ORIGINAL ARTICLE

# Early LDL-C Lowering Efficacy of High-intensity Atorvastatin and Ezetimibe Combination Compared with High-intensity Atorvastatin Alone in Acute Coronary Syndrome: The LAI EARLY ACS Study

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## Abstract

**Background:** High-intensity statins are recommended in patients experiencing acute coronary syndrome (ACS) to lower low-density lipoprotein cholesterol (LDL-C) levels, but evidence-based recommended LDL-C goals often remain unmet. We assessed the therapeutic benefit of early LDL-C lowering and the safety of high-intensity atorvastatin and ezetimibe combination versus high-intensity atorvastatin alone in ACS.

**Methods:** In this investigator-initiated trial, 254 patients admitted with ACS were randomized 1:1 to either atorvastatin 80 mg once daily (group A) or a combination of atorvastatin 80 mg and ezetimibe 10 mg once daily (group B). The first dose was administered orally immediately after diagnosis and then continued daily. The primary and secondary endpoints were percentage reductions in direct LDL-C measurements over the initial 4-week period and at 12 weeks, respectively.

**Results:** The mean percentage reduction in LDL-C was 8.12% in group A vs 14.43% in group B ($p < 0.001$) at week 1, 16.62% in group A vs 28.34% in group B at 2 weeks ($p < 0.001$), 29.43% in group A vs 45.15% in group B at 4 weeks ($p < 0.001$), and 41.88% in group A vs 60.76% in group B ($p < 0.001$) at 12 weeks. Adverse events were similar in both groups.

**Conclusion:** Ezetimibe added to high-intensity statin therapy was well tolerated and resulted in an immediate and robust additional decrease in circulating LDL-C concentrations, with a markedly higher proportion of participants achieving LDL-C goals at 4 and 12 weeks. These promising results show that dual therapy started immediately at the diagnosis of ACS has the potential to improve cardiovascular outcomes in ACS.

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## Introduction

Patients experiencing an acute coronary syndrome (ACS) face the greatest probability of subsequent cardiac events during the early post-event period,[1] underscoring the importance of prompt initiation of evidence-based preventive strategies. Although the control of conventional risk factors and comorbidities such as hypertension and diabetes is necessary, the management of lipid-associated risk is of extreme importance, as ACS most commonly results from the disruption of vulnerable coronary plaque, which is characterized by a large lipid burden and a structurally fragile fibrous cap. Hence, early robust LDL-C reduction after ACS can reduce adverse CV events by stabilizing the vulnerable plaque.[2]

Increased levels of LDL-C are a well-recognized adjustable determinant influencing both the onset and advancement of atherosclerotic CV disease (ASCVD).[3] Extensive clinical evidence demonstrates that reductions in LDL-C achieved with statin therapy translate into proportional decreases in cardiovascular morbidity and mortality among patients with established ASCVD, thus suggesting that lower LDL-C levels improve outcomes.[4] Clinical trials conducted in the post-ACS setting have shown that initiation of high-intensity statin therapy confers superior cardiovascular protection compared with lower-intensity regimens.[5,6] Further, pretreatment with high-intensity atorvastatin in participants with non-ST-segment elevation ACS being treated with angioplasty followed by atorvastatin 40 mg/day in the ARMYDA-ACS trial significantly lowered the rate of major adverse cardiac outcomes within 30 days, driven primarily by a reduction in myocardial infarction (MI) (5% vs 15%; $p = 0.04$).[7] Additionally, patients randomized to treatment with the non-statin therapies, such as ezetimibe or alirocumab, added to high-intensity statin therapy days to weeks after ACS had lower rates of CV events compared with statin therapy alone.[8,9] Despite these data, real-world utilization of adjunctive non-statin lipid-lowering therapies, such as ezetimibe, remains limited even among patients classified as having extremely high CV risk.

Although statins potently lower LDL-C levels, the addition of non-statin therapy immediately after the index acute coronary event may be required for rapid further LDL-C lowering, which may result in additional reduction in adverse CV events. Recent trials in which subcutaneous evolocumab was initiated within 24 hours of ACS as an adjunct to high-intensity statin treatment demonstrated rapid attainment of markedly low LDL-C concentrations without safety concerns, with most patients achieving guideline-directed LDL-C goals.[10] Further, very early (within 24 hours) initiation of PCSK9 inhibitors with high-intensity statin therapy after ACS is associated with significant plaque regression along with plaque stabilization as evidenced by thickening of the fibrous cap.[11] However, there are many limitations to the integration of PCSK9 inhibitors into clinical practice, including the need for regular injections and high cost, particularly

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in India, where the cost of the medication most commonly is paid directly by the patient due to the absence of insurance coverage [average cost approximately Rs. 50,000 (US $600) per month]. Therefore, there is an unmet need to identify cheaper and more feasible alternatives.

