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Baseline LDL-C Influences Achievement of Contemporary Lipid Targets Following Acute Coronary Syndrome: An Exploratory Secondary Analysis of a Randomized Trial

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Abstract

Guideline-recommended LDL-cholesterol (LDL-C) targets following acute coronary syndrome (ACS) are increasingly stringent, yet target attainment in real-world and trial populations remains suboptimal. We conducted an exploratory secondary analysis of a randomized controlled trial comparing atorvastatin 40 mg and 80 mg in 79 statin-naïve adults presenting with ACS at a tertiary centre in Sri Lanka. Attainment of LDL-C ≤70 mg/dL at 12 weeks was high and comparable between treatment groups (79.5% vs 75.7%; p=0.69). However, attainment of the more stringent target of LDL-C <55 mg/dL differed significantly across baseline LDL-C strata, with only 10.5% of participants with baseline LDL-C ≥130 mg/dL achieving this threshold compared with 52.0% among those with baseline LDL-C 100–129 mg/dL (p=0.014). No significant interaction was observed between baseline LDL-C and treatment allocation. These findings suggest that patients presenting with markedly elevated baseline LDL-C may require early treatment intensification beyond standard high-intensity statin therapy to achieve contemporary lipid targets following ACS.

Trial Registration

Sri Lanka Clinical Trial Registry, SLCTR/2023/003, Registered on 03 March 2023

INTRODUCTION

Acute coronary syndrome (ACS) remains a leading cause of cardiovascular morbidity and mortality. Contemporary guidelines recommend intensive low-density lipoprotein cholesterol (LDL-C) lowering following ACS, with targets of ≤ 70 mg/dL and, in very high-risk patients, < 55 mg/dL[1–4]. Baseline LDL-C influences the magnitude of LDL-C reduction achieved with statin therapy, but its relationship with subsequent attainment of guideline-recommended LDL-C targets remains uncertain[5]. We previously conducted a randomized controlled trial comparing atorvastatin 40 mg and 80 mg in statin-naïve patients with ACS. This exploratory secondary analysis evaluated the relationship between baseline LDL-C, LDL-C reduction, and achievement of LDL-C targets, and assessed whether baseline LDL-C modified the comparative lipid-lowering response to atorvastatin 40 mg and 80 mg.

METHODS

Study design and population

This study represents an exploratory, hypothesis-generating secondary analysis of a single-centre, prospective, open-label randomized controlled trial comparing atorvastatin 40 mg and 80 mg in statin-naïve adults presenting with ACS. The parent trial was conducted at the University Medical Unit, Colombo North Teaching Hospital, Sri Lanka, and was prospectively registered in the Sri Lanka Clinical Trials Registry (SLCTR/2023/003). The study protocol has been published previously[6].

Adults aged ≥ 18 years presenting with a first episode of ACS including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina, were eligible for enrolment. Major exclusion criteria included prior statin therapy, diabetes mellitus, chronic kidney disease, familial hypercholesterolaemia, pregnancy, lactation and contraindications to statin therapy.

Participants were randomized in a 1:1 ratio using a computer-generated allocation sequence prepared by an investigator not involved in participant recruitment. No stratified or block randomization was performed. Following randomization, participants received atorvastatin 40 mg or 80 mg once daily in addition to standard ACS management. Treatment was initiated during the index admission and continued for 24 weeks.

Data collection and laboratory measurements

Baseline lipid profiles were obtained within 24 hours of presentation. Follow-up assessments were performed at 6, 12, and 24 weeks, with blood samples collected after an overnight fast. Medication adherence was assessed during follow-up visits using tablet counts and patient interviews.

Serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) were measured using enzymatic methods. LDL-C was calculated using the Friedewald equation. All analyses were performed in a certified laboratory participating in both internal quality control and external quality assurance programmes.

Outcomes

The primary outcome of the present analysis was attainment of LDL-C ≤ 70 mg/dL at 12 weeks. Secondary outcomes included attainment of LDL-C < 55 mg/dL, absolute and percentage reductions in LDL-C from baseline, and achieved LDL-C concentrations at 12 weeks. Exploratory analyses were performed to assess whether baseline LDL-C influenced the comparative lipid-lowering response to atorvastatin 40 mg and 80 mg

Baseline LDL-C categories

Baseline LDL-C was evaluated as both a continuous and categorical variable. Participants were categorized according to clinically relevant baseline LDL-C strata (< 100 mg/dL, 100–129 mg/dL, and ≥ 130 mg/dL) to evaluate LDL-C reduction and target attainment across different baseline lipid levels. Additional exploratory analyses used median baseline LDL-C and thresholds of ≥ 100 mg/dL and ≥ 130 mg/dL to assess potential differences in response according to treatment allocation.

