

Original Article

Statin Monotherapy Versus Statin Plus Ezetimibe in Type 2 Diabetes Mellitus: A 12-Week Prospective Cohort Study

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Abstract

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Objective: This study compared 12-week LDL-C reduction and target attainment with atorvastatin 20 mg alone versus atorvastatin 20 mg plus ezetimibe 10 mg.

Methodology: This single-centre prospective observational cohort study was conducted at a tertiary care hospital in Rawalpindi, Pakistan, from March to July 2026. Adults aged 30 to 70 years with T2DM and LDL-C ≥ 70 mg/dL were consecutively enrolled in two routine-care cohorts according to the regimen prescribed by their treating physician. Seventy participants received atorvastatin 20 mg once daily, and 70 received atorvastatin 20 mg plus ezetimibe 10 mg once daily. The primary outcome was the absolute change in LDL-C levels at week 12. An analysis of covariance model was used, with week-12 LDL-C as the dependent variable, treatment group as the fixed factor, and baseline LDL-C as the covariate.

Results: All 140 participants completed the follow-up. The mean baseline LDL-C was 125.3 ± 23.1 mg/dL with atorvastatin alone and 127.9 ± 24.8 mg/dL with combination therapy. The mean LDL-C reductions were 35.6 and 54.0 mg/dL, respectively. After adjusting for baseline LDL-C, combination therapy was associated with an additional 18.4 mg/dL reduction (95% CI 12.8 to 24.0; $p < 0.001$). LDL-C < 70 mg/dL was achieved by 26 of 70 participants (37.1%) and 45 of 70 (64.3%) ($p = 0.001$). A reduction of at least 50% occurred in 9 of 70 (12.9%) and 21 of 70 (30.0%) patients ($p = 0.01$). Adverse events were recorded in 10 of 70 (14.3%) and 12 of 70 (17.1%) participants ($p = 0.64$).

Conclusion: Atorvastatin 20 mg plus ezetimibe 10 mg was associated with greater 12-week LDL-C reduction and target attainment than atorvastatin 20 mg alone. The observational design, short follow-up, and limited sample size preclude causal inference, safety equivalence assessment, and assessment of cardiovascular benefits.

Keywords: Diabetes Mellitus, Type 2; Dyslipidemias; Hydroxymethylglutaryl-CoA.

Introduction

Type 2 diabetes mellitus is a serious health problem in Pakistan. National surveys have documented a considerable prevalence of both diabetes and prediabetes among adults, with important consequences for cardiovascular morbidity and the utilisation of healthcare services.^{1,2} Cardiovascular disease remains a leading cause of illness and death in people with diabetes. Current diabetes and cardiovascular guidelines therefore place lipid management within a broader strategy that also addresses blood pressure, glycaemia, smoking, kidney disease, and established atherosclerotic cardiovascular disease.^{3,4}

Dyslipidaemia in diabetes is typically characterised by elevated triglyceride levels, reduced high-density lipoprotein cholesterol levels, and a preponderance of small, dense low-density lipoprotein particles.⁵ Low-density lipoprotein cholesterol (LDL-C) continues to serve as the principal therapeutic target, since reducing LDL-C lowers atherosclerotic cardiovascular risk. Statins are the first-line pharmacological therapy. When LDL-C levels remain above the risk-stratified target despite the maximally tolerated statin dose, guidelines endorse the addition of a non-statin agent, most commonly ezetimibe.^{3,6,7}

Ezetimibe suppresses cholesterol absorption in the intestine by inhibiting Niemann-Pick C1-like 1. It complements the reduction in hepatic cholesterol synthesis induced by

statins. Randomised evidence shows that statin plus ezetimibe can produce greater LDL-C lowering than statin monotherapy. In patients with atherosclerotic cardiovascular disease, the RACING trial demonstrated that a regimen combining moderate-intensity statin therapy with ezetimibe was non-inferior to high-intensity statin therapy with respect to major cardiovascular outcomes, while producing fewer instances of discontinuation or dose reduction attributable to intolerance.⁸ A randomised trial in adults with type 2 diabetes also showed effective LDL-C lowering with rosuvastatin plus ezetimibe compared with high-intensity rosuvastatin.⁹ In the IMPROVE-IT trial, the absolute cardiovascular benefit of adding ezetimibe after acute coronary syndrome was greater among participants with diabetes than among those without diabetes.¹⁰

The response to treatment in routine practice may differ from that observed in controlled trials because statin dose, adherence, cardiovascular risk, comorbidity, and prescription preference are more variable. Comparative prospective data from Pakistani clinical settings are limited. Therefore, this study compared 12-week lipid changes, LDL-C target attainment, and recorded adverse events in adults with type 2 diabetes who received statin monotherapy or statin plus ezetimibe in routine care. We hypothesised that combination therapy would be associated with a greater reduction in LDL-C. Locally generated evidence may help clinicians identify patients who require treatment intensification and support more consistent use of guideline-based lipid-lowering therapy.