Given that the effectiveness of combination LDL-C lowering with a high potency statin and ezetimibe started immediately at diagnosis of ACS has not been previously reported prospectively, this study—the Lipid Association of India: Ezetimibe Atorvastatin combination for Rapid LDL-C lowering in Acute Coronary Syndrome (LAI EARLY ACS study), analyzed the therapeutic benefit and risk profile of the dual approach of high intensity atorvastatin 80 mg/day with ezetimibe 10 mg/day compared with high intensity atorvastatin 80 mg/day alone in Indian individuals presenting with an acute coronary event.

## Materials and Methods

This randomized controlled trial was carried out in the Govind Ballabh Pant Institute of Postgraduate Medical Education and Research, a tertiary care academic hospital associated with Maulana Azad Medical College, New Delhi, India, upon securing ethical approval from the institutional ethics committee in compliance with the Declaration of Helsinki. Consent for participation was taken in writing from all enrolled participants. The study population comprised 254 statin naïve, hemodynamically stable patients with ACS who presented within a 24-hour timeframe of symptom onset and who gave informed consent, between January 2023 and June 2024. Patients were randomized into two groups: atorvastatin 80 mg once daily (group A) or atorvastatin 80 mg plus ezetimibe 10 mg once daily (group B). Both groups were given the first dose of either statin or dual therapy in the emergency ward, along with dual antiplatelet therapy after collecting initial blood samples.

Acute coronary syndrome was defined as acute ischemic chest pain with ischemic ST–T changes on electrocardiogram (ECG) and/or acute elevations in serum cardiac troponin T (cTnT) concentrations. This included patients with acute myocardial infarction (AMI) [both ST-segment elevation (STEMI) and non-ST-segment elevation (NSTEMI)] and unstable angina (UA). The diagnosis of MI was made based on the fourth universal definition of MI.[12] Unstable angina was defined as typical symptoms of myocardial ischemia at rest or on minimal exertion in the absence of ST-elevation or acute cardiomyocyte injury/necrosis, evidenced by a negative troponin t-test. The participants who had a previous diagnosis of coronary artery disease, who were already on any lipid-lowering therapy, or had known moderate-severe hepatic (Child-Pugh class B or C) or renal dysfunction (eGFR less than 45 mL/min/1.73 $m^2$) were excluded.

### Demographic Data and Investigations

Demographic data were recorded along with detailed history, including the presence of risk factors and comorbidities such as smoking, history of hypertension, and diabetes. The electrocardiogram (ECG) was recorded, and 10 mL of blood was collected at emergency triage in an EDTA vacutainer for complete hemogram, in a SST vacutainer for serum levels of transaminases, urea, creatinine, high-sensitivity C-reactive protein (hsCRP), lipid profile tests, and a fluoride vacutainer for blood sugar levels. Routine clinical chemistry and the concentrations of total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using a fully automated biochemistry analyzer (Roche Cobas c501). LDL-C levels were measured using direct enzyme assays. The lipoprotein (a) [Lp(a)] concentration was assessed using an isoform-insensitive particle-enhanced immunoturbidometric assay. Complete blood count was assessed using a fully automated hematology analyzer (Sysmex XN1000).

### Endpoints

Subjects were followed for a total duration of 12 weeks with on-site visits at 1 week (± 3 days), 2 weeks (± 3 days), 4 weeks (± 3 days), and 12 weeks (± 7 days). During each follow-up visit, vital signs were recorded, and blood samples were collected for measurements of total cholesterol, LDL-C, triglyceride, and HDL-C levels. The concentrations of hsCRP and Lp(a) were assessed initially and at 12 weeks. Blood samples were analyzed blindly, irrespective of the treatment allocation. The primary outcome assessed was decline in LDL-C levels at 4 weeks, and the secondary outcome was decline in LDL-C levels at 12 weeks.

### Statistical Analysis

The data obtained were analyzed employing statistical software SPSS version 25 (IBM Corp. Armonk, NY, IBM Corp). Continuous data are described by their means and standard deviations, while categorical data are summarized as frequencies and percentages values. The difference between means of the two groups for patients' baseline characteristics was tested by Student's *t*-test for numerical variables and chi-square test for descriptive data. The linear mixed model was applied with first-order autoregressive covariance structure on the percentage change in lipid variables to compare mean percentage change between the groups at different follow-up time points, with Bonferroni correction. *p*-values < 0.05 were considered statistically significant.