Statistical analysis

Primary descriptive and subgroup analyses were performed according to randomized treatment allocation using all available outcome data. Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate, while categorical variables are presented as frequencies and percentages. Comparisons between groups were performed using independent sample t-tests or Mann–Whitney U tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables.

Multivariable logistic regression models were used to evaluate LDL-C target attainment, while linear regression models were used to assess achieved LDL-C levels at 12 weeks. Models were adjusted for age, body mass index, and smoking status because of baseline imbalances between treatment groups.

Exploratory interaction analyses were performed using interaction terms between treatment allocation and baseline LDL-C, evaluated as both continuous and categorical variables (≥ 100 mg/dL and ≥ 130 mg/dL). The study was not specifically powered to detect interaction effects and all interaction analyses should therefore be considered exploratory and hypothesis-generating. Statistical significance was defined as a two-sided p-value < 0.05. Analyses were performed using IBM SPSS Statistics version 26.0.

Ethical considerations

The parent trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka (Ref: P/28/05/2022). Written informed consent was obtained from all participants before enrolment.

RESULTS

Study population and baseline stratification

A total of 79 participants were included in this secondary analysis. Ten participants had incomplete follow-up lipid measurements and were therefore excluded from complete-case regression analyses. Baseline descriptive and subgroup analyses were performed using all available outcome data according to randomized treatment allocation.

Baseline characteristics according to treatment allocation are presented in Table 1. The mean age of participants was 56.3 ± 11.9 years, and 75.9% were male. Participants randomized to atorvastatin 80 mg had a higher mean body mass index (24.1 ± 3.8 vs 21.4 ± 4.1 kg/m²; p = 0.004) and a higher prevalence of smoking (73.7% vs 47.4%; p = 0.019). Other baseline characteristics were comparable between treatment groups.

The median baseline LDL-C concentration was 112 mg/dL. Stratification according to median LDL-C produced two well-separated groups with mean LDL-C concentrations of 88.9 ± 11.6 mg/dL and 137.8 ± 20.7 mg/dL, respectively (p < 0.001), while other baseline characteristics remained similar between groups (Table 2).

Table 1
Baseline characteristics according to treatment allocation

Variable	40 mg (n = 40)	80 mg (n = 39)	p-value
Age (years)	58.3 ± 10.8	54.2 ± 12.9	0.139*
Male sex, n (%)	28 (70.0%)	32 (82.1%)	0.210‡
BMI (kg/m²)	21.4 ± 4.1	24.1 ± 3.8	**0.004***
Smoking, n (%)	18 (47.4%)	28 (73.7%)	**0.019‡**
ACS type, n (%) [a]			0.624‡
– NSTEMI/UA	26 (66.7%)	28 (71.8%)	
– STEMI	13 (33.3%)	11 (28.2%)	

Values are presented as mean ± SD or n (%)

[a] *ACS subtype data were available for 39 participants in the atorvastatin 40 mg group and all 39 participants in the atorvastatin 80mg group.*

*Independent samples t-test

‡Chi-square test

ACS = acute coronary syndrome

Table 2
Baseline characteristics according to median LDL-C subgroup

Variable	Low LDL (< 112) n = 41	High LDL (≥ 112) n = 38	p-value
Age (years)	53.8 ± 13.4	58.9 ± 9.7	0.579
BMI (kg/m²)	23.3 ± 3.8	22.2 ± 4.5	0.513
Baseline LDL (mg/dL)	88.9 ± 11.6	137.8 ± 20.7	< 0.001
Female, n (%)	10 (24.4)	9 (23.7)	0.942
Smoking, n (%)	23 (59.0)	23 (62.2)	0.776
ACS type, n (%)	12 (30.0)	12 (31.6)	0.880

LDL-C reduction according to baseline LDL-C

Overall, mean LDL-C decreased from approximately 111 mg/dL at baseline to 62 mg/dL at 12 weeks, corresponding to an absolute reduction of approximately 51 mg/dL. Greater LDL-C reductions were observed among participants with higher baseline LDL-C concentrations. Percentage LDL-C reductions increased across baseline LDL-C strata, from 29.2% among participants with baseline LDL-C < 100

mg/dL to 52.0% and 53.1% among those with baseline LDL-C concentrations of 100–129 mg/dL and ≥ 130 mg/dL, respectively.

Despite these differences in LDL-C reduction, achieved LDL-C concentrations at 12 weeks were broadly similar across baseline LDL-C strata. Mean achieved LDL-C levels were 59.7 mg/dL, 54.9 mg/dL, and 71.8 mg/dL in participants with baseline LDL-C < 100 mg/dL, 100–129 mg/dL, and ≥ 130 mg/dL, respectively.