Methodology

This single-centre prospective observational cohort study was conducted from March to July 2026 at the Department of Medicine of a tertiary care hospital in Rawalpindi, Pakistan. Treatment was prescribed by the treating physician as part of routine clinical care, and the investigators did not assign any treatment. The manuscript was prepared in accordance with the STROBE statement for cohort studies, and a completed STROBE checklist accompanies the resubmission.¹¹

Adults aged 30 to 70 years were eligible if they had an established diagnosis of type 2 diabetes mellitus for at least six months and an LDL-C concentration of at least 70 mg/dL despite lifestyle measures or a clinical indication for drug treatment. Eligible patients who presented during the study period were screened and enrolled after providing written informed consent. A non-probability consecutive sampling technique was used, and all eligible patients presenting during the recruitment period were invited to participate.

The exclusion criteria were as follows: active liver disease; estimated glomerular filtration rate < 30 mL/min/1.73 m²; pregnancy or lactation; current use of ezetimibe or another non-statin lipid-lowering drug before enrolment; hypersensitivity to a study drug; uncontrolled hypothyroidism; active myopathy; a recent major cardiovascular event; and glycated haemoglobin > 10%.

Participants were classified according to the lipid-lowering regimen selected by the treating physician in consultation with the patient. Group A received atorvastatin 20 mg orally once daily, whereas Group B received atorvastatin 20 mg orally once daily plus ezetimibe 10 mg orally once daily. Atorvastatin 20 mg was classified as a moderate-intensity statin. The background statin agents and doses were identical in both treatment cohorts. Treatment allocation was not randomised and remained part of routine clinical care. The prescribed regimen was continued for 12 weeks unless treatment modification or discontinuation was required because of intolerance or safety concerns. The participants were reassessed at week 12.

The required sample size was calculated for a two-sided comparison of two independent means with equal group sizes. The formula was $n \text{ per group} = 2 \times (Z_{\alpha/2} + Z_{\beta})^2 \times SD^2 / \Delta^2$. With $Z_{\alpha/2} = 1.96$ for a two-sided alpha of 0.05, $Z_{\beta} = 0.84$ for 80% power, an anticipated common standard deviation of 20 mg/dL, and a minimum between-group difference of interest of 10 mg/dL, the calculated requirement was 62.72 participants per group, rounded up to 63 participants. Allowing 10% for non-completion gave $63/0.90 = 70$ participants per group, for a total target sample size of 140.

Data collected at baseline included age, body mass index, sex, diabetes duration, hypertension, glycated haemoglobin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides. Liver function, renal function, creatine kinase levels, and adverse events were recorded at baseline and week 12. Venous blood samples were obtained at baseline and at the 12-week follow-up visit after an overnight fast of 8–12 h. The week-12 sample was collected within seven days before or after the scheduled visit. Serum total cholesterol, triglycerides, HDL-C, alanine aminotransferase, serum creatinine, and creatine kinase levels were measured in the same hospital laboratory using routine automated enzymatic methods. LDL-C levels were measured directly. The laboratory followed routine internal quality control procedures throughout the study.

The primary outcome was defined as the absolute change in LDL-C levels between baseline and week 12. The secondary outcomes included the percentage change in LDL-C, alterations in total cholesterol, HDL-C, and triglyceride levels, attainment of LDL-C levels below 70 mg/dL, achievement of an LDL-C reduction of at least 50%, and documented adverse events. The safety endpoints included myalgia, alanine aminotransferase levels exceeding

three times the upper limit of normal, creatine kinase levels exceeding five times the upper limit of normal, and cessation of treatment due to an adverse event.

Exposure was defined by the regimen prescribed at enrolment: atorvastatin 20 mg once daily or atorvastatin 20 mg plus ezetimibe 10 mg once daily. The primary and secondary outcomes were defined before the analysis, as described above. Potential confounders included baseline LDL-C, age, sex, body mass index, diabetes duration, hypertension, glycated haemoglobin, adherence, diet, cardiovascular risk, comorbidity, and the clinical reason for treatment selection. Only baseline LDL-C levels were included in the primary adjusted model. Other factors were either recorded for descriptive comparison or not measured sufficiently for adjustment. Consecutive recruitment was used to reduce selective enrolment. However, treatment selection by clinicians and patients may have introduced confounding by indication, and residual confounding cannot be excluded from this study.