## Results

The study comprised of 254 participants. The cohort had a mean age of 53.7 ± 11.9 years; 192 individuals (75.6%) were men. Nearly half of the participants were current or former smokers ($n = 125$, 49.2%), with a mean smoking exposure of 10.2 ± 11.3 pack-years. A history of hypertension was documented in 88 patients (34.6%), while diabetes mellitus was present in 40 patients (15.8%). The majority of patients (161; 63.3%) presented with STEMI, while NSTEMI and unstable angina were the presenting diagnosis in 54 (21.3%) and 39 (15.4%) patients, respectively. The prevalence of STEMI, NSTEMI, and unstable angina did not differ between the groups (Table 1). The follow-up period averaged 94.6 ± 11.2 days, with mean follow-up in group A being 95.4 ± 14.7 days and in group B 93.8 ± 16.7 days, $p$ = NS. Of the enrolled participants, 243 (95.7%) were followed for the entire 3-month study duration. Two patients were lost to follow-up after 1 week, six after 2 weeks, and three after 4 weeks. The baseline profile of both groups is shown in Table 1.

Mean baseline levels of total cholesterol, triglycerides, HDL-C, non-HDL-C, and Lp(a) are given in Table 1. The mean LDL-C level at baseline was 114.7 ± 29.2 mg/dL in group A and 123.2 ± 31.7 mg/dL in group B, $p = 0.03$. Groups A and B were not matched for total cholesterol and LDL-C, resulting in 7.5% higher initial LDL-C levels in the combination therapy group B. Levels of total cholesterol, triglycerides, HDL-C and non-HDL-C at each follow-up visit are shown in Table 2.

The percent LDL-C reduction achieved at each follow-up time was calculated from the baseline LDL-C values using a linear mixed model with a first-order autoregressive correlation that gives the minimum Akaike Information criterion. The interaction was statistically significant ($F = 34.44$, $p < 0.0001$), indicating the pattern of percentage change over time was not similar between the two groups. However, within groups, there was a decrease in the mean LDL-C over time. The intergroup differences in mean percent change in LDL-C were statistically significant at 1 week,

**Table 1:** Baseline characteristics of the two groups

| *Baseline characteristics* | *Atorvastatin 80 mg daily (group A, n =124)* | *Atorvastatin 80 mg + ezetimibe 10 mg daily (group B, n =130)* | *p-value* |
|---|---|---|---|
| Age, years | 53.1 ± 12.2 | 54.3 ± 11.7 | 0.43 |
| Females, n (%) | 35 (28.2%) | 27 (20.8%) | 0.17 |
| Males, *n* (%) | 89 (71.8%) | 103 (79.2%) | |
| Diabetes, *n* (%) | 23 (18.5%) | 17 (13.1%) | 0.23 |
| Hypertension, *n* (%) | 38 (30.6%) | 50 (38.5%) | 0.19 |
| Body mass index (BMI), kg/m$^2$ | 23.57 ± 1.59 | 23.72 ± 1.69 | 0.45 |
| Smokers, *n* (%) | 59 (47.6%) | 66 (50.8%) | 0.61 |
| No. of pack-years | 10.3 ± 13.2 | 10.2 ± 11.3 | 0.95 |
| Systolic blood pressure, mm Hg | 133.62 ± 9.62 | 133.64 ± 11.48 | 0.99 |
| ACS Presentation | | | |
| STEMI, *n* (%) | 81 (65.4%) | 80 (61.6%) | 0.37 |
| NSTEMI, *n* (%) | 22 (17.7%) | 32 (24.6%) | |
| Unstable angina, *n* (%) | 21 (16.9%) | 18 (13.8%) | |
| Waist circumference, cm | 78.39 ± 10.30 | 80.0 ± 8.53 | 0.18 |
| Hemoglobin, gm/dL | 12.40 ± 1.57 | 12.66 ± 1.31 | 0.16 |
| Total leukocyte count, per mm$^3$ | 10.46 ± 2.04 | 10.96 ± 1.81 | 0.10 |
| Random serum glucose, mg/dL | 128.10 ± 40.62 | 125.36 ± 32.59 | 0.55 |
| SGOT (AST), U/L | 53.05 ± 6.75 | 53.58 ± 6.56 | 0.52 |
| SGPT (ALT), U/L | 52.20 ± 7.81 | 52.04 ± 8.64 | 0.87 |
| Total cholesterol, mg/dL | 195.2 ± 43.06 | 205.08 ± 43.52 | 0.02 |
| Triglycerides, mg/dL | 190.48 ± 69.46 | 200.85 ± 71.90 | 0.24 |
| LDL-C, mg/dL | 114.66 ± 29.22 | 123.22 ± 31.74 | 0.03 |
| HDL-C, mg/dL | 35.08 ± 6.68 | 36.22 ± 7.10 | 0.19 |
| Non-HDL-C, mg/dL | 160.19 ± 44.13 | 168.86 ± 44.23 | 0.12 |
| Lipoprotein(a)-(median), mg/dL | 35.2 | 35.7 | 0.72 |
| hsCRP, mg/L | 9.70 ± 2.55 | 9.61 ± 2.76 | 0.78 |

