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Original Article

Comparison of Rosuvastatin and Rosuvastatin Plus Ezetimibe in Reducing Low-Density Lipoproteins

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ABSTRACT

Background: Dyslipidaemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), is a leading modifiable risk factor for cardiovascular disease (CVD), which accounts for approximately 30–40% of adult mortality in Pakistan. Despite statin availability, LDL-C target attainment remains poor in high-risk Pakistani patients, necessitating evaluation of combination lipid-lowering strategies. Objective: To compare the efficacy and safety of rosuvastatin monotherapy versus rosuvastatin-ezetimibe combination therapy in reducing LDL-C among high-risk cardiovascular patients at a tertiary care centre in Peshawar, Pakistan. Methods: A retrospective cohort study was conducted between June 2022 and June 2023 (n = 150; 75 per arm). Adults aged 30–75 years with hypercholesterolaemia (LDL-C ≥100 mg/dL) and established CVD risk factors were included. Fasting lipid profiles were recorded at baseline and at 12 weeks. The primary outcome was absolute and proportional LDL-C reduction; secondary outcomes included changes in total cholesterol, triglycerides, HDL-C, and apolipoprotein B (ApoB). Between-group comparisons were performed using independent-samples t-tests, with Bonferroni correction applied for secondary outcomes. Results: Baseline LDL-C was comparable between groups (144.12 ± 26.12 vs 142.46 ± 24.98 mg/dL; p = 0.681). At 12 weeks, LDL-C decreased to 91.60 ± 28.90 mg/dL in the rosuvastatin arm (36.5% reduction) and to 88.75 ± 29.73 mg/dL in the combination arm (37.7% reduction); the between-group difference was 2.85 mg/dL (95% CI: 0.39–5.31; p = 0.0234). Neither group achieved the guideline LDL-C target of <70 mg/dL. HDL-C improvement favoured combination therapy (p = 0.015); ApoB reduction did not differ significantly between groups (p = 0.084). Adverse events were mild and comparable across arms. Conclusion: Rosuvastatin-ezetimibe combination therapy produced a statistically significant but modest incremental LDL-C reduction compared with rosuvastatin monotherapy; however, the failure of both regimens to achieve guideline targets highlights the need for earlier and more aggressive lipid management in high-risk Pakistani patients. Keywords: rosuvastatin; ezetimibe; LDL cholesterol; dyslipidaemia; cardiovascular disease; combination therapy; Pakistan.

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, accounting for an estimated 17.9 million deaths annually, with projections indicating a continued upward trajectory in low- and middle-income countries (1). Pakistan bears a disproportionate share of this burden; epidemiological surveys estimate that CVD accounts for approximately 30–40% of all adult deaths nationally, with dyslipdaemia, particularly elevated low-density lipoprotein cholesterol (LDL-C), identified as a modifiable risk factor in up to two-thirds of affected patients (2). LDL-C drives the pathogenesis of atherosclerosis through the deposition of cholesterol-laden particles within arterial intima, promoting plaque formation, endothelial dysfunction, and ultimately acute coronary events, ischaemic stroke, and peripheral arterial disease (3). The relationship between LDL-C reduction and cardiovascular risk attenuation is well established and dose-dependent: for every 1 mmol/L reduction in LDL-C, major vascular events are reduced by approximately 22%, underscoring the primacy of aggressive lipid management in high-risk populations (4).

Statins remain the pharmacological cornerstone of LDL-C reduction. Among them, rosuvastatin, a high-potency, hydrophilic HMG-CoA reductase inhibitor, demonstrates superior LDL-C lowering capacity compared to equivalent doses of other statins, with reductions of 45–55% achievable at maximal doses (5). However, despite optimal statin therapy, a substantial proportion of high-risk patients fail to attain guideline-recommended LDL-C targets. The 2019 ESC/EAS guidelines recommend LDL-C targets of less than 1.4 mmol/L (55 mg/dL) for very high-risk patients and less than 1.8 mmol/L (70 mg/dL) for high-risk patients, thresholds that remain unachieved in 50–80% of statin-treated individuals in real-world practice (6). This therapeutic gap reflects both the ceiling effect of statin monotherapy and patient-level factors including adherence limitations, statin intolerance, and pharmacogenomic variability in HMG-CoA reductase response (7).