Data were analysed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were summarised as mean and standard deviation, and categorical variables as number and percentage. The Shapiro-Wilk test was used to assess normality. Within-group changes were assessed using paired t-tests or Wilcoxon signed-rank tests, as appropriate. For the primary between-group comparison, analysis of covariance (ANCOVA) was used, with week-12 LDL-C as the dependent variable, treatment group as the fixed factor, and baseline LDL-C as the covariate. The treatment group coefficient was reported as the adjusted between-group difference in LDL-C reduction with a 95% confidence interval. Categorical outcomes were compared using the chi-square test or Fisher's exact test, as appropriate. All 140 participants had complete baseline characteristics, week-12 LDL-C measurements, target attainment outcomes, and recorded adverse event outcomes. No imputation was performed. All tests were two-sided, and statistical significance was set at $p < 0.05$. Secondary analyses were exploratory, and no adjustments for multiple comparisons were made. The primary model was adjusted only for baseline LDL-C. No multivariable, propensity score, subgroup, interaction, or sensitivity analyses were performed. Statin agents and intensity were not included as covariates because both cohorts received the same atorvastatin dose. Residual confounding related to treatment selection, adherence, cardiovascular risk, and other clinical factors remains a possibility.

The Institutional Review Board/Ethics Committee of the Combined Military Hospital Rawalpindi approved the study before participant enrolment (reference no. 1003, dated 16 March 2026). All participants provided written informed consent before their enrolment. Study data were de-identified before analysis and were handled in accordance with institutional confidentiality requirements. This study was conducted in accordance with the Declaration of Helsinki.

Results

A total of 325 patients were assessed for eligibility during the study period. Of these, 185 were not enrolled because they did not meet the predefined eligibility criteria, had LDL-C levels below 70 mg/dL, had HbA1c levels above 10%, were already receiving ezetimibe or another non-statin lipid-lowering drug, had significant renal or hepatic disease, had a recent major cardiovascular event, or declined participation. The remaining 140 eligible participants were enrolled (70 participants in each treatment cohort) and included in the final analysis. Participants in Group A received atorvastatin 20 mg once daily, while those in Group B received atorvastatin 20 mg once daily plus ezetimibe 10 mg once daily. All 140 enrolled participants completed the 12-week assessment and had complete primary outcome data available for analysis. The mean age was 57.8 ± 8.5 years in the statin monotherapy group and 58.3 ± 8.1 years in the statin plus ezetimibe group. Men accounted for 55.7% and 54.3% of the groups. The mean baseline LDL-C was 125.3 ± 23.1 mg/dL in Group A and 127.9 ± 24.8 mg/dL in Group B. The other recorded baseline characteristics are summarised in Table 1. Baseline significance testing was not used to claim equivalence because the treatment allocation was not randomised.

LDL-C decreased by a mean of 35.6 mg/dL (28.4%) with atorvastatin 20 mg and 54.0 mg/dL (42.2%) with atorvastatin 20 mg plus ezetimibe 10 mg, as shown in Figure 2A. In the ANCOVA model, with week-12 LDL-C as the dependent variable and baseline LDL-C as the covariate, combination therapy was associated with an additional 18.4 mg/dL reduction (95% confidence interval 12.8 to 24.0; $P < 0.001$) (Table 2 and Figure 2B). This adjusted estimate describes an association within the observational cohort and does not eliminate the possibility of residual confounding.

By week 12, an LDL-C value below 70 mg/dL was reached by 26 of 70 participants (37.1%) on statin monotherapy and by 45 of 70 (64.3%) on statin plus ezetimibe ($p = 0.001$), corresponding to an odds ratio of 3.05 (95% confidence interval 1.52 to 6.11). An LDL-C reduction of at least 50% occurred in nine of 70 participants (12.9%) in Group A and 21 of 70 (30.0%) in Group B ($p = 0.01$). Both groups exhibited a decline in total cholesterol and triglyceride

levels, along with an increase in HDL-C levels. The between-group difference in HDL-C levels was not statistically significant ($p=0.07$). The descriptive baseline and week-12 lipid values for both treatment groups are presented in Figure 1.