**Table 2:** Total cholesterol, triglycerides, LDL-C, HDL-C, and non-HDL-C levels at each follow-up visit

| *Lipid profile (mg/dL)* | *1st week* | | *2nd week* | | *4th week* | | *12th week* | |
|---|---|---|---|---|---|---|---|---|
| | *Group A n = 124* | *Group B n = 130* | *Group A n = 123* | *Group B n = 129* | *Group A n = 120* | *Group B n = 126* | *Group A n = 119* | *Group B n = 124* |
| Total cholesterol | 179.11 ± 40.33 | 181.53 ± 38.72 | 164.89 ± 36.44 | 158.54 ± 34.50 | 145.24 ± 30.37 | 133.70 ± 25.95 | 121.33 ± 21.87 | 109.19 ± 18.29 |
| LDL-C | 105.52 ± 27.96 | 104.95 ± 28.94 | 96.06 ± 26.52 | 87.92 ± 24.21 | 80.83 ± 20.81 | 67.37 ± 18.32 | 65.51 ± 15.65 | 47.29 ± 14.35 |
| Triglycerides | 168.00 ± 56.08 | 170.38 ± 54.21 | 151.50 ± 45.12 | 150.23 ± 44.87 | 133.55 ± 33.85 | 127.42 ± 30.89 | 115.63 ± 26.47 | 104.45 ± 21.45 |
| HDL-C | 38.20 ± 5.48 | 38.84 ± 5.71 | 39.68 ± 5.06 | 41.28 ± 5.29 | 41.81 ± 5.63 | 43.29 ± 5.70 | 42.05 ± 5.55 | 45.12 ± 5.06 |
| Non-HDL-C | 140.91 ± 40.98 | 142.69 ± 39.10 | 124.20 ± 38.93 | 116.36 ± 36.11 | 100.93 ± 34 | 86.94 ± 32.26 | 78.62 ± 23.81 | 63.55 ± 20.01 |

2 weeks, 4 weeks, and 12 weeks. The mean percentage reduction in LDL-C was 8.12% in group A vs 14.43% in group B ($p < 0.001$) at 1 week, 16.62% in group A and 28.34% in group B at 2 weeks ($p < 0.001$), 29.43% in group A and 45.15% in group B at 4 weeks ($p < 0.001$) and 41.88% in group A and 60.76% in group B ($p < 0.001$) at 12 weeks. Table 3 and Figure 1 show percentage reductions in LDL-C and other lipid parameters at each follow-up. The absolute reductions in LDL-C levels at various time-points were also significantly greater with combination therapy in group B compared to group A. Comparable changes in non-HDL-C were observed.

The proportion of patients achieving LDL-C goals in the two study groups according to various guidelines, American College of Cardiology (LDL-C goal <70 mg/dL), European guidelines (LDL-C goal <55 mg/dL), and Lipid Association of India (LDL-C goal <50 mg/dL) is given in Table 4. The dual therapy of atorvastatin 80 mg and ezetimibe 10 mg once a day led to a significantly greater number of patients achieving LDL-C goals at 4 and 12 weeks (Fig. 2). Median Lp(a) levels at baseline in groups A and B were 35.2 and 35.7 mg/dL, respectively. At 12 weeks, the median Lp(a) levels were 35.6 mg/dL in group A and 37.9 mg/dL in group B ($p$ = NS). The mean baseline hsCRP levels in groups A and B were 9.70 ± 2.55 mg/L and 9.61 ± 2.76 mg/L, respectively. The hsCRP levels significantly decreased to 3.18 ± 1.53 mg/L in group A ($p < 0.0001$ compared to

