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Original Research

Changes in lipoprotein(a) and their association with LDL-C in patients with ACS treated with triple oral lipid-lowering therapy

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KEYWORDS
Acute coronary syndrome;
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BACKGROUND: Lipoprotein(a) [Lp(a)] is a well-established, genetically determined risk factor for atherosclerotic cardiovascular disease, but its short-term response to aggressive lipid-lowering therapy after acute coronary syndrome (ACS) remains unclear.

OBJECTIVE: To evaluate 1-month changes in Lp(a) and assess whether baseline Lp(a) levels are associated with low-density lipoprotein cholesterol (LDL-C) goal achievement in statin-naive ACS patients undergoing triple oral lipid-lowering therapy.

METHODS: We retrospectively analyzed 345 patients with ACS treated with rosuvastatin (20-40 mg), ezetimibe (10 mg), and bempedoic acid (180 mg) for 1 month after percutaneous coronary intervention. Lp(a) and LDL-C were measured at baseline and 1 month. Multivariable logistic regression identified predictors of achieving the LDL-C goal (< 50 mg/dL).

RESULTS: Despite a 59.1 ± 17.3% reduction in the mean LDL-C, the average Lp(a) increased by 91% (from 42.2 ± 39.2 mg/dL to 80.5 ± 66.3 mg/dL, $P < .001$). LDL-C targets of < 50 mg/dL and < 55 mg/dL were achieved in 68.9% and 78.6% patients, respectively. Baseline Lp(a) independently predicted failure to reach LDL-C goals (adjusted odds ratio [OR] 0.97; 95% CI 0.96-0.98; $P < 0.001$), while diabetes mellitus increased the likelihood of achieving targets (adjusted OR 2.69; 95% CI 1.36-5.61; $P = .006$). A strong inverse relationship was observed between Lp(a) change and LDL-C goal achievement ($\rho = -0.38$, $P < 10^{-12}$).

CONCLUSION: In Indian patients with ACS, aggressive triple oral lipid-lowering therapy quickly reduces LDL-C, while being accompanied by a substantial rise in Lp(a) levels, likely reflecting an acute-phase response. Baseline Lp(a) may independently limit LDL-C target attainment. Early Lp(a) testing may improve residual risk assessment and help guide the use of emerging Lp(a)-focused treatments.

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Introduction

Cardiovascular disease (CVD) and its related manifestations remain the leading cause of morbidity and mortality worldwide, and acute coronary syndrome (ACS) represents a high-risk setting for recurrent events.[1] India faces a disproportionate burden of CVD, with the onset occurring nearly a decade earlier than in Western populations, and also over 25% of all deaths are attributed to cardiovascular causes.[2–4] Lipid-lowering therapy (LLT), including statins in addition to ezetimibe and bempedoic acid or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), targets low-density lipoprotein cholesterol (LDL-C) and has been a cornerstone of secondary prevention post-ACS.[5] Early initiation of aggressive LLT is critical in the acute phase of coronary syndromes, as timely LDL-C reduction improves outcomes and reduces recurrent events. However, Indian cohorts have demonstrated persistent "residual dyslipidemia" and suboptimal LDL-C goal attainment despite therapy.[6,7] Consequently, Indian guidelines, including those from the Lipid Association of India (LAI), recommend more stringent LDL-C targets and earlier intensive therapy in high-risk patients.[7,8] International guidelines similarly endorse an aggressive "strike early, strike hard" approach, yet a significant proportion of patients fail to reach recommended LDL-C targets, reflecting residual risk and variability in therapeutic response.[9,10]

Lipoprotein(a) [Lp(a)] has emerged as an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD) and is considered a "risk-enhancing factor" in multiple international and Indian guidelines.[11,12] Elevated Lp(a) is associated with increased ASCVD risk independent of LDL-C, and its proatherogenic and prothrombotic properties are well described.[11,12] Non-statin LDL-C–lowering agents such as ezetimibe and bempedoic acid have minimal effects on Lp(a); however, conflicting data exist with statins.[13–16] Some studies suggest a modest increase in Lp(a),[13,14] while others, including a latest meta-analysis, showed no effect of statins on Lp(a) levels.[16,17] In contrast, PCSK9i demonstrated modest Lp(a)-lowering benefits (15%-25% reduction).[18,19] Although Lp(a) levels are thought to remain stable over a lifetime as are genetically mediated, recent observational studies have demonstrated a rise in Lp(a) levels after an acute coronary event, though mechanism behind this remains unclear.[20–22] Lipid levels fluctuate during the acute phase of myocardial infarction (MI) as LDL-C typically decreases transiently due to inflammatory and metabolic changes.[23] Lp(a) may also follow dynamic shifts early after ACS, highlighting the need for cautious interpretation of lipid levels measured at ACS presentation and underscoring the value of follow-up testing.[23,24] Data are limited on how intensive LDL-C lowering affects Lp(a) levels in patients with ACS and how elevated Lp(a) influences LDL-C reduction with aggressive combination therapy, important in early LDL-C goal achievement.

