a key determinant of cardiovascular risk reduction after ACS. In the present study, LDL-C target attainment at 1 month was 36.0% in the statin monotherapy group, 53.0% in the dual therapy group, and 72.0% in the triple therapy group. At 3 months, target attainment increased to 64.2%, 80.7%, and 90.9%, respectively.

These findings compare favorably with contemporary international data. The EUROASPIRE V survey reported that only approximately 29% of very high-risk patients achieved ESC-recommended LDL-C targets [15]. Similarly, the DA VINCI study demonstrated that fewer than 40% of high-risk patients attained guideline LDL-C goals despite ongoing lipid-lowering therapy[23].

The present findings are also consistent with the LAI-REACT study, in which rosuvastatin, ezetimibe, and bempedoic acid therapy enabled 76.3% of patients to achieve LDL-C levels below 50 mg/dL and 92.2% to achieve LDL-C levels below 70 mg/dL within 2 weeks following ACS [14]. The high rates of LDL-C target attainment observed in the present study further support the role of intensive oral combination therapy in achieving guideline-recommended lipid goals.

Limitations

However, certain limitations should be acknowledged. First, the study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other populations and healthcare settings. Second, the follow-up period was limited to 3 months and therefore did not permit assessment of long-term cardiovascular outcomes, recurrent ischemic events, or medication adherence beyond the study period. Third, a proportion of patients were lost to follow-up, which may have introduced attrition bias. Large multicenter randomized studies with longer follow-up durations are required to further evaluate the long-term efficacy, safety, and cardiovascular outcome benefits of intensive multidrug lipid-lowering therapy in patients with acute coronary syndrome.

CONCLUSION

In conclusion, intensive lipid-lowering therapy significantly reduced LDL-C levels in patients with acute coronary syndrome. Among the treatment strategies evaluated, triple therapy comprising a statin, ezetimibe, and bempedoic acid achieved the greatest LDL-C reduction and the highest rate of LDL-C target attainment. These findings suggest that early combination therapy may be an effective approach for achieving guideline-recommended LDL-C goals in high-risk ACS patients, particularly in populations with a high burden of residual cardiovascular risk. Further large-scale studies with longer follow-up are needed to evaluate the impact of this strategy on long-term cardiovascular outcomes...

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