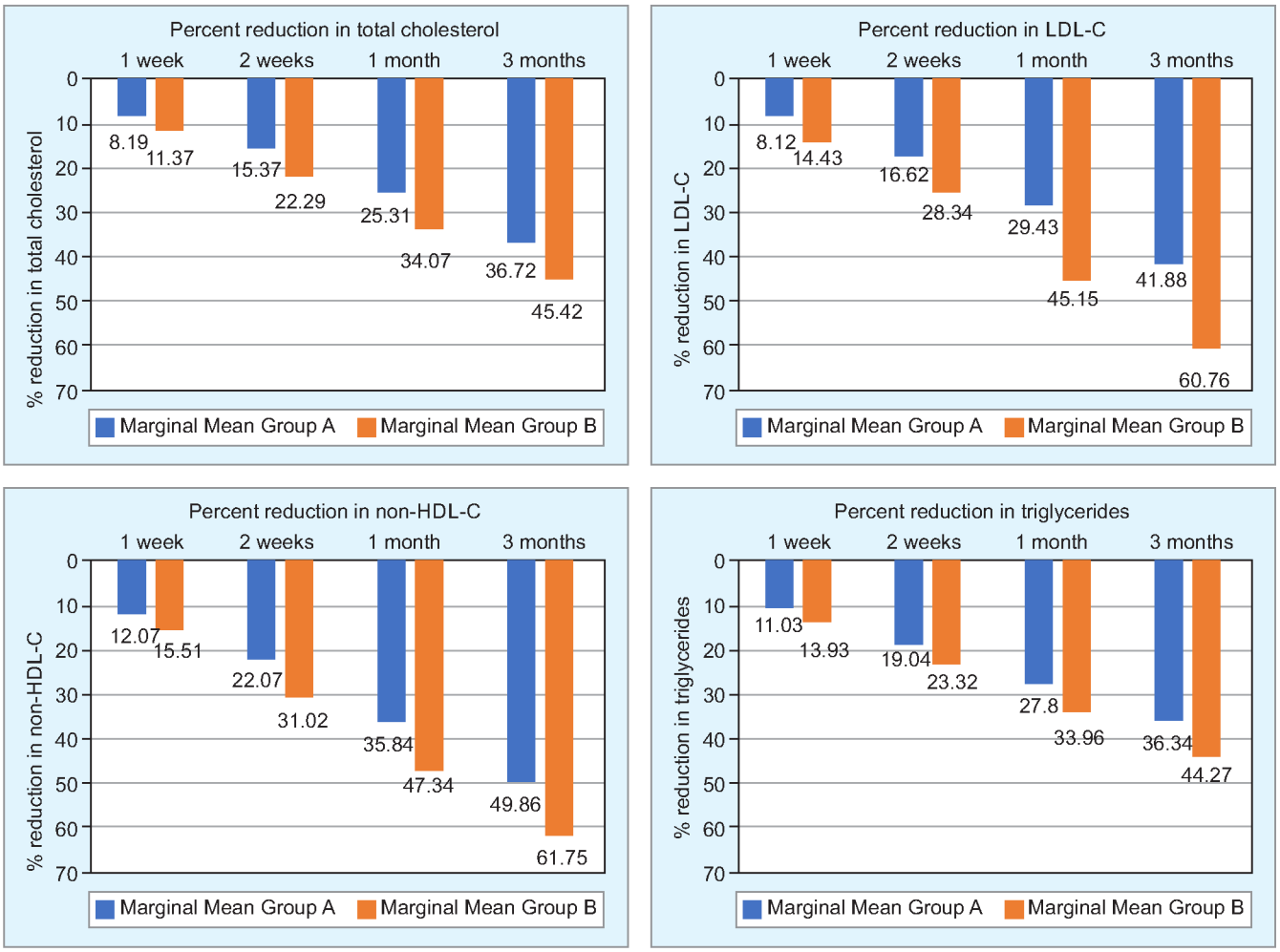


**Fig. 1:** Percent reduction in lipid parameters at various study visits

**Table 3:** Percent decrease in LDL-C, total cholesterol, triglycerides, and non-HDL-C at each follow-up

| *Follow-up time* | *Marginal mean (95% CI)* | | *Mean intergroup difference of marginal mean (95% CI)* | *p-value with Bonferroni correction* |
|---|---|---|---|---|
| | *Group A* | *Group B* | | |
| Percent decrease in LDL-C | | | | |
| 1 week | 8.12 (6.73–9.52) | 14.43 (13.07–15.80) | 6.31 (4.36–8.26) | <0.001 |
| 2 weeks | 16.62 (15.22–18.02) | 28.34 (26.97–29.71) | 11.72 (9.76–13.68) | <0.001 |
| 4 weeks | 29.43 (28.02–30.84) | 45.15 (43.76–46.53) | 15.72 (13.74–17.69) | <0.001 |
| 12 weeks | 41.88 (40.46–43.30) | 60.76 (59.36–62.15) | 18.87 (16.88–20.86) | <0.001 |
| Percent decrease in total cholesterol | | | | |
| 1 week | 8.19 (6.91–9.47) | 11.37 (10.11–12.62) | 3.18 (1.39–4.97) | 0.004 |
| 2 weeks | 15.37 (14.09–16.65) | 22.29 (21.03–23.54) | 6.92 (5.13–8.71) | <0.001 |
| 4 weeks | 25.31 (24.02–26.59) | 34.07 (32.81–35.34) | 8.77 (6.96–10.57) | <0.001 |
| 12 weeks | 36.72 (35.42–38.02) | 45.42 (44.14–46.69) | 8.70 (6.88–10.52) | <0.001 |
| Percent decrease in triglycerides | | | | |
| 1 week | 11.03 (9.03–13.03) | 13.93 (11.97–15.88) | 2.90 (0.10–5.70) | 0.172 |
| 2 weeks | 19.04 (17.03–21.05) | 23.32 (21.35–25.28) | 4.28 (1.47–7.08) | 0.012 |
| 4 weeks | 27.80 (25.78–29.82) | 33.96 (31.98–35.94) | 6.16 (3.34–8.99) | <0.001 |
| 12 weeks | 36.34 (34.31–38.37) | 44.27 (42.28–46.26) | 7.93 (5.09–10.78) | <0.001 |
| Percent decrease in non-HDL-C | | | | |
| 1 week | 12.07 (10.38–13.75) | 15.51 (13.87–17.15) | 3.44 (1.09–5.80) | 0.012 |
| 2 weeks | 22.07 (20.39–23.76) | 31.02 (29.37–32.66) | 8.94 (6.59–11.30) | <0.001 |
| 4 weeks | 35.84 (34.14–35.54) | 47.34 (45.69–48.50) | 11.50 (9.13–3.87) | <0.001 |
| 12 weeks | 49.86 (48.15–51.57) | 61.75 (60.08–63.42) | 11.89 (9.50–14.29) | <0.001 |