With this background, the present study aimed to evaluate 1-month changes in Lp(a) after aggressive oral LLT in statin-naive patients with ACS and to determine whether baseline Lp(a) independently predicts LDL-C target achievement. Our findings demonstrate that while LDL-C significantly decreased at 1 month post-ACS, Lp(a) levels increased over the same period. Notably, the baseline Lp(a) could independently predict LDL-C target achievement at 1 month. These observations have important implications for post-ACS lipid management, risk stratification, and highlight the need to incorporate Lp(a)-targeted therapies into future treatment regimens.

Materials and methods

Study cohort

This retrospective cohort study included patients diagnosed with ACS, including ST-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina, who underwent percutaneous coronary intervention (PCI) between October 2022 and June 2025. Figure 1 summarizes the selection criteria of the study cohort. Patients were eligible for inclusion if they had confirmed ACS, received stable triple oral LLT—comprising rosuvastatin (20-40 mg daily), ezetimibe (10 mg daily), and bempedoic acid (180 mg daily)—for at least 4 weeks, and had available measurements of LDL-C and Lp(a) at both baseline and 1-month post-admission. Patients were excluded if they died in hospital or before completing the 1-month follow-up, lacked baseline or 1-month LDL-C or Lp(a) data, did not receive consistent triple LLT throughout the first month, including any drug or dose changes, had a baseline LDL-C level below 50 mg/dL, or were already on LLT before PCI. The study protocol complied with the Declaration of Helsinki and received approval from the Institutional Ethics Committee of Himachal Heart Institute (approval no: HHI/IEC/2025/03). Given the retrospective study design, informed consent was waived.

Various international guidelines consider Lp(a) levels of > 50 mg/dL as a high-risk factor for future cardiovascular events.[7,25] Participants were grouped based on their Lp(a) levels at baseline and follow-up (1 month) using a threshold of 50 mg/dL.

Laboratory measurements

The samples were analyzed at the 2 hospital-affiliated laboratories, both accredited by the National Accreditation Board for Testing and Calibration Laboratories, utilizing similar standard assays. In this study, we analyzed lipid profiles, including Lp(a) and LDL-C, with both laboratories employing standardized assays for direct LDL-C measurement (direct enzymatic method) and Lp(a) (immunoturbidimetry) to ensure comparability.

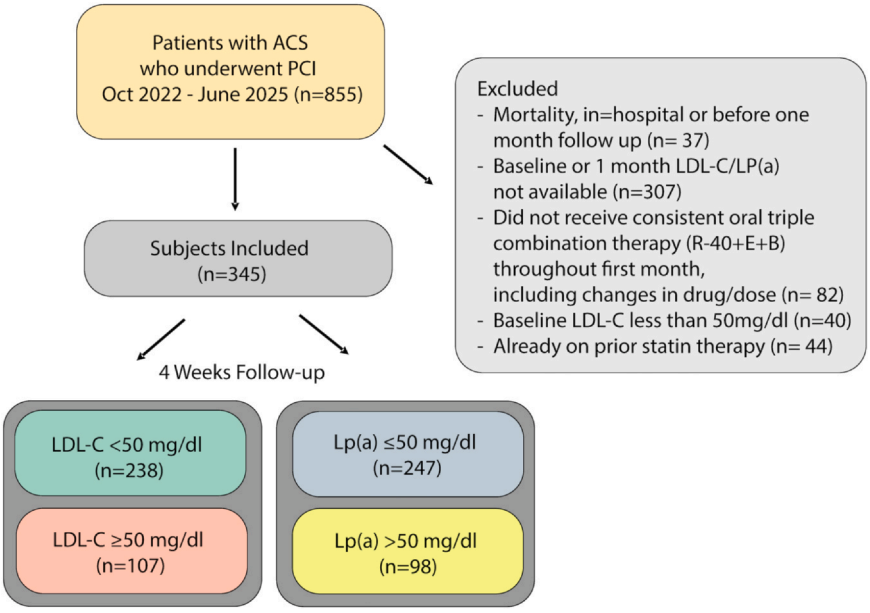

Figure 1. Flowchart of patient enrollment, exclusion, and LDL-C- and Lp(a)-based grouping after PCI. Stepwise exclusion criteria were applied because some patients met more than 1 criterion. Abbreviations: ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCI, percutaneous coronary intervention.

