ORIGINAL ARTICLE

Comparison of Rosuvastatin and Atorvastatin Regimens in the Achievement of LDL-C Goals: A Malaysian Real-World Cohort Study.

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Abstract

Background: Despite potent lipid-lowering therapies (LLT), achieving low-density lipoprotein cholesterol (LDL-C) targets remains challenging, especially in high-risk populations. This study evaluated the comparative efficacy of atorvastatin and rosuvastatin regimens and goal attainment within a Malaysian public tertiary care setting. **Methodology:** We conducted a retrospective cohort study of adults treated with atorvastatin or rosuvastatin (as monotherapy or combined with ezetimibe) at Hospital Taiping. Patients with continuous treatment (≥12 months) and paired lipid profiles (baseline 2022; follow-up 2023) were included. The primary outcome was 2019 ESC/EAS guideline target achievement. The secondary outcome was the mean reduction in LDL-C levels. **Results:** A total of 255 patients were included. Overall, only 19.2% (49/255) achieved their risk-stratified LDL-C targets. Goal attainment was notably poor in the high- and very-high-risk subgroups, with 85.8% failing to reach targets. Rosuvastatin plus ezetimibe demonstrated the greatest mean LDL-C reduction, significantly outperforming atorvastatin monotherapy (mean difference (MD) 0.65 mmol/L, p=0.045) and atorvastatin plus ezetimibe (MD 0.59 mmol/L, p=0.013). Analysis of treatment gaps revealed that 46.6% (96/206) of patients who failed to reach targets had not been titrated to the maximum tolerated statin dose. **Conclusion:** While rosuvastatin plus ezetimibe emerged as the most effective regimen, overall goal attainment remained suboptimal. Clinical inertia was a primary barrier, evidenced by the high proportion of uncontrolled patients remaining on sub-maximal doses. To bridge this gap, institutional strategies in the public health setting must prioritize earlier initiation of combination therapy and automated prompts for dose intensification in high-risk individuals.

Keywords: *Atorvastatin, cardiovascular risk, ezetimibe, LDL, rosuvastatin.*

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains a leading global health burden and a significant contributor to morbidity and mortality [1]. Low-density lipoprotein cholesterol (LDL-C) is established as a primary causal factor in the pathogenesis of ASCVD. Elevated circulating LDL-C drives the formation of atherosclerotic plaques within arterial walls, thereby increasing the risk of major adverse cardiovascular events, including myocardial infarction, stroke, and peripheral artery disease [2]. Consequently, the effective reduction of LDL-C levels forms the cornerstone of contemporary prevention strategies. International guidelines strongly advocate for the achievement of individualized LDL-C targets, particularly for individuals at elevated cardiovascular risk [3].

Statins, including high-potency agents such as rosuvastatin and atorvastatin, constitute the established first-line pharmacological intervention for LDL-C lowering [4]. While statin monotherapy is often effective, a substantial proportion of patients require more intensive therapy to reach guideline-recommended targets. In this context, combination therapies—notably the addition of ezetimibe to a statin regimen—serve as a valuable strategy to achieve further LDL-C reductions and improve the likelihood of goal attainment, as demonstrated in pivotal clinical trials [5].

However, the efficacy observed in highly controlled clinical trials does not always translate directly to routine clinical practice. Real-world populations exhibit greater heterogeneity in terms of patient demographics, co-existing medical conditions, medication adherence, and concomitant drug use. These factors significantly influence the magnitude of LDL-C reduction and the achievement of therapeutic goals. Therefore, understanding the performance of different statin regimens within a real-world setting is crucial for optimizing clinical decision-making.

To bridge this gap, this study evaluates the real-world effectiveness of rosuvastatin and atorvastatin (monotherapy versus combination) in meeting therapeutic targets and reducing LDL-C within a Malaysian specialist hospital. This research is particularly critical for developing nations, where formulary access and resource constraints often dictate treatment choices, and where local data are essential to validate whether global guidelines translate effectively into local practice.

Materials and Methods

Study design and setting

A retrospective cohort study was conducted at Hospital Taiping, Perak, Malaysia, to evaluate LDL-C target attainment and the magnitude of LDL-C reduction among patients prescribed atorvastatin or rosuvastatin. Target LDL-C levels were defined based on the patient's cardiovascular risk profile at baseline, in accordance with the 2019 European Society of Cardiology and the European Atherosclerosis Society ESC/EAS guidelines. [6] Specifically, targets were set at <1.4 mmol/L (<55 mg/dL) for very-high-risk patients, <1.8 mmol/L (<70 mg/dL) for high-risk patients, and <2.6 mmol/L (<100 mg/dL) for moderate-risk patients dan <3.0 mmol/L (<116 mg/dL) for low-risk patients.(Appendix 1) The study spanned 24 months (January 1, 2022, to December 31, 2023). We defined 2022 as the baseline identification period and 2023 as the follow-up period, ensuring a minimum 12-month interval to assess therapeutic response. Data extraction was completed in January 2024.