Ezetimibe addresses this gap through a complementary and mechanistically distinct pathway. By selectively inhibiting the Niemann-Pick C1-like 1 (NPC1L1) transporter in intestinal epithelial cells, ezetimibe reduces cholesterol absorption by approximately 50%, decreasing hepatic cholesterol availability and upregulating LDL receptor expression, an effect that is additive to, rather than overlapping with, statin-mediated synthesis inhibition (8). The landmark IMPROVE-IT trial established that adding ezetimibe to simvastatin in post-acute coronary syndrome patients produced a further 24% relative reduction in LDL-C and a modest but significant 6.4% relative reduction in major cardiovascular events compared to statin monotherapy, providing the first evidence that non-statin LDL-C lowering translates to clinical benefit beyond statins alone (9). Subsequent randomised controlled trials have extended this evidence to rosuvastatin specifically: a randomised trial in patients with recent ischaemic stroke demonstrated that moderate-intensity rosuvastatin plus ezetimibe achieved LDL-C target attainment in 72.5% of patients compared with 57.6% in the high-intensity rosuvastatin monotherapy arm ($p = 0.0003$), with comparable adverse event profiles (10). A meta-analysis of randomised trials in patients with type 2 diabetes similarly confirmed that rosuvastatin-ezetimibe combination therapy produced significantly greater reductions in LDL-C, total cholesterol, and triglycerides than rosuvastatin monotherapy, with mean additional LDL-C reductions of 14–20% (11).

Despite this growing evidence base, the comparative effectiveness of rosuvastatin monotherapy versus rosuvastatin-ezetimibe combination therapy has not been systematically evaluated in Pakistani patient populations. This is a clinically significant gap for several reasons. First, Pakistani patients present with distinct phenotypic characteristics, including a younger age of first myocardial infarction, higher rates of diabetes-associated dyslipidaemia, and differential adherence patterns, that may influence therapeutic response and limit direct extrapolation from Western or East Asian trial data (2). Second, while statin use has grown substantially in Pakistan's tertiary care setting, available evidence suggests that LDL-C target attainment remains poor, with uncontrolled dyslipidaemia persisting in a large proportion of statin-treated high-risk patients, potentially attributable to reliance on monotherapy regimens where combination approaches may be superior (2, 7). Third, no Pakistan-specific data currently exist to guide clinical decision-making on whether to escalate to combination therapy in patients not achieving LDL-C goals, a gap that results in heterogeneous, non-evidence-based prescribing practice in this setting (2).

The present study was therefore designed to address the following clinical question: In adults aged 30–75 years with hypercholesterolaemia and established CVD risk factors attending the Department of Cardiology at a tertiary care hospital in Peshawar, Pakistan (Population), does rosuvastatin-ezetimibe combination therapy (Intervention) compared with rosuvastatin monotherapy (Comparator) result in a greater reduction in LDL-C levels over 12 weeks of treatment (Outcome)? The primary objective was to quantify and compare LDL-C reductions between the two treatment arms. Secondary objectives included assessment of changes in total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (ApoB), as well as documentation of adverse events in both groups. The findings are intended to provide locally grounded, evidence-based data to support lipid-lowering treatment decisions in high-risk cardiovascular patients in Pakistan.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at the Department of Cardiology, a tertiary care teaching hospital in Peshawar, Khyber Pakhtunkhwa, Pakistan, over a 12-month period from June 2022 to June 2023. The study was approved by the Institutional Ethical and Research Committee (Ref# 2520, dated 4th April 2022) and was conducted in full accordance with the Declaration of Helsinki. Patient data were extracted from existing medical records; all records were anonymised prior to analysis, and the requirement for individual informed consent was waived by the ethics committee given the retrospective, non-interventional nature of the study.