Statistical analysis

All analyses were conducted using R (version 4.5.0) and Python (version 3.12.2). The distribution of continuous variables was assessed with the Shapiro–Wilk test. Continuous variables were expressed as mean ± SD for normally distributed data or as absolute numbers (percentages) for categorical data. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of LDL-C target achievement at 1 month, using baseline demographic, clinical, and biochemical variables. Results are reported as odds ratios (ORs) with 95% CIs. A nonparametric Spearman rank correlation was used to assess the relationship between the change in Lp(a) and LDL-C target failure. Statistical significance was set at $P < .05$.

Results

Patient characteristics

Patients with ACS who underwent PCI between October 2022 and June 2025 (n = 855) were initially screened. A total of 345 statin-naive subjects met the inclusion criteria (Fig 1). Table 1 shows the characteristics of the study cohort, aged 32 to 84 years, with a mean age of 59.7 ± 10.4 years. The majority of the study population was male (81.7%), reflecting a gender bias. Smoking and hypertension were the most common comorbidities (42.9% and 40.9%, respectively). Clinically, STEMI was observed in 77.4% of patients. We divided the study population into 2 groups: those with Lp(a) concentrations of ≤50 mg/dL and Lp(a) > 50 mg/dL at baseline. A significant difference in hypertension (HTN) and smoking at baseline between these 2 subgroups was observed. Also, a significantly high number of patients with STEMI were observed in subjects who had Lp(a) ≤50 mg/dL (Table 1). On the contrary, we did not observe any significant differences in lipid parameters between the 2 groups.

Lp(a) and LDL-C levels

Table 2 shows the comparison of variation in Lp(a) levels according to the target LDL-C achievement. At baseline, the majority of the study participants (n = 247; 71.6%) had Lp(a) levels below risk levels (≤50 mg/dL), which significantly decreased after 1 month of therapy (n = 134, 38.9%). The proportion of participants with Lp(a) > 50 mg/dL increased to 61.1% (n = 211), indicating a significant rise in Lp(a) concentrations over time. Importantly, we observed approximately a 91% increase in the mean level of Lp(a) at 1 month (80.5 ± 66.3 mg/dL) compared with the baseline value of 42.2 ± 39.2 mg/dL. Figure 2A shows that the majority of the subjects have an increase in the Lp(a) levels compared with their baseline values (n = 308; 89.3%) over the 1-month follow-up period. When stratified by the magnitude of Lp(a) increase from baseline to 1 month, 268 participants (77.7%) experienced a rise greater than 10 mg/dL. Notably, 195 individuals (56.5%) had an increase greater than 25 mg/dL, 105 (30.4%) had an increase greater than 50 mg/dL, and 21 (6.1%) had a substantial increase exceeding 100 mg/dL. These findings indicate that a substantial subset experienced significant increases within a short period (Table 2). We observed no significant difference in baseline LDL-C levels when subjects were grouped by Lp(a) levels; however, LDL-C levels were significantly

Table 1. Characteristics of the study cohort.