Study population and selection criteria

The source population comprised all adult patients (aged ≥ 18 years) attending medical specialist outpatient clinics at Hospital Taiping in 2022. Using the Pharmacy Information System (PHIS), we identified a specific cohort prescribed continuous (≥ 12 months) atorvastatin or rosuvastatin therapy, either as monotherapy or combined with ezetimibe. Inclusion required a documented baseline lipid profile (late 2021–2022) and a follow-up measurement in 2023 to enable longitudinal efficacy assessment. Finally,

to ensure data integrity and homogeneity, we excluded patients with incomplete records or those on alternative primary statins, strictly focusing on the comparative efficacy of the target high-intensity regimens.

Demographic characteristics, comorbidities, cardiovascular risk factors, and lipid-lowering therapy details (drug, dose, duration) were systematically extracted from electronic medical records using a standardized data collection form. Serum LDL-C levels were retrieved from Schuynet, the institution's web-based laboratory portal. Baseline LDL-C was defined as the measurement recorded in 2022, and follow-up LDL-C as the measurement in 2023, ensuring a minimum 12-month interval for evaluating therapeutic efficacy.

Study outcomes

The primary outcome was the mean change in LDL-C levels from baseline to follow-up across the treatment groups. This outcome aimed to compare the relative efficacy of atorvastatin and rosuvastatin— as monotherapy or combined with ezetimibe— in a real-world setting.

The secondary outcome was the proportion of patients in each group achieving their guideline-defined LDL-C targets (Appendix 1) at the follow-up assessment. This provides insight into the clinical effectiveness of these regimens in meeting major guideline recommendation.

Sample size was calculated using G*Power (version 3.1.9.4) based on an ANOVA: repeated measures, within-between interaction design. This design accounts for the four treatment groups (between-subject factor) and the two time points (baseline and follow-up; within-subject factor).We specified a moderate effect size ($f = 0.25$), a two-sided significance level (α) of 0.05, and a power ($1-\beta$) of 80%. We assumed a moderate correlation ($r=0.50$) between baseline and follow-up measurements. Based on these parameters, the minimum total sample size required to detect a significant treatment-by-time interaction was calculated to be 108 participants (approx. 27 per group). To account for potential data incompleteness, we targeted a total sample size of 128 patients.

Statistical analysis

Statistical analyses were performed using SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY). The normality of continuous variables was assessed via the Shapiro-Wilk test and visual inspection of histograms. Descriptive statistics for continuous data are expressed as mean ± standard deviation (SD) for normally distributed variables, or median and interquartile range (IQR) for non-normally distributed variables. Categorical data are reported as frequencies and percentages (n, %).To evaluate the primary outcome—the mean percentage change in LDL-C levels across the four treatment groups—a One-Way Analysis of Variance (ANOVA) was utilized. Homogeneity of variances was assessed using Levene's test. In the event of a statistically significant omnibus ANOVA, post-hoc pairwise comparisons were conducted using Tukey's Honestly Significant Difference (HSD) or Games-Howell (for unequal variances). Secondary outcomes (LDL-C goal attainment) and baseline categorical characteristics (e.g., gender, race) were compared across groups using Pearson's Chi-Square ($\chi 2$) test. Fisher's Exact test was employed when expected cell counts were fewer than five. All statistical tests were two-tailed, with statistical significance defined as $p < 0.05$.

Ethical considerations

The study protocol was registered with the National Medical Research Registry (NMRR ID-23-03503-RUL) and approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

To ensure confidentiality, all data were fully anonymized prior to analysis, and no unique identifiers are included in any report. Data are securely stored with restricted access limited to the Principal Investigator and will be archived for five years before secure disposal. Administrative permission was obtained from the Director of

Hospital Taiping and the Director General of Health, Malaysia.

Results

A total of 255 eligible patients were included in the final analysis. The flow of participants through screening, group allocation, and analysis is detailed in Figure 1. The distribution of participants across the four treatment arms was as follows: 115 (45.1%) received atorvastatin plus ezetimibe, 55 (21.6%) received rosuvastatin monotherapy, 50 (19.6%) received rosuvastatin plus ezetimibe, and 35 (13.7%) received atorvastatin monotherapy. These unequal group sizes reflect real-world clinical practice, where treatment selection was based on physician discretion rather than random assignment. The mean age of the overall cohort was 63.3 ±11.5 years. Analysis of variance indicated no statistically significant difference in mean age across the treatment groups ($F(3,251)=0.192$, $p=0.902$). However, a significant difference was observed in the prevalence of pre-existing ASCVD ($\chi2=8.840$, $df=3$, $p=0.032$). Specifically, patients prescribed combination therapies (atorvastatin or rosuvastatin plus ezetimibe) had a significantly higher prevalence of ASCVD compared to those on monotherapy, indicating a higher baseline cardiovascular risk profile in the combination cohorts. Variations in demographic distribution were also noted (Table 1). A higher proportion of Chinese patients were treated with rosuvastatin monotherapy or atorvastatin combination therapy, whereas Malay patients were most frequently prescribed atorvastatin plus ezetimibe. Additionally, male patients comprised a larger proportion of the atorvastatin plus ezetimibe group.