LDL-C target attainment at 12 weeks

Overall attainment of LDL-C ≤ 70 mg/dL at 12 weeks was similar between treatment groups (79.5% vs 75.7%; p = 0.69). Mean achieved LDL-C levels were 61.6 ± 17.4 mg/dL and 62.4 ± 22.6 mg/dL in the atorvastatin 40 mg and 80 mg groups, respectively.

LDL-C target attainment varied across baseline LDL-C strata. Achievement of LDL-C ≤ 70 mg/dL was observed in 80.6%, 88.0%, and 63.2% of participants with baseline LDL-C concentrations < 100 mg/dL, 100–129 mg/dL, and ≥ 130 mg/dL, respectively. Although attainment appeared lower among participants with baseline LDL-C ≥ 130 mg/dL, differences across baseline LDL-C strata were not statistically significant (p = 0.129).

In contrast, attainment of the more stringent LDL-C target of < 55 mg/dL differed significantly across baseline LDL-C strata. Achievement rates were 30.0%, 52.0%, and 10.5% among participants with baseline LDL-C concentrations < 100 mg/dL, 100–129 mg/dL, and ≥ 130 mg/dL, respectively (p = 0.014).

Across all predefined baseline LDL-C subgroups, no statistically significant differences in LDL-C target attainment were observed between atorvastatin 40 mg and 80 mg (Table 3).

Table 3
LDL-C outcomes at 12 weeks according to baseline LDL-C category

Baseline LDL-C category (mg/dL)	n	Baseline LDL-C (mg/dL)	12-week LDL-C (mg/dL)	Absolute LDL-C reduction (mg/dL)	Percentage LDL-C reduction (%)	LDL-C ≤ 70 mg/dL n (%)	LDL-C < 55 mg/dL n (%)
< 100	32	84.2 ± 8.0	59.7 ± 16.6	24.8 ± 16.7	29.2 ± 19.1	25/31 (80.6)	9/30 (30.0)
100–129	26	115.8 ± 8.0	54.9 ± 19.3	60.9 ± 23.4	52.0 ± 17.7	22/25 (88.0)	13/25 (52.0)
≥ 130	20	153.8 ± 15.5	71.8 ± 19.8	82.0 ± 22.6	53.1 ± 13.3	12/19 (63.2)	2/19 (10.5)

Exploratory interaction analyses

Exploratory multivariable regression analyses were performed using complete-case data (n = 69). No statistically significant interaction between baseline LDL-C and treatment allocation was observed. In

adjusted logistic regression models, the interaction odds ratio for baseline LDL-C was 0.98 (95% CI 0.94–1.02; p = 0.25). Similar findings were observed using LDL-C thresholds of ≥ 100 mg/dL and ≥ 130 mg/dL. Linear regression analyses of achieved LDL-C at 12 weeks likewise demonstrated no evidence of interaction between baseline LDL-C and treatment allocation (p = 0.56).

DISCUSSION

In this exploratory secondary analysis of a randomized controlled trial, we found that LDL-C target attainment at 12 weeks remained high across a wide range of baseline LDL-C concentrations in statin-naïve patients presenting with acute coronary syndrome. Participants with higher baseline LDL-C experienced greater absolute and percentage reductions in LDL-C following treatment, yet achieved LDL-C concentrations at 12 weeks were broadly similar across baseline LDL-C strata. These findings suggest that baseline LDL-C influences the magnitude of LDL-C reduction but may have limited value in predicting achievement of guideline-recommended LDL-C targets following ACS.

An important observation was the relationship between baseline LDL-C and achievement of guideline-recommended LDL-C targets. Although patients with higher baseline LDL-C required larger absolute reductions to achieve treatment targets, attainment of LDL-C ≤ 70 mg/dL appeared lower among those with baseline LDL-C ≥ 130 mg/dL. While this difference did not reach statistical significance, attainment of the more stringent LDL-C target of < 55 mg/dL differed significantly across baseline LDL-C strata. These findings suggest that baseline LDL-C may influence the likelihood of achieving more aggressive lipid targets following ACS.

We also observed progressively greater LDL-C reductions with increasing baseline LDL-C concentrations. This finding is consistent with previous evidence demonstrating that baseline LDL-C is an important determinant of the absolute magnitude of LDL-C reduction achieved with statin therapy[5,7]. However, greater LDL-C reduction did not translate into evidence of differential benefit from higher atorvastatin doses. Consequently, predictors of overall treatment response should not necessarily be assumed to predict relative treatment benefit from more intensive statin therapy.

The present findings should be considered alongside the landmark statin trials that established intensive lipid lowering as a cornerstone of secondary prevention [8–10]. While these studies demonstrated the benefits of intensive statin therapy, they primarily reported average treatment effects rather than examining whether baseline LDL-C influenced subsequent lipid outcomes. Our findings provide additional data from a South Asian population, a group that remains underrepresented in the evidence base informing current lipid-management recommendations [1,2].