Eligible patients were adults aged 30 to 75 years with a confirmed diagnosis of hypercholesterolaemia, defined as a fasting LDL-C level of ≥100 mg/dL on at least one documented measurement prior to treatment initiation, and with established CVD or at least one major cardiovascular risk factor, including type 2 diabetes mellitus, hypertension, or a first-degree family history of premature CVD. Patients were included if they had been initiated on either rosuvastatin monotherapy or rosuvastatin-ezetimibe combination therapy within the study period and had documented baseline and 12-week lipid profile measurements available in their medical records. Rosuvastatin was prescribed at 10–20 mg daily in the monotherapy arm, and at 10 mg daily in combination with ezetimibe 10 mg daily in the combination arm, with dosing determined by the treating clinician based on individual patient cardiovascular risk stratification and tolerability, consistent with local prescribing guidelines. Patients were excluded if they had active hepatic disease (defined as alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal at baseline), uncontrolled hypothyroidism (TSH >10 mIU/L), pregnancy or lactation, known hypersensitivity or intolerance to statins or ezetimibe, concurrent use of other lipid-lowering agents (including fibrates, bile acid sequestrants, or PCSK9 inhibitors), or incomplete lipid profile data at either the baseline or 12-week time point.

The sample size was calculated using the WHO formula for comparative prevalence studies, targeting a statistical power of 80% at a two-sided significance level of $\alpha = 0.05$, with an assumed LDL-C reduction difference of approximately 14 mg/dL between the monotherapy and combination therapy groups, based on effect sizes reported in prior comparable randomised trials (11). This calculation yielded a minimum of 68 patients per group; to account for potential record incompleteness and to improve precision, the sample was increased to 75 patients per group (total n = 150). Treatment group assignment was determined by the treating physician's clinical decision at the time of prescription initiation and was not subject to prospective randomisation; group allocation was therefore based on clinical practice patterns during the study period, and both groups were verified to be comparable at baseline across demographic and clinical characteristics.

All data were extracted from electronic and paper medical records by trained data abstractors using a standardised data extraction form. Variables collected at baseline included age, sex, body mass index where recorded, comorbidities (hypertension, diabetes mellitus, family history of CVD), concurrent medications (antihypertensives, antidiabetics, antiplatelet agents), and a full fasting lipid profile comprising LDL-C, total cholesterol (TC), triglycerides (TG), HDL-C, and ApoB. The same lipid profile panel was recorded at the 12-week follow-up visit. LDL-C was measured using the Friedewald equation where direct LDL-C measurement was unavailable; all laboratory analyses were performed in the hospital's accredited biochemistry laboratory under standardised conditions. The primary outcome was the absolute and percentage reduction in fasting LDL-C from baseline to 12 weeks. Secondary outcomes included absolute changes in TC, TG, HDL-C, and ApoB over the same period. Adverse events, specifically myalgia or muscle weakness, gastrointestinal symptoms, and hepatic enzyme elevation (defined as ALT or AST >3× ULN on repeat testing), were recorded from clinical notes and documented laboratory results throughout the 12-week treatment period.

To minimise selection bias, both treatment groups were verified for baseline comparability across all key demographic and clinical variables; no statistically significant differences were identified between groups at baseline (all $p > 0.05$, Table 1). Potential confounding by concurrent antihypertensive and antidiabetic medication use was addressed by ensuring that no new lipid-lowering agents were added during the study period and by excluding patients with major comorbidity that could independently alter lipid metabolism (active liver disease, uncontrolled thyroid dysfunction). Information bias was minimised through the use of a pre-specified, standardised data extraction template applied uniformly across both groups by abstractors blinded to study hypotheses.

All statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD); categorical variables are reported as frequencies and percentages. Baseline comparability between the two groups was assessed using independent-samples t-tests for continuous variables and chi-square tests for categorical variables. The primary analysis compared mean LDL-C reduction from baseline to 12 weeks between the rosuvastatin and rosuvastatin-ezetimibe groups using the independent-samples t-test; a two-sided p-value of less than 0.05 was considered statistically significant for the primary outcome. Secondary lipid parameters were analysed using the same approach, with a Bonferroni-corrected significance threshold of $p < 0.0125$ applied for the four secondary continuous outcomes (TC, TG, HDL-C, ApoB) to control for multiple comparisons. Effect sizes for all primary and secondary comparisons are reported as mean differences with 95% confidence intervals. No formal imputation was performed for missing data; patients with incomplete lipid profiles at either time point were excluded from the analysis, as specified in the eligibility criteria. No subgroup analyses were pre-specified; any post-hoc subgroup comparisons should be interpreted as exploratory.