Characteristic	Total (n = 345)	Low Lp(a) (≤50 mg/dL) (n = 247)	High Lp(a) (> 50 mg/dL) (n = 98)	*P* value
Age (y), mean ± SD	59.7 ± 10.4	58.9 ± 10.2	61.7 ± 10.6	.08
Male sex, n (%)	282 (81.7)	204 (82.6)	78 (79.6)	.67
BMI (kg/m²), mean ± SD	24.5 ± 3.9	24.4 ± 3.8	24.6 ± 3.9	.86
Diabetes mellitus, n (%)	88 (25.5)	60 (24.3)	28 (28.6)	.41
Hypertension, n (%)	141 (40.9)	91 (36.8)	50 (51.1)	.01
Current smoking, n (%)	148 (42.9)	117 (47.4)	31 (31.6)	.02
ACS type – STEMI, n (%)	267 (77.4)	199 (80.6)	68 (69.4)	.03
ACS type – NSTEMI/UA, n (%)	78 (22.6)	48 (19.4)	30 (30.6)	.03
LDL-C (mg/dL), mean ± SD	115.8 ± 31.1	115.8 ± 29.7	115.6 ± 34.4	.48
Total cholesterol (mg/dL), mean ± SD	188.5 ± 43.6	188.1 ± 40.9	189.4 ± 50.1	.82
HDL-C (mg/dL), mean ± SD	43.7 ± 11.7	43.6 ± 12.1	43.8 ± 10.8	.90
Triglycerides (mg/dL), mean ± SD	163.1 ± 89.5	166.9 ± 93.8	153.5 ± 77.3	.21
Lipoprotein(a) (mg/dL), mean ± SD	42.2 ± 39.2	22.3 ± 11.6	92.4 ± 39.5	< .001
1-mo LDL-C (mg/dL), mean ± SD	44.9 ± 15.7	41.5 ± 14.1	53.6 ± 16.6	< .001
Absolute LDL-C reduction (mg/dL), mean ± SD	70.8 ± 30.9	74.3 ± 29.5	62.1 ± 32.9	.001
Percentage LDL-C reduction, (%) mean ± SD	59.1 ± 17.3	62.3 ± 16.2	50.8 ± 17.3	< .001
Percentage LDL-C reduction ≥50%, n (%)	264 (76.5)	210 (85.1)	54 (55.1)	< .001
LDL-C < 50 mg/dL at 1 mo, n (%)	238 (68.9)	200 (80.9)	38 (38.8)	< .001
LDL-C < 55 mg/dL at 1 mo, n (%)	271 (78.6)	213 (86.2)	58 (59.2%)	< .001
LDL-C < 70 mg/dL at 1 mo, n (%)	317 (91.8)	234 (94.7)	83 (84.7)	< .001

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NSTEMI, Non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

lower in the low Lp(a) groups at 1 month ($P < .001$). Also, the percentage change in the LDL-C values was statistically different in low Lp(a) and high Lp(a) groups at 1 month ($P < .001$). The average per-person increase in Lp(a) over the 1-month period was 38.3 ± 41.3 mg/dL, while the average decrease in LDL-C was −70.8 ± 30.9 mg/dL. Figure 2B clearly demonstrates that the majority of subjects had an increase in the percentage change in Lp(a) at 1 month, in contrast to a decrease in LDL-C levels.

Shift in Lp(a) category distribution

We further made the different categories based on Lp(a) levels. Interestingly, we observed a marked shift toward higher concentration categories from baseline over the 1-month follow-up (Fig 3). Change in the Lp(a) category distribution revealed a marked shift toward higher concentration categories from baseline to 1 month. The proportion of individuals in the < 30 mg/dL category declined from 53.3% to 23.2%, and in the > 70 mg/dL group, the percentage increased to 47.2% from 20.9% at 1-month follow-up. Intermediate categories also shifted, with 30 to 50 mg/dL declining from 18.3% to 15.7%, and the 50 to 70 mg/dL group rose from 7.5% to 13.9% at 1 month. These findings further support the observed trend of upward shifts in Lp(a) levels over time, suggesting a progressive elevation in Lp(a) concentration among a substantial proportion of the cohort. These findings indicate a significant upward shift in Lp(a) levels over the 1-month period, with a marked increase in the proportion of individuals falling into higher Lp(a) risk categories.

Table 2. Comparison of variation in Lp(a) levels according to the target LDL-C achievement.

Characteristic	Total (n = 345)	LDL-C < 50 mg/dL (n = 238)	LDL-C ≥50 mg/dL (n = 107)	*P* value
Baseline Lp(a) (mg/dL), median (IQR 25-75)	27.7 (14.7-56.7)	21.8 (10.7-38.5)	58.5 (30.1-85.3)	< .001
Lp(a) at 1 mo (mg/dL), median (IQR)	66.8 (32.9-110.1)	50.3 (24.8-82.6)	114.6 (70.9-170)	< .001
Median change in Lp(a) in mg/dL (1 mo-baseline)	+31.2	+23.1	+58.5	< .001
Baseline lipoprotein(a) > 50 mg/dL, n (%)	98 (28.4)	38 (15.9)	60 (56.1)	< .001
Lp(a) at 1 mo > 50 mg/dL, n (%)	211 (61.2)	121 (50.8)	90 (84.1)	< .001
Increase in Lp(a) > 10 mg/dL, n (%)	268 (77.7)	174 (73.1)	94 (87.8)	< .001
Increase in Lp(a) > 25 mg/dL, n (%)	195 (56.5)	114 (47.9)	81 (75.7)	
Increase in Lp(a) > 50 mg/dL, n (%)	105 (30.4)	42 (17.6)	63 (58.8)	
Increase in Lp(a) > 100 mg/dL, n (%)	21 (6.1)	6 (2.5)	15 (14.1)	

Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

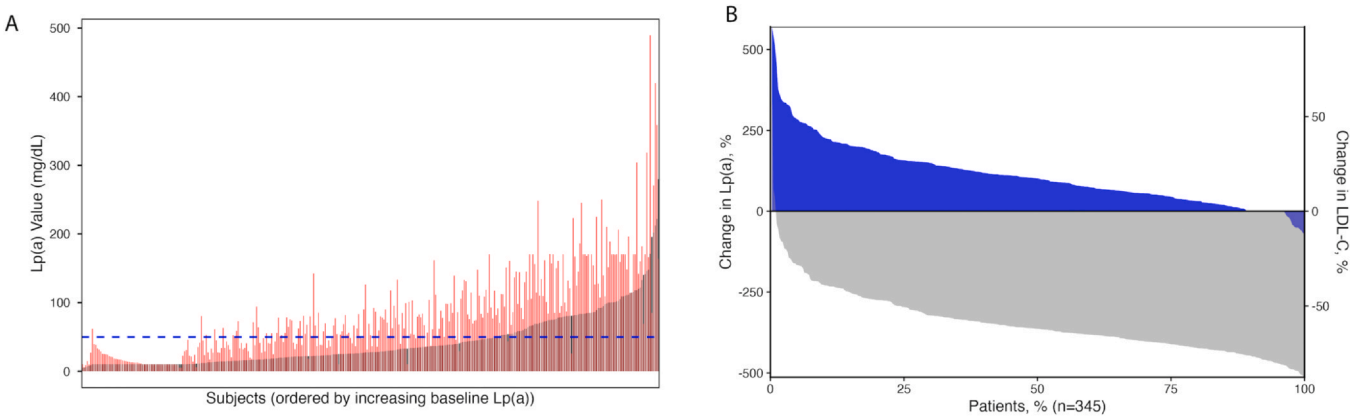

Figure 2. Baseline and 1-month changes in Lp(a) and LDL-C levels. (A) Baseline and 1-month follow-up Lp(a) levels of the study cohort. The baseline Lp(a) levels (red) are plotted in increasing values, and the respective 1-month follow-up levels (black) are shown in the background behind an Lp(a) value. The dashed blue line denotes the population median Lp(a) level (50 mg/dL). (B) Dual-axis waterfall plot showing individual percent changes in Lp(a) levels (left y-axis, blue) and corresponding changes in LDL-C (right y-axis, gray). Positive values indicate increases, and negative values indicate decreases relative to baseline. Abbreviations: LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

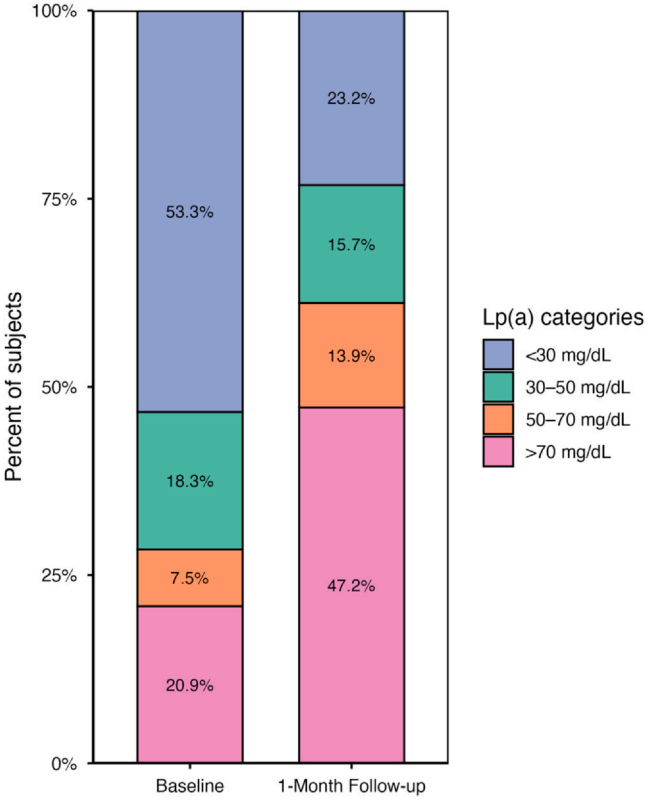

Figure 3. Shifts in Lp(a) risk categories from baseline to 1-month follow-up. Distribution of subjects across Lp(a) categories at baseline and at 1-month follow-up.

Table 3. Predictors of achieving LDL-C target at 1 month: univariate and multivariate logistic regression.