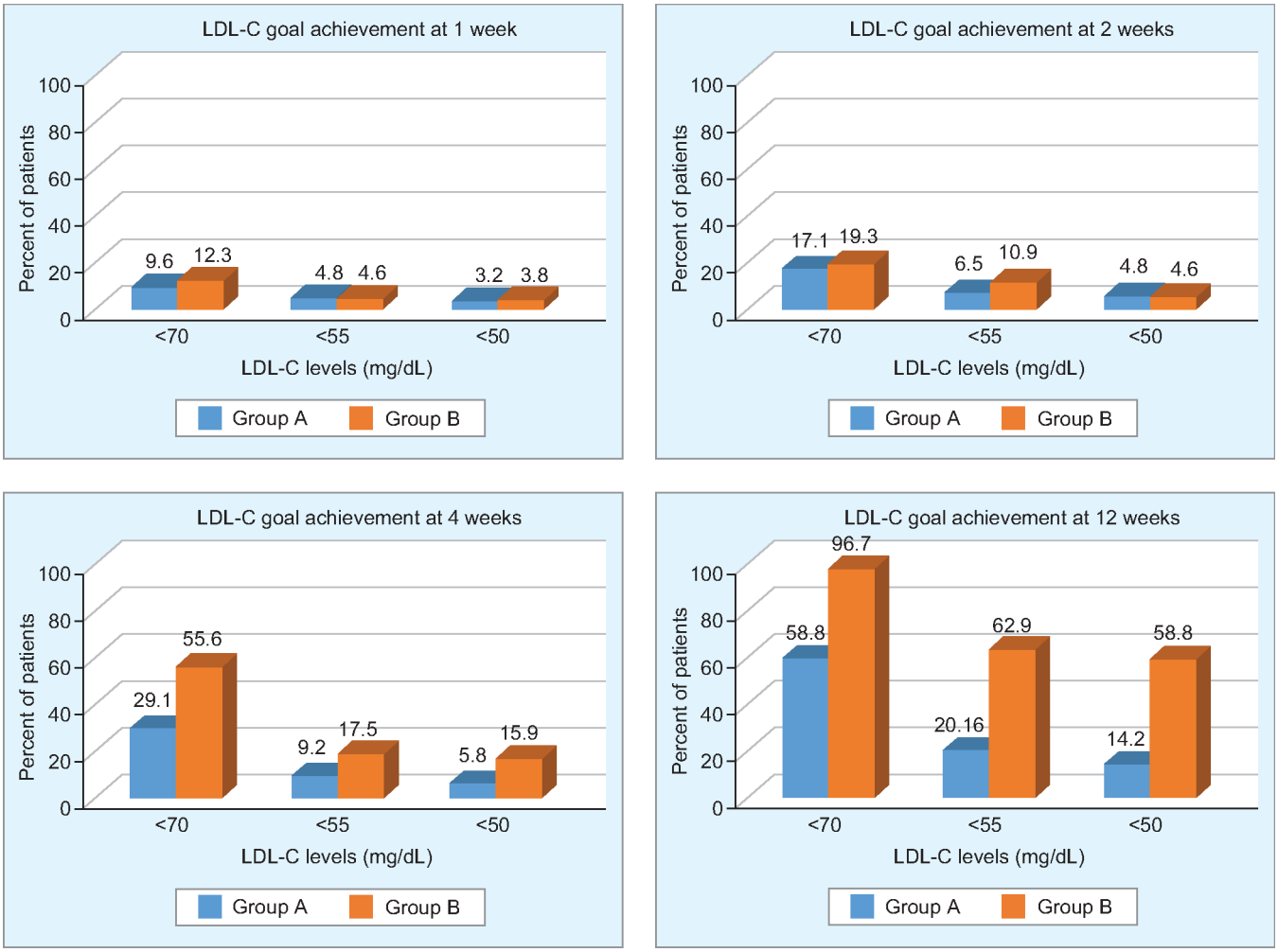


**Fig. 2:** Percentage of patients in both study groups achieving LDL-C goals according to various guidelines at defined time points