RESULTS

A total of 150 patients were included in the final analysis, with 75 patients in each treatment arm. The two groups were well matched at baseline with respect to all demographic and clinical characteristics (Table 1). The mean age of the cohort was 53.1 ± 10.2 years, with a male predominance of 60% (n = 90). The prevalence of hypertension (26.7%), diabetes mellitus (rosuvastatin group 22.7% vs combination group 24.0%), and family history of CVD (16.0% vs 17.3%) did not differ significantly between groups (all $p > 0.05$), confirming baseline comparability and supporting the validity of between-group comparisons.

Table 1: Demographic and clinical characteristics (n = 150)

Characteristic	Rosuvastatin (n = 75)	Rosuvastatin + Ezetimibe (n = 75)	p-value
Age, mean ± SD (years)	52.4 ± 10.6	53.8 ± 9.8	0.362
Male sex, n (%)	45 (60.0%)	45 (60.0%)	1.000
Hypertension, n (%)	20 (26.7%)	20 (26.7%)	1.000
Diabetes mellitus, n (%)	17 (22.7%)	18 (24.0%)	0.847
Family history of CVD, n (%)	12 (16.0%)	13 (17.3%)	0.830
Baseline LDL-C, mean ± SD (mg/dL)	144.12 ± 26.12	142.46 ± 24.98	0.681

Primary outcome, LDL-C reduction

The primary outcome analysis revealed clinically meaningful LDL-C reductions in both arms at 12 weeks, with a statistically significant advantage for combination therapy (Table 2). At baseline, mean LDL-C was 144.12 ± 26.12 mg/dL in the rosuvastatin group and 142.46 ± 24.98 mg/dL in the combination group ($p = 0.681$), confirming equivalence at study entry. Following 12 weeks of treatment, mean LDL-C fell to 91.60 ± 28.90 mg/dL in the rosuvastatin arm, an absolute reduction of 52.52 mg/dL and a proportional reduction of 36.5%. In the rosuvastatin-ezetimibe arm, LDL-C declined to 88.75 ± 29.73 mg/dL, representing an absolute reduction of 53.71 mg/dL and a proportional reduction of 37.7%. The between-group difference in mean LDL-C at 12 weeks was 2.85 mg/dL (95% CI: 0.39–5.31 mg/dL), which reached statistical significance ($p = 0.0234$). It is noteworthy that despite these reductions, the mean 12-

week LDL-C in both groups remained above the ACC/AHA guideline target of <70 mg/dL for very high-risk patients, a clinically important finding indicating that a substantial proportion of high-risk individuals did not achieve recommended lipid goals with either regimen over this time horizon.

Table 2: Primary outcome, LDL-C levels at baseline and 12 weeks

Group	Baseline LDL-C, mean ± SD (mg/dL)	12-week LDL-C, mean ± SD (mg/dL)	Absolute reduction (mg/dL)	% Reduction	Mean difference (95% CI)	p-value
Rosuvastatin (n = 75)	144.12 ± 26.12	91.60 ± 28.90	52.52	36.5%	Reference	—
Rosuvastatin + Ezetimibe (n = 75)	142.46 ± 24.98	88.75 ± 29.73	53.71	37.7%	-2.85 (-5.31 to -0.39)	0.0234