Predictor	OR (95% CI)	*P* value
Univariate Logistic regression analysis		
Lp(a)	0.975 (0.967-0.982)	< .0001
LDL-C	0.986 (0.978-0.994)	< .0001
NHDL-C	0.990 (0.984-0.995)	< .0001
Total Cholesterol	0.991 (0.986-0.996)	< .0001
Diabetes mellitus	2.060 (1.176-3.761)	.014
STEMI	1.520 (0.839-2.717)	.161
Age	0.986 (0.964-1.008)	.199
Unstable angina	1.789 (0.595-6.139)	.320
Triglycerides	1.001 (0.998-1.003)	.623
Sex	1.140 (0.628-2.021)	.660
Hypertension	0.931 (0.587-1.484)	.764
HDL-C	1.001 (0.982-1.021)	.884
Multivariable logistic regression analysis		
Lp(a)	0.973 (0.965-0.981)	< .0001
Diabetes mellitus	2.686 (1.356-5.61)	.006

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NHDL-C, non–high-density lipoprotein cholesterol; OR, odds ratio.

Association of baseline variables with LDL-C target achievement: univariate and multivariable logistic regression analysis

Table 3 shows the results of univariate and multivariate logistic regression to predict the LDL-C target achievement at 1 month. Elevated Lp(a), LDL-C, non–high-density lipoprotein cholesterol, and total cholesterol were associated with lower odds of achieving the target, with ORs of 0.991, 0.986, 0.986, and 0.996, respectively. Diabetes mellitus increased the odds (OR: 2.060, $P = .0143$). In the multivariable logistic regression analysis, adjusted for potential confounders, only baseline Lp(a) levels and the presence of diabetes remained statistically significant predictors. Lp(a) continued to show a strong inverse association with LDL-C goal achievement (adjusted OR: 0.973, 95% CI: 0.965-0.981, $P < .001$), indicating that higher Lp(a) independently reduced the likelihood of achieving LDL-C < 50 mg/dL. Conversely, individuals with diabetes had significantly higher odds of attaining the LDL-C target (adjusted OR: 2.686, 95% CI: 1.356-5.61, $P = .006$).

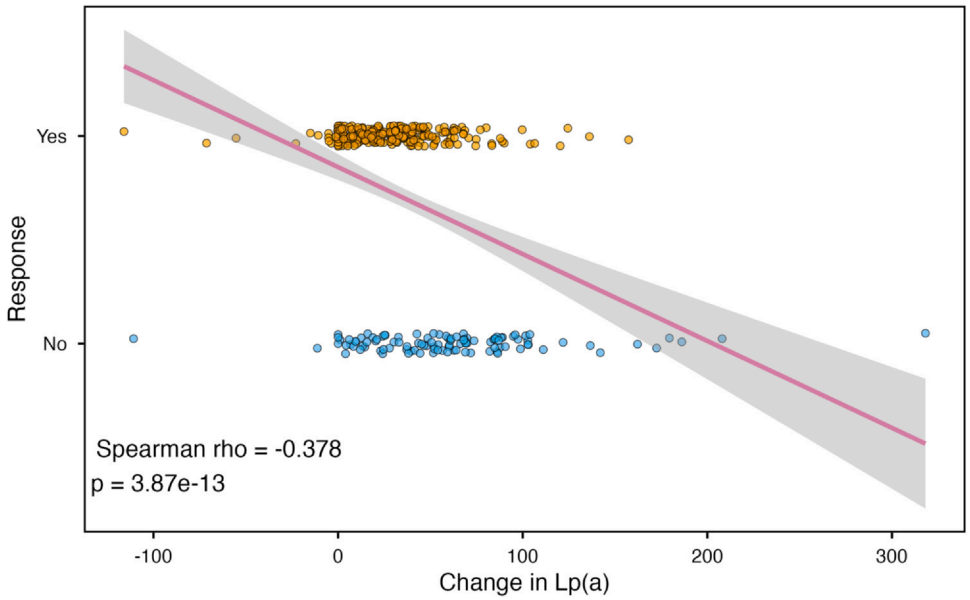

Figure 4. Inverse association between change in Lp(a) and treatment response. Association between percent change in Lp(a) and treatment response status in the study cohort. Abbreviation: Lp(a), lipoprotein(a).

Additionally, we observed a statistically significant inverse correlation between the change in Lp(a) and LDL-C target failure (Spearman $\rho = -0.378$, $P = 3.87 \times 10^{-13}$) (Fig 4). Participants who experienced greater increases in Lp(a) were more likely to fail to achieve the LDL-C goal of < 50 mg/dL at 1 month. Conversely, those with reductions in Lp(a) were more likely to meet the LDL-C target.