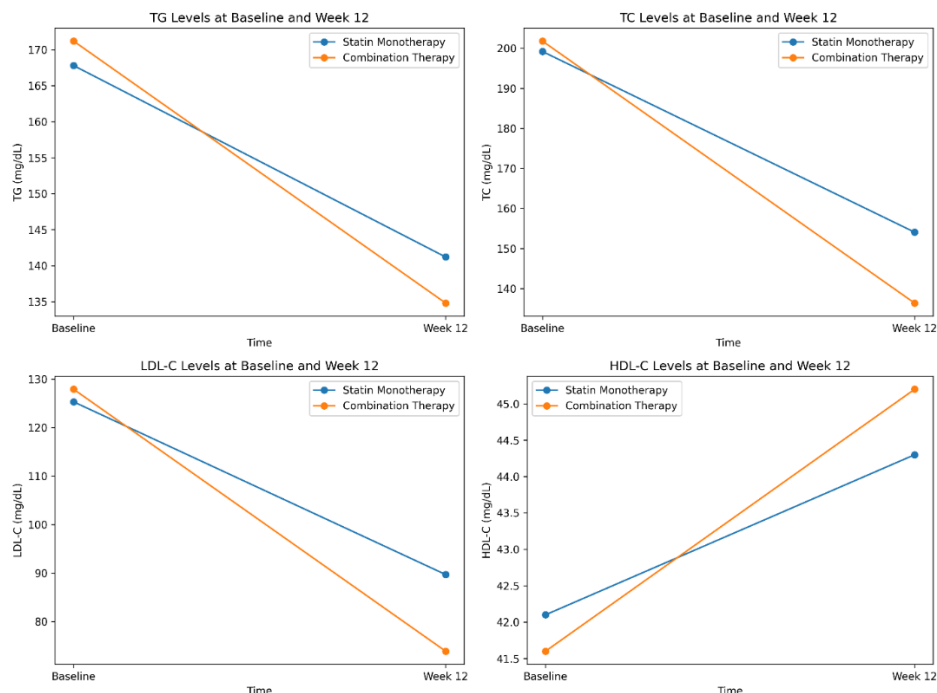


Figure 1: Changes in lipid parameters from baseline to week 12 according to treatment group. The panels show mean triglyceride, total cholesterol, LDL-C, and HDL-C concentrations at baseline and after 12 weeks in participants receiving atorvastatin 20 mg once daily or atorvastatin 20 mg plus ezetimibe 10 mg once daily. Values are expressed in mg/dL. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Any adverse event was recorded in 10 of 70 participants (14.3%) in Group A and 12 of 70 (17.1%) in Group B ($p=0.64$). Myalgia occurred in five and four participants. Alanine aminotransferase levels above three times the upper limit of normal occurred in one and two participants. Creatine kinase levels above five times the upper limit of normal occurred in none of the participants receiving monotherapy and in one participant receiving combination therapy. Treatment was discontinued because of adverse events in one and two participants, respectively. The small number of events and wide statistical uncertainty do not establish safety equivalence in this study.

Table 1: Baseline characteristics of the study participants

Characteristic	Group A: atorvastatin 20 mg (n=70)	Group B: atorvastatin 20 mg + ezetimibe 10 mg (n=70)
Age, years	57.8 ± 8.5	58.3 ± 8.1
Male sex, n (%)	39 (55.7)	38 (54.3)
BMI, kg/m ²	27.5 ± 3.6	27.9 ± 3.9
Duration of diabetes, years	8.4 ± 4.3	8.9 ± 4.6
Hypertension, n (%)	48 (68.6)	51 (72.9)
HbA1c, %	7.7 ± 0.9	7.8 ± 1.0
Total cholesterol, mg/dL	199.2 ± 29.1	201.8 ± 30.5
LDL-C, mg/dL	125.3 ± 23.1	127.9 ± 24.8
HDL-C, mg/dL	42.1 ± 8.5	41.6 ± 9.0
Triglycerides, mg/dL	167.8 ± 53.1	171.2 ± 56.2

Values are expressed as the mean $\pm$ standard deviation unless otherwise stated. BMI: body mass index; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol. All treatments were administered orally once daily.