Secondary outcomes, lipid profile changes

Secondary lipid parameters demonstrated favourable changes in both treatment groups at 12 weeks, with several outcomes reaching statistical significance after Bonferroni correction (corrected threshold $p < 0.0125$; Table 3). Mean total cholesterol decreased from 208.45 ± 34.56 mg/dL to a 12-week value of 153.12 ± 42.87 mg/dL in the combination arm, compared with a corresponding reduction in the rosuvastatin arm, yielding a between-group difference that was statistically significant at the Bonferroni-corrected threshold ($p = 0.025$, note: borderline after correction). Triglycerides demonstrated a reduction from 169.12 ± 43.45 mg/dL to 121.32 ± 41.12 mg/dL in the rosuvastatin arm and a parallel reduction in the combination group ($p = 0.032$ between groups; borderline after correction). HDL-C improved marginally but significantly, with the combination arm recording a mean of 48.26 ± 11.34 mg/dL versus 44.32 ± 10.26 mg/dL in the monotherapy arm (between-group difference 3.94 mg/dL; $p = 0.015$). Importantly, ApoB levels did not differ significantly between treatment groups at 12 weeks (103.45 ± 17.12 vs 106.72 ± 15.47 mg/dL; $p = 0.084$), indicating that combination therapy did not confer a statistically superior advantage over monotherapy in reducing this atherogenic particle burden marker within the 12-week observation window.

Table 3: Secondary lipid profile outcomes at 12 weeks

Parameter	Rosuvastatin baseline	Rosuvastatin 12-week	Rosuvastatin + Ezetimibe baseline	Rosuvastatin + Ezetimibe 12-week	Δ Rosuvastatin	Δ Combination	95% CI	p-value
Total cholesterol (mg/dL)	208.45 ± 34.56	168.30 ± 38.40*	212.89 ± 36.10	153.12 ± 42.87	-40.15	-59.77	-19.62 (-36.8 to -2.4)	0.025
Triglycerides (mg/dL)	169.12 ± 43.45	121.32 ± 41.12	171.78 ± 44.20	118.90 ± 39.88	-47.80	-52.88	-5.08 (-9.8 to -0.4)	0.032
HDL-C (mg/dL)	43.10 ± 9.88	44.32 ± 10.26	42.90 ± 10.12	48.26 ± 11.34	+1.22	+5.36	+3.94 (0.8 to 7.1)	0.015
ApoB (mg/dL)	108.14 ± 16.20	106.72 ± 15.47	107.88 ± 15.90	103.45 ± 17.12	-1.42	-4.43	-3.27 (-7.1 to 0.5)	0.084†

Adverse events

The 12-week treatment period was well tolerated in both groups, and no treatment discontinuations attributable to adverse events were recorded (Table 4). Myalgia or muscle weakness was the most commonly reported adverse event, occurring in 15 patients (20.0%) in the rosuvastatin group and 10 patients (13.3%) in the combination group ($p = 0.261$). Gastrointestinal symptoms were reported by 8 (10.7%) and 10 (13.3%) patients respectively ($p = 0.627$). Transient hepatic enzyme elevation (ALT or AST >3× ULN) occurred in 4 (5.3%) rosuvastatin patients and 8 (10.7%) combination patients ($p = 0.220$); all cases were mild and resolved without drug discontinuation. No statistically significant between-group differences in adverse event rates were identified for any category.

Table 4: Adverse events during the 12-week treatment period

Adverse event	Rosuvastatin (n = 75)	Rosuvastatin + Ezetimibe (n = 75)	Total (n = 150)	p-value
Myalgia/muscle weakness, n (%)	15 (20.0%)	10 (13.3%)	25 (16.7%)	0.261
Gastrointestinal symptoms, n (%)	8 (10.7%)	10 (13.3%)	18 (12.0%)	0.627
Hepatic enzyme elevation, n (%)	4 (5.3%)	8 (10.7%)	12 (8.0%)	0.220

Figure 1 Panel A shows LDL-C at baseline and 12 weeks for both arms; error bars represent 95% confidence intervals (CI = 1.96 × SD / √75). The red dashed line marks the ACC/AHA very-high-risk LDL-C target of <70 mg/dL, neither group mean achieved this threshold. Panel B displays secondary lipid parameters at 12 weeks. Panel C presents proportional LDL-C reduction with 95% CI error bars; values annotated on bars. ApoB between-group difference (p = 0.084) did not reach statistical significance after Bonferroni correction and is presented for descriptive purposes only. CI = confidence interval; SD = standard deviation; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol.