Discussion

In our real-world cohort of statin-naive patients with ACS, we found a paradoxical and striking rise in Lp(a) levels, despite a significant reduction in LDL-C after 1 month of triple oral LLT. Approximately 70% of participants achieved the target LDL-C levels, underscoring the short-term efficacy of the oral triple LLT in the Indian cohort, as demonstrated earlier in the Lipid Association of India- Recommended Early and Aggresive lipid lowering in ACS with Triple combination therapy (LAI-REACT) study.[26] However, the concurrent elevation of Lp(a) suggests a complex interplay between intensive LDL-C lowering and compensatory lipoprotein metabolism in the early post-ACS phase.

The observed increase in Lp(a) in our study aligns with previous reports across diverse populations.[22,27,28] In a Chinese study cohort, Zhu et al. examined 488 patients with ACS treated with statins and reported a mean 19.3% rise in Lp(a) after 1 month, with 62.9% of patients showing measurable increases and a median elevation of 4.1 mg/dL.[22] Similarly, a large meta-analysis of 39 randomized trials (n = 24,448) by de Boer et al. found that statin therapy was associated with a small but statistically significant mean increase in Lp(a) of 1.1 mg/dL (95% CI 0.5-1.6 mg/dL, $P < .001$) compared with placebo.[16] These data support the notion that statins moderately raise Lp(a) levels, potentially amplifying residual atherogenic risk even when LDL-C is well controlled. Complementing these observations, a small Polish study found that 22.5% of subjects with ACS exhibited elevations in Lp(a) levels after 3 months of statin therapy.[21] In contrast, the present study revealed a far greater rise, of approximately 91% within 1 month (42.2 ± 39.2 mg/dL to 80.5 ± 66.3 mg/dL, $P < .001$), suggesting that the magnitude of Lp(a) change may vary substantially across ethnic and clinical contexts. While prior meta-analyses have indicated that statins generally exert minimal or clinically insignificant effects on Lp(a) in most patients,[16] the heterogeneity of response is likely influenced by apolipoprotein(a) isoform size, baseline Lp(a) concentration, and assay methodology.[16,29–31] Emerging therapies like PCSK9i and antisense therapies show a far greater Lp(a)-reducing potential.[11,32] Collectively, the evolving evidence regarding Lp(a) behavior after ACS and during LLT underscores the importance of routine Lp(a) monitoring in statin-treated patients and supports the growing role of Lp(a)-specific therapies in comprehensive cardiovascular risk management.

Our univariate and multivariable logistic regression analyses revealed 2 independent predictors of LDL-C goal attainment at 1 month: baseline Lp(a) and diabetes mellitus status. Specifically, higher baseline Lp(a) levels were associated with lower odds of achieving LDL-C targets (adjusted OR: 0.973, 95% CI: 0.965-0.981, $P < .001$), while the presence of diabetes was associated with a greater likelihood of LDL-C goal achievement (adjusted OR: 2.686, 95% CI: 1.356-5.61, $P = .006$). These findings add new insights into Lp(a) as a residual risk factor and therapeutic modifier. Zhu et al. found a 19.3% increase in Lp(a)

following ACS, with larger increases associated with higher major adverse cardiovascular events (MACE) risk.[22] Few prior studies have connected baseline Lp(a) to short-term LDL-C nonresponse, particularly in the setting of oral combination LLT.[33,34] Our findings confirm that elevated Lp(a) may blunt the LDL-C–lowering response, supporting the concept that Lp(a)-associated cholesterol remains refractory to standard therapies and may require specific interventions.[16] Interestingly, patients with diabetes were more likely to achieve LDL-C targets, which may reflect higher baseline LDL-C allowing greater absolute reduction, or possibly better adherence and closer medical follow-up in this high-risk group.