**Table 4:** Percentage of patients achieving LDL-C goal according to various guidelines

| *LDL-C at 1 week (mg/dL)* | *Group A (n = 124)* | *Group B (n = 130)* | *p-value (group A vs B)* |
|---|---|---|---|
| <70, *n* (%) | 12 (9.6%) | 16 (12.3%) | 0.50 |
| <55, *n* (%) | 6 (4.8%) | 6 (4.6%) | 1.0 |
| <50, *n* (%) | 4 (3.2%) | 5 (3.8%) | 1.0 |
| *LDL-C at 2 weeks (mg/dL)* | *Group A (n = 123)* | *Group B (n = 129)* | *p-value* |
| <70, *n* (%) | 21 (17.1%) | 25 (19.3%) | 0.63 |
| <55, *n* (%) | 8 (6.5%) | 14 (10.9%) | 0.22 |
| <50, *n* (%) | 6 (4.8%) | 6 (4.6%) | 1.0 |
| *LDL-C at 4 weeks (mg/dL)* | *Group A (n = 120)* | *Group B (n = 126)* | *p-value* |
| <70, *n* (%) | 35 (29.1%) | 70 (55.6%) | <0.001 |
| <55, *n* (%) | 11 (9.2%) | 22 (17.5%) | 0.05 |
| <50, *n* (%) | 7 (5.8%) | 20 (15.9%) | 0.01 |
| *LDL-C at 12 weeks (mg/dL)* | *Group A (n = 119)* | *Group B (n = 124)* | *p-value* |
| <70, *n* (%) | 70 (58.8%) | 120 (96.7%) | <0.001 |
| <55, *n* (%) | 24 (20.16%) | 78 (62.9%) | <0.001 |
| <50, *n* (%) | 17 (14.2%) | 73 (58.8%) | <0.001 |

baseline) and to 3.17 ± 1.54 mg/L in group B ($p < 0.0001$ compared to baseline) at 12 weeks. The decrease in hsCRP levels was statistically similar between the two groups.

Five patients in group A and six patients in group B reported mild bilateral lower limb muscle pain that resolved after counselling without need to modify the statin dose. Two patients in group A and one patient in group B had recurrent angina; one patient in each group required percutaneous intervention in a nonculprit vessel.

## Discussion

This study compared the clinical benefit and tolerability of LDL-C lowering from dual therapy with ezetimibe 10 mg and atorvastatin 80 mg daily versus atorvastatin 80 mg daily, started at admission to the cardiology emergency department in patients presenting with ACS. We demonstrated significantly greater decline in LDL-C with dual therapy compared with atorvastatin alone at all time points studied. Furthermore, the achievement of evidence-based recommended LDL-C goals at 4 weeks and 12 weeks was significantly greater in patients treated with combination therapy compared to monotherapy. This prospective study is the first to report on early achievement of LDL-C lowering shortly after ACS presentation resulting from high-potency statin therapy in combination with ezetimibe.

Acute coronary syndrome is linked to substantial disease burden and death rates. A large retrospective cohort study from Swedish national registries reported that out of 108,315 patients hospitalized with a primary MI, 97,254 (89.8%) survived through the first week following hospital discharge, showing that acute MI is associated with high short-term mortality with standard-of-care treatment.[13] The pathophysiology of ACS is most often linked to plaque disruption, either rupture or erosion, occurring within lesions that possess a substantial lipid component and reduced structural stability, referred to as vulnerable plaque.[14] Hence, plaque stabilization is an important strategy for prevention of complications in ACS management. A multipronged approach that includes risk factor management involving intensive LDL-C lowering, antithrombotic, and anti-inflammatory treatment is necessary. Statins result in significant reductions in adverse CV events, both in ACS patients and stable ASCVD patients, but event rates and mortality remain high when LDL-C levels are persistently elevated despite statin therapy.[5,6,15,16]

Although statin therapy significantly lowers cardiovascular risk, a substantial proportion of adverse events continue to occur in high-risk patients, reflecting the presence of residual risk beyond statin monotherapy, partly due to inadequate LDL-C and non-HDL-C lowering.[17] While high-potency statin therapy reduces LDL-C levels by an average of about 50%, there is great interindividual variability, with many patients not achieving this degree of LDL-C reduction nor achieving evidence-based recommended LDL-C goals. Early reduction of LDL-C after ACS is coupled with reduced rates of reinfarction and adverse CV events.[5,6] Contemporary international guidelines advocate early initiation of high-intensity statins following ACS, with escalation to combination lipid-lowering therapy when LDL-C targets are not promptly achieved. However, the addition of non-statin therapy is often nonexistent or at best delayed, and is typically not started until 4–8 weeks after the index event.[18,19] Such delays may defer optimal LDL-C lowering during a period when patients are particularly vulnerable to recurrent ischemic events.