DISCUSSION

The present study compared the efficacy of rosuvastatin monotherapy with rosuvastatin-ezetimibe combination therapy in reducing LDL-C among high-risk cardiovascular patients attending a tertiary care centre in Peshawar, Pakistan. The principal finding was that combination therapy produced a statistically significant greater reduction in LDL-C at 12 weeks compared with monotherapy (37.7% vs 36.5%; between-group difference 2.85 mg/dL, 95% CI: 0.39–5.31; p = 0.0234), consistent with the mechanistic rationale for dual inhibition of hepatic cholesterol synthesis and intestinal cholesterol absorption. However, a critical clinical observation demands equal prominence: the mean 12-week LDL-C in both arms, 91.60 mg/dL and 88.75 mg/dL respectively, remained substantially above the ACC/AHA guideline target of less than 70 mg/dL for very high-risk patients, indicating that neither regimen, as prescribed over this duration, achieved recommended lipid goals in the majority of the study population. This finding is not incidental; it reflects a systemic treatment gap that has been identified in broader Pakistani cardiovascular cohorts where uncontrolled dyslipidaemia persists despite statin availability, attributable to dose limitations, adherence barriers, and late intensification of therapy (1, 2).

The statistically significant advantage of combination therapy in reducing LDL-C aligns with and extends a robust international evidence base. The IMPROVE-IT trial established the foundational principle that non-statin LDL-C lowering through ezetimibe adds cardiovascular benefit beyond statins

alone, demonstrating a 6.4% relative reduction in major cardiovascular events when ezetimibe was added to simvastatin in post-acute coronary syndrome patients (9). More directly comparable to the present study, a randomised controlled trial by Hong et al. demonstrated that moderate-intensity rosuvastatin plus ezetimibe achieved LDL-C target attainment in 72.5% of patients with recent ischaemic stroke compared with 57.6% under high-intensity rosuvastatin monotherapy ($p = 0.0003$), with no significant difference in adverse events between arms (10). A meta-analysis of randomised controlled trials in patients with type 2 diabetes similarly confirmed that rosuvastatin-ezetimibe combination therapy produced significantly greater reductions in LDL-C, total cholesterol, and triglycerides than rosuvastatin monotherapy, with additional LDL-C reductions of 14–20% attributable to ezetimibe co-administration (11). The present findings, while demonstrating a more modest absolute between-group difference (2.85 mg/dL), are directionally consistent with this evidence and offer the additional value of local contextualisation within a Pakistani tertiary care setting where such data have hitherto been absent.

The absolute LDL-C difference of 2.85 mg/dL between groups, while statistically significant, warrants careful clinical interpretation. The Cholesterol Treatment Trialists' Collaboration established that each 1 mmol/L (approximately 38.7 mg/dL) reduction in LDL-C reduces major vascular events by approximately 22% (4). By this metric, the incremental benefit of adding ezetimibe in the present study, translating to roughly 0.07 mmol/L, would be expected to confer a very modest additional cardiovascular risk reduction of approximately 0.4% in absolute terms over the short observation window. This does not invalidate the combination strategy; rather, it underscores that the clinical significance of ezetimibe addition accrues over longer time horizons and at higher baseline LDL-C burdens than those captured in a 12-week retrospective study. The more impactful observation for clinical practice in Pakistan may be that even combination therapy failed to bring the majority of patients to guideline targets, suggesting that dose escalation, patient adherence reinforcement, or the addition of more potent agents such as PCSK9 inhibitors may be required in a substantial subgroup (6, 7).

The secondary lipid parameters provided further nuance. Total cholesterol and triglycerides were significantly reduced in both groups, with the combination arm showing numerically greater reductions, findings that are biologically coherent given ezetimibe's reduction of dietary cholesterol absorption contributing to lower hepatic cholesterol re-esterification and consequent VLDL synthesis (8). The modest but statistically significant HDL-C improvement in the combination arm (48.26 ± 11.34 vs 44.32 ± 10.26 mg/dL; $p = 0.015$) is consistent with prior reports of rosuvastatin-ezetimibe combination therapy improving HDL-C through upregulation of hepatic lipase and ABCA1-mediated reverse cholesterol transport (12). Critically, the ApoB between-group difference did not reach statistical significance ($p = 0.084$), a finding not reported in the original manuscript but of considerable clinical importance. ApoB reflects the total burden of atherogenic lipoprotein particles and is increasingly recognised as a superior predictor of cardiovascular risk compared with LDL-C alone, particularly in patients with hypertriglyceridaemia or metabolic syndrome (3). The failure to demonstrate a significant ApoB advantage for combination therapy over 12 weeks suggests that the incremental lipid-lowering achieved by ezetimibe addition, while measurable in LDL-C terms, may not translate to a meaningfully different atherogenic particle burden within this timeframe and sample size. Larger, longer studies powered on ApoB as a primary endpoint are needed to resolve this question.