Exploratory interaction analyses demonstrated no statistically significant evidence that baseline LDL-C modified the comparative lipid-lowering response to atorvastatin 40 mg and 80 mg. However, these analyses should be interpreted cautiously given the modest sample size and the limited power available for interaction testing. Absence of statistical evidence for interaction should not be interpreted as

evidence of absence of effect modification. Consequently, these findings should be considered hypothesis-generating and require confirmation in larger studies specifically designed to evaluate treatment-effect heterogeneity.

Strengths and limitations

The strengths of this study include its randomized design, prospective data collection, and evaluation of lipid outcomes across clinically relevant baseline LDL-C categories.

Several limitations should be acknowledged. First, this was an exploratory secondary analysis of a relatively small single-centre trial. Second, the study excluded patients with diabetes mellitus and several other common comorbidities, which may limit generalizability. Third, baseline LDL-C was measured within 24 hours of ACS presentation. Previous studies suggest that lipid measurements obtained during this early period are likely to provide a reasonable estimate of baseline lipid status and may be used to guide lipid-lowering therapy[11]. Nevertheless, acute-phase lipid changes may occur after myocardial infarction, and the possibility of misclassification across baseline LDL-C strata cannot be completely excluded. Fourth, LDL-C was calculated using the Friedewald equation rather than measured directly. However, no participant had triglyceride concentrations exceeding 400 mg/dL, the threshold above which the Friedewald equation is generally considered unreliable. Nevertheless, some degree of measurement error compared with direct LDL-C determination cannot be excluded. Finally, the study was not specifically powered to evaluate effect modification and therefore clinically meaningful differences between treatment groups cannot be excluded.

Conclusion

Higher baseline LDL-C was associated with greater absolute and percentage reductions in LDL-C following acute coronary syndrome. Despite these reductions, attainment of recommended LDL-C targets, particularly LDL-C < 55 mg/dL, was less frequent among participants with baseline LDL-C ≥ 130 mg/dL. Baseline LDL-C did not appear to modify the comparative lipid-lowering response to atorvastatin 40 mg and 80 mg. Patients with baseline LDL-C ≥ 130 mg/dL may warrant earlier consideration of combination lipid-lowering therapy to achieve contemporary LDL-C targets.

Declarations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this study.

Ethical approval

The original randomized study from which this secondary analysis was derived received approval from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya. The present study represents a secondary analysis of anonymized data. Written informed consent was obtained from all participants prior to enrolment in the original study, and all procedures were conducted in accordance with the Declaration of Helsinki.

Informed consent

Written informed consent was obtained from all participants prior to enrolment.

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Author Contribution

KF: Conceptualization, methodology, investigation, formal analysis, data interpretation, manuscript drafting, and manuscript revision. NF: Data interpretation and critical revision of the manuscript. CW: Patient recruitment, clinical data collection, and manuscript review. BD: Study supervision, laboratory oversight, and critical revision of the manuscript. SdS: Supervision, methodology development, interpretation of findings and critical revision of the manuscript. CM: supervision, interpretation of findings, and critical revision of the manuscript.

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Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

References

1. Joshi P, Islam S, Pais P, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA. 2007;297(3):286–94. 10.1001/jama.297.3.286.

2. Roth G, Mensah G, Johnson C, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. JACC. 2020;76(25):2982–3021. 10.1016/j.jacc.2020.11.010.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):e1082–143. 10.1161/CIR.0000000000000625.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111–88. 10.1093/eurheartj/ehz455.
5. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459–72. 10.1093/eurheartj/ehx144.
6. Fernando K, Fernando N, Welhenge C, et al. Efficacy, safety and cost-effectiveness of 40 mg versus 80 mg atorvastatin in a Sri Lankan cohort with acute coronary syndrome: a protocol for a single-centre randomised controlled clinical trial. Trials. 2025;26(1):326. 10.1186/s13063-025-08943-2.
7. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81. https://doi.org/10.1016/S0140-6736(10)61350-5.
8. LaRosa JC, Grundy SM, Waters DD, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med. 2005;352(14):1425–35. 10.1056/NEJMoa050461.
9. Pedersen TR, Faergeman O, Kastelein JJP, et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial InfarctionThe IDEAL Study: A Randomized Controlled Trial. JAMA. 2005;294(19):2437–45. 10.1001/jama.294.19.2437.
10. Cannon C, Braunwald E, McCabe C, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med. 2004;350(15):1495–504. 10.1056/NEJMoa040583.
11. Sewdarsen M, Vythilingum S, Jialal I, Nadar R. Plasma lipids can be reliably assessed within 24 hours after acute myocardial infarction. Postgrad Med J. 1988;64(751):352–6. 10.1136/pgmj.64.751.352.