Table 2: Primary, target-attainment, and safety outcomes at 12 weeks

Outcome	Group A: atorvastatin 20 mg (n=70)	Group B: atorvastatin 20 mg + ezetimibe 10 mg (n=70)	Between-group result
LDL-C change, mg/dL	-35.6	-54.0	Adjusted additional reduction 18.4 mg/dL (95% CI 12.8 to 24.0); $p < 0.001$
LDL-C <70 mg/dL, n (%)	26 (37.1)	45 (64.3)	OR 3.05 (95% CI 1.52 to 6.11); $p = 0.001$
LDL-C reduction $\geq 50\%$, n (%)	9 (12.9)	21 (30.0)	$p = 0.01$
Any adverse event, n (%)	10 (14.3)	12 (17.1)	$p = 0.64$

CI: confidence interval; LDL-C: low-density lipoprotein cholesterol; OR: odds ratio. The adjusted mean difference was estimated using ANCOVA with week-12 LDL-C as the dependent variable, treatment group as the fixed factor, and baseline LDL-C as the covariate. No other confounders were included. Positive values indicated a greater LDL-C reduction in Group B.

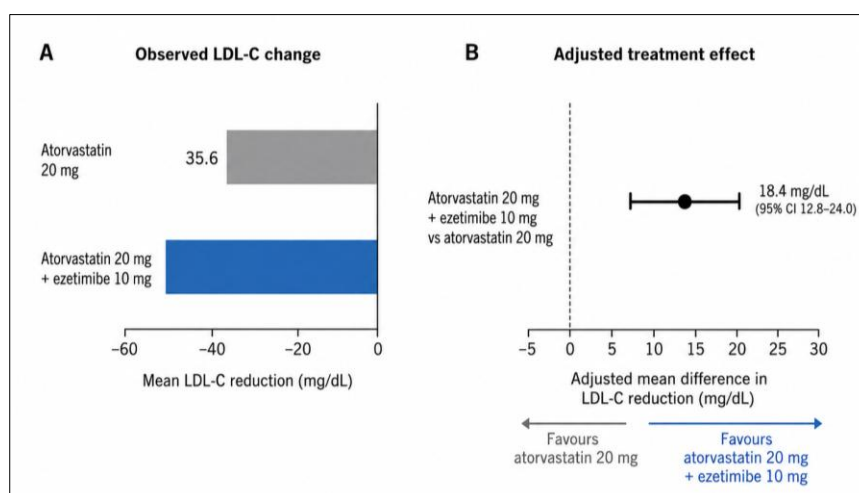


Figure 2: Observed and adjusted LDL-C reductions at 12 weeks. Panel A shows the mean reduction in LDL-C from baseline to week 12 in participants receiving atorvastatin 20 mg alone or atorvastatin 20 mg plus ezetimibe 10 mg once daily. Panel B shows the adjusted between-group difference in LDL-C reduction after adjustment for baseline LDL-C. The point represents the adjusted mean difference, and the horizontal line represents the 95% confidence interval. Positive values in Panel B favour atorvastatin plus ezetimibe.

CI: confidence interval; LDL-C: low-density lipoprotein cholesterol.

Discussion

This prospective observational cohort study found that statin therapy combined with ezetimibe was associated with a larger 12-week reduction in LDL-C levels than statin monotherapy. The adjusted additional reduction was 18.4 mg/dL. Combination therapy was also associated with a higher proportion of participants reaching LDL-C levels below 70 mg/dL and a higher proportion achieving at least 50% LDL-C reduction. The recorded adverse events were uncommon and did not differ statistically, although the study was too small and short to establish comparative safety.

The direction of the LDL-C effect was consistent with the randomised evidence. In RACING, moderate-intensity statin plus ezetimibe provided cardiovascular outcomes that were non-inferior to high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease and produced more frequent LDL-C target attainment.⁸ The trial in adults with type 2 diabetes by Moon et al. also found effective LDL-C lowering with rosuvastatin plus ezetimibe compared with high-intensity rosuvastatin.⁹ The present study cannot be compared directly with those trials because treatment allocation was not randomised, both cohorts received a fixed moderate-intensity atorvastatin regimen, and the study population was defined by diabetes and dyslipidaemia rather than a uniform history of atherosclerotic cardiovascular disease.

The higher rate of LDL-C target attainment may be clinically relevant in this context. The IMPROVE-IT diabetes analysis showed that adding ezetimibe after acute coronary syndrome reduced cardiovascular events, with a larger absolute benefit among patients with diabetes.¹⁰ A network meta-analysis also found that adding ezetimibe or a proprotein convertase subtilisin/kexin type 9 inhibitor to statin therapy can reduce non-fatal myocardial infarction and stroke in patients at a higher cardiovascular risk.¹² These findings support treatment intensification when LDL-C remains above the appropriate risk-based target. However, the current study measured lipid outcomes over 12 weeks. It did not measure cardiovascular events and could not show that the observed LDL-C difference caused a reduction in clinical events.