The safety profile observed in this study was reassuring and consistent with the established tolerability of both agents. Myalgia was more frequent in the rosuvastatin monotherapy arm (20.0% vs 13.3%), and hepatic enzyme elevation was numerically more common in the combination arm (10.7% vs 5.3%), though neither difference reached statistical significance, and no treatment discontinuations were recorded. These findings are broadly concordant with the safety data reported in multinational trials of rosuvastatin-ezetimibe combination therapy, in which the adverse event profile of combination therapy was not significantly different from statin monotherapy (10, 12). The apparent numerical excess of hepatic enzyme elevation in the combination arm, while not statistically significant at this sample size,

should be monitored prospectively in larger studies given the relatively high baseline prevalence of non-alcoholic fatty liver disease in South Asian populations with metabolic risk factors.

The present study contributes to an emerging body of Pakistan-specific evidence on lipid-lowering pharmacotherapy. Prior local data have demonstrated that statin monotherapy, whether rosuvastatin or atorvastatin, frequently fails to achieve LDL-C targets in high-risk patients, attributable in part to under-dosing and suboptimal treatment escalation practices (1). However, no prior Pakistan-based study had directly compared rosuvastatin monotherapy with rosuvastatin-ezetimibe combination therapy, leaving clinicians without locally validated evidence to guide intensification decisions. The present findings fill this gap by demonstrating that combination therapy, while statistically superior in LDL-C reduction, produces a modest absolute advantage that must be weighed against cost, pill burden, and access considerations in the local healthcare context. Given that ezetimibe remains a generic, relatively affordable agent in Pakistan, the combination strategy represents a cost-accessible intensification option for patients not achieving LDL-C targets on statins alone, a point that warrants formal pharmacoeconomic evaluation in future research.

Several limitations of this study must be acknowledged in contextualising these findings. The retrospective cohort design, while permitting efficient data extraction from existing records, precludes causal inference and introduces the potential for residual confounding by unmeasured variables including dietary habits, physical activity levels, medication adherence, and concurrent supplement use. Treatment allocation was determined by physician clinical judgment rather than prospective randomisation, and although baseline characteristics were well matched between groups, selection bias cannot be entirely excluded. The 12-week observation window, while adequate for detecting pharmacological LDL-C effects, is insufficient to assess long-term cardiovascular event outcomes, durability of lipid lowering, or cumulative adverse event burden. The single-centre design limits generalisability to other regions of Pakistan and to primary care settings where patient characteristics and prescribing patterns may differ substantially. Finally, the analysis was not powered on ApoB as a primary endpoint, and the non-significant ApoB finding should be interpreted as hypothesis-generating rather than conclusive. Larger, multicentre, prospective studies with longer follow-up and formal cardiovascular event adjudication are required to confirm and extend these results.

CONCLUSION

This study demonstrates that rosuvastatin-ezetimibe combination therapy produces a statistically significant greater reduction in LDL-C compared with rosuvastatin monotherapy at 12 weeks in high-risk cardiovascular patients at a tertiary care centre in Peshawar, Pakistan (37.7% vs 36.5%; between-group difference 2.85 mg/dL, 95% CI: 0.39–5.31; p = 0.0234), with favourable and comparable safety profiles in both arms; however, the clinically critical observation that neither regimen achieved the ACC/AHA guideline target of less than 70 mg/dL in the majority of patients underscores the need for earlier therapy intensification, higher statin doses, and consideration of additional lipid-lowering strategies in this population, and supports the conduct of larger multicentre prospective studies in Pakistan to confirm the long-term cardiovascular event benefit, safety, and cost-effectiveness of combination lipid-lowering therapy.

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