Changes in the Lp(a) during the early post-ACS period should be interpreted with caution. As an acute-phase reactant, Lp(a) may fluctuate in response to post-ACS inflammation.[20] Given this and the limited impact of standard LLTs on Lp(a),[16] the observed rise is unlikely to be solely due to the triple oral therapy. The mechanisms underlying the paradoxical rise in Lp (a) during the early post-ACS period remain unclear, but several plausible explanations have been proposed. Rapid LDL-C depletion may upregulate hepatic LPA gene expression, thereby increasing apo(a) production. In the immediate post-ACS phase, heightened systemic inflammation could transiently stimulate Lp(a) synthesis or mobilization. Genetic predisposition may also contribute, particularly the prevalence of smaller apo (a) isoforms among South Asians, which may make this population more prone to marked fluctuations in Lp(a) during LLT.[11,14,32,35] Moreover, because Lp(a) particles contain cholesterol-rich apolipoprotein B (apoB), a reduction in circulating LDL-C may be partially overestimated when this component is not analytically separated. Notably, the cholesterol content within Lp(a) particles is highly variable, ranging from roughly 6% to 57% across individuals, depending on apo(a) isoform size and assay technique. Consequently, formulas that attempt to "correct" LDL-C by subtracting an estimated Lp(a)-cholesterol component are unreliable and have not been shown to improve cardiovascular risk prediction compared with uncorrected LDL-C.[36,37] In clinical practice, this variability has important implications: when a considerable proportion of measured LDL-C is actually contributed by Lp(a)-bound cholesterol—unaffected by statins, ezetimibe, or bempedoic acid—the apparent "failure" to achieve LDL-C targets may broadly reflect this unaddressed component. This further reinforces the rationale for early Lp(a) assessment and the incorporation of Lp(a)-lowering therapies in future treatment algorithms.

Our study has some limitations. More than 90% of participants exhibited an increase in Lp(a) alongside a reduction in LDL-C following high-intensity LLT, yet the biological mechanism driving this paradox remains unclear. Genetic and ethnic determinants, particularly those unique to the Indian population, may partly explain this variable response. Second, as this was a single-center study, caution is warranted when extrapolating these results to the general population. Third, we did not objectively assess the adherence during the 1-month follow-up. While all participants were prescribed standardized therapy and adherence was reinforced, individual variability may have influenced LDL-C and LP(a) concentration. Finally, the relatively short follow-up duration of 1 month limits the ability to assess long-term trends in Lp(a) behavior and their relationship with clinical outcomes.

To our knowledge, this is the first Indian study to demonstrate that Lp(a) not only rises under aggressive LLT in statin-naive subjects but also independently predicts the likelihood of achieving LDL-C targets, even after adjusting for key confounders. This observation carries important clinical implications because Lp(a)-related cholesterol may limit the apparent effectiveness of conventional therapy, underscoring the potential need for targeted therapies such as antisense or small interfering RNA (siRNA)-based drugs specifically targeting Lp (a). A significant reduction in LDL-C with a concurrent rise in Lp(a) within 1 month of LLT, given that both these molecules are well-established independent risk factors for CVD, raises an important question: are we overly focused on lowering LDL-C while underestimating the risk contributed by elevated Lp(a)? If this paradoxical Lp(a) elevation is indeed real, particularly among genetically predisposed individuals, it represents a form of residual risk that should not remain unaddressed. We believe that this is the time for discussion within the research and clinical community to have a more comprehensive and personalized lipid management strategy. One that not only targets LDL-C but also integrates Lp(a) into routine assessment and decision-making, especially in post-ACS care. Xie et al., in a recent comprehensive meta-analysis of randomized controlled trials, concluded that among currently available LLTs, PCSK9 monoclonal antibodies, inclisiran, Cholesteryl ester transfer protein (CETP) inhibitors, and niacin significantly reduce Lp(a) levels.[17] Future studies with longer follow-up, detailed phenotypic stratification, serial Lp(a) monitoring, and evaluation of emerging Lp(a)-targeted agents such as pelacarsen and olpasiran will be crucial to clarify long-term outcomes and refine therapeutic strategies. High-quality, multiethnic data examining the interaction between LDL-C and Lp(a) responses to therapy are urgently needed, particularly in South Asian populations where this interplay remains poorly understood.

CRediT authorship contribution statement

Kunal Mahajan: Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Nitin Mahajan:** Writing – original draft, Validation, Formal analysis. **Jai Bharat Sharma:** Writing – original draft, Investigation. **Surender Himral:** Writing – original draft, Investigation. **Tanuj Bhatia:** Writing – original draft, Validation. **Deep Dutta:** Writing – original draft, Validation, Project administration.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol

was reviewed and approved by the Institutional Ethics Committee of Himachal Heart Institute, Mandi, Himachal Pradesh, India (approval no: HHI/IEC/2025/03). Given the retrospective, observational nature of the study and the use of anonymized data, the requirement for informed consent was waived by the Ethics Committee.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI or AI-assisted technologies were used in the writing or editing of this manuscript.

Declaration of competing interest

N.M. is an independent freelance consultant in Data Science and Translational Research. This work was conducted independently and is not related to or supported by the author's full-time employment. All authors have nothing to disclose.

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