The absence of a statistically significant difference in the recorded adverse events should also be interpreted carefully. Large blinded statin trials have shown that most muscle symptoms reported during statin treatment are not caused by the statin, although a small excess occurs, particularly during the first year of treatment.¹³ Ezetimibe is generally used when additional LDL-C lowering is required or when the escalation of statin intensity is limited by tolerability. The present data are reassuring at a descriptive level, but only 22 participants had any adverse events, and follow-up was limited to 12 weeks. Rare hepatic or muscular events could not be assessed precisely.

The findings also have local implications. A recent Pakistani study of lipid-lowering practice in patients at high atherosclerotic cardiovascular risk identified gaps between recommended and observed statin use.¹⁴ Studies from Khyber Pakhtunkhwa and Rawalpindi have also documented a substantial burden of dyslipidaemia in patients receiving cardiovascular and tertiary care services.^{15,16} These reports support the need for systematic risk assessment, documentation of statin intensity, and timely addition of non-statin therapy when targets are not achieved. The current cohort adds prospective short-term data from a routine care setting; however, it should not be used to estimate national treatment effects.

Several factors may explain these observed differences. Ezetimibe and statins act at different points of cholesterol homeostasis; therefore, their effects on LDL-C are complementary. The magnitude of the response also depends on the baseline LDL-C, statin potency, dose, adherence, diet, genetic variation, and comorbidity. Observational evidence in diabetes suggests that the cardiovascular value of statin treatment varies with baseline risk and LDL-C level.¹⁷ A propensity-matched cohort of adults with impaired fasting glucose reported lower cardiovascular risk with statin plus ezetimibe than with statin alone, but residual confounding remains possible in such analyses.¹⁸ Comparative meta-analyses further show that statin regimens differ in their effects on non-HDL cholesterol and LDL-C.^{19,20} The use of the same atorvastatin dose in both groups reduces confounding from differences in statin agents and intensity. However, variations in adherence, diet, cardiovascular risk, comorbidity, and clinical reasons for treatment selection may have influenced the observed response.

This study had several strengths. Data were collected prospectively for this study. Both groups had the same follow-up intervals. The primary outcome was quantitative and clinically familiar to the authors. The analysis adjusted the main comparison for baseline LDL-C and reported a confidence interval in addition to the p-value. This study also reported target attainment and specific safety events, which are useful for clinical interpretation.

These limitations are substantial. Treatment allocation was non-randomised and influenced by physician prescriptions and patient preferences. Therefore, confounding by indication is likely. In both treatment groups, background statin exposure improved with moderate-intensity atorvastatin treatment. However, treatment allocation was not random and may have been affected by clinical characteristics not accounted for in the adjusted analysis. The use of a single statin agent and dose also reduces the generalisability to patients taking other statins or high-intensity statins. Cardiovascular risk, kidney disease, smoking, prior atherosclerotic cardiovascular disease, and other factors influencing treatment choice were not included in the adjusted models. The propensity score or inverse-probability method was not used. It was performed at a single centre, the follow-up period was short (12 weeks), and the sample size was not sufficiently large to detect rare adverse events or cardiovascular outcomes. Objective adherence, diet, physical activity, medication possession, apolipoprotein B, and lipoprotein(a) were not reported. These restrictions diminish causal certainty and generalisability.

Subsequent research should contrast varying statin intensities and combination regimens, quantify adherence using objective measures, stratify participants according to primary or secondary prevention status, and account for major

cardiovascular risk factors. Adopting a randomised or rigorously emulated target trial design would yield more robust comparative evidence. Extended follow-up is required to evaluate durable target attainment, persistence with treatment, cost, patient acceptability and cardiovascular outcomes.

Conclusions

Within this prospective observational cohort, the combination of a statin with ezetimibe was associated with a more pronounced 12-week decline in LDL-C and a greater degree of target attainment than statin therapy alone. The documented rates of adverse events showed no statistically significant difference, although the study was not powered to establish safety equivalence. These results warrant cautious interpretation in light of non-randomised treatment allocation, reliance on a single moderate-intensity atorvastatin regimen, incomplete adjustment for cardiovascular risk factors, and limited follow-up. Larger controlled investigations featuring standardised treatment exposure and more prolonged follow-up are required.

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Contributions:

FAS EA KAS MNQ SS - Conception, Design

HI - Acquisition, Analysis, Interpretation

HI - Drafting

FAS EA KAS MNQ SS - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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