Recent PCSK9 inhibitor trials in ACS patients have shown that initiation of treatment with evolocumab in combination with statin therapy within 24 hours of ACS presentation results in early achievement of guideline-directed LDL-C goals in the majority of patients without safety concerns versus high-intensity statin therapy alone.[10,20] This strategy also significantly induces plaque regression and fibrous cap thickening over 52 weeks.[11] PCSK9 inhibitor monoclonal antibodies are associated with an early marked reduction in LDL-C levels, but are an injectable therapy and very expensive. Due to the high cost, PCSK9 inhibitors are out of reach of most patients in India, and hence, affordable alternative management pathways are needed that can be easily applied to routine patients. Accordingly, we utilized treatment with high-intensity atorvastatin and ezetimibe.

In the present study, treatment with a high-intensity statin in combination with ezetimibe resulted in LDL-C reductions of 45.15% at 1 month and 60.76% at 3 months. These findings are comparable to those reported in the evolocumab in acute coronary syndrome (EVACS) study, where a 62% reduction in LDL-C at one month was observed with high-intensity statin therapy plus evolocumab.[20]

Given its favorable cost profile and oral administration, ezetimibe represents a practical adjunct to high-intensity statin therapy, offering a well-tolerated and scalable approach to intensifying lipid lowering in ACS [average cost approximately Rs. 1,200 (US $15) per month]. These results further emphasize that clinicians need to consider the benefits of using dual therapy with a high-intensity statin plus ezetimibe in lieu of statin monotherapy in patients with ACS.

Our study results corroborate the Lipid Association of India recommendation to initiate treatment with a combination of high-intensity statin and ezetimibe in ACS patients at emergency triage, soon after initial phlebotomy for laboratory investigations. This recommendation was based on expert opinion in conjunction with extrapolation of data from trials of intensive lipid-lowering therapy in ASCVD patients.[2] This strategy has the potential to reduce adverse CV event rates by stabilizing vulnerable plaque and increasing the fibrous cap thickness.

## Study Limitations

There are a few limitations of this study. First, this is a single-center investigator-initiated study enrolling a relatively small number of patients with only 12 weeks of follow-up. However, the study clearly demonstrates the feasibility and efficacy of dual therapy with ezetimibe added to high-intensity atorvastatin in achieving significantly earlier and greater reductions in LDL-C levels compared to statin therapy alone. Second, the impact of further LDL-C lowering with dual therapy on CV events cannot be inferred from this study. Nevertheless, it was proven in other studies that greater LDL-C lowering is associated with lower rates of CV events, regardless of the type of lipid-lowering therapy.[2,8,9]

## Conclusion

Our study results demonstrate that the levels of LDL-C and non-HDL-C can be rapidly lowered after ACS by dual therapy with a high-intensity statin in combination with ezetimibe. Although treatment with PCSK9 inhibitors after ACS is proven to rapidly lower LDL-C and non-HDL-C levels and reduce ASCVD events, the high cost of PCSK9 inhibitors are a barrier to access to this treatment, particularly in India. Hence, for many patients, dual therapy with high-intensity statins plus ezetimibe is an affordable and well-tolerated treatment option that will rapidly achieve goal-directed LDL-C levels after ACS.

## Author Contributions

VM: Conceptualization, methodology, investigation, validation, data curation, formal analysis, writing—original draft preparation, writing—review and editing, and supervision; NA: Methodology, data curation, resources, investigation, formal analysis, software, and writing—review and editing; PM: Methodology, investigation, data curation, formal analysis, and writing—original draft preparation; PKD: Investigation, validation, and writing—review and editing; NM: Methodology, formal analysis, and writing—review and editing; JY: Data curation, validation, and writing—review and editing; SS: writing—review and editing; SS: Writing—review and editing; MDG: Writing—review and editing; SK: methodology, and writing—review and editing; SK: Methodology, and writing—review and editing; AK: Writing—review and editing; PBD: Writing—review and editing; KKP: Writing—review and editing; RP: Conceptualization, methodology, software, and writing—review and editing.

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## Informed Consent Statement

Informed consent was obtained from all the subjects.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

## Conflict of Interest

The authors declare no conflicts of interest related to this manuscript. However, other industry affiliations are reported as follows:

- Vimal Mehta: Institutional Research Grants from Novo Nordisk, Eli Lilly, LIB Therapeutics, AstraZeneca.
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- Other authors have no conflict of interest.

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