The primary efficacy outcome was the proportion of patients achieving guideline-defined LDL-C targets at the conclusion of the one-year follow-up. Overall, 49 of 255 participants (19.2%) successfully reached their specific LDL-C goals. Regarding the trajectory of LDL-C control, 17 patients (6.7%) successfully converted from uncontrolled baseline levels to achieving their target at one year. Thirty-two patients (12.5%) maintained goal attainment at both baseline and follow-up. Conversely, 10 patients (3.9%) who were at target at baseline experienced a regression, ending the observation period above their target threshold.

Goal attainment was notably lower among patients with elevated cardiovascular risk. Analysis revealed a statistically significant disparity in goal attainment between risk categories ($p < 0.001$). As illustrated in Figure 1, failure to achieve LDL-C targets was markedly higher in the high and very-high-risk groups (85.8%) compared to the low- and moderate-risk groups. This finding highlights the significant challenge of achieving stringent lipid goals in the population that stands to benefit most from intensive lipid-lowering therapy.

When comparing goal attainment across the four treatment regimens, the proportion of patients achieving LDL-C targets was numerically higher in the monotherapy arms compared to the combination therapy arms. However, this observed difference did not reach statistical significance ($\chi2=5.017$, $df=3$, $p=0.17$).

Despite low overall goal attainment, prescribing patterns demonstrated a statistically significant alignment between treatment intensity and baseline cardiovascular risk ($\chi2=10.445$, $df=3$, $p=0.010$). Patients categorized as moderate, high, or very-high risk were significantly more likely to be prescribed high-potency statin regimens compared to low-risk individuals. This indicates that while risk stratification principles were applied during treatment selection, this strategy alone was insufficient to ensure LDL-C goal attainment for the majority of the high-risk cohort. To compare the efficacy of the treatment regimens, we analyzed the mean reduction in LDL-C levels from baseline to one year. A one-

way ANOVA revealed a statistically significant difference in LDL-C reduction across the four treatment groups ($F(3,251)=3.987$, $p=0.008$), indicating that therapeutic response varied significantly by regimen. Post-hoc multiple comparisons identified rosuvastatin plus ezetimibe as the most effective regimen as shown in Table 3. It demonstrated a significantly greater LDL-C reduction compared to; atorvastatin monotherapy (mean difference [MD] 0.65; 95% CI 0.01, 1.30; $p=0.045$); rosuvastatin monotherapy (MD 0.64; 95% CI 0.07, 1.21; $p=0.021$); atorvastatin plus ezetimibe (MD 0.59; 95% CI 1.08, 0.93; $p=0.013$).

Analysis of treatment pathways identified deviations from standard intensification protocols in a small subset of patients. Specifically, 10 patients (6.1% of the combination therapy group; 3.9% of the total cohort) initiated ezetimibe prior to the maximization of their statin dosage. Our analysis identified a significant opportunity for treatment optimization. Of the 206 patients who did not achieve their LDL-C goals, 46.6% (n=96) were not prescribed the maximum tolerated statin dose. This highlights a critical area for improvement, suggesting that addressing therapeutic inertia and maximizing statin intensity could benefit nearly half of the patients.

Discussion

This study highlights a critical and persistent disconnect in contemporary cardiovascular risk management. While potent reductions in LDL-C were achieved using both rosuvastatin- and atorvastatin-based regimens, the proportion of patients attaining guideline-recommended LDL-C targets remained markedly suboptimal. This shortfall was particularly pronounced among patients classified at very high cardiovascular risk, a population for whom aggressive LDL-C reduction is strictly indicated to mitigate future CV events [2].

Our primary finding reveals that only 19.2% of the overall cohort successfully reached their guideline-defined LDL-C objectives. This low attainment rate underscores the substantial challenge clinicians face in translating the efficacy of lipid-lowering therapies, demonstrated rigorously in randomized controlled trials, into routine clinical practice. This observation is not isolated but reflects a broader, well-documented "treatment gap" in global cardiovascular prevention [7].

When situated within the context of large-scale observational data, our findings provide a valuable perspective. The 19.2% attainment rate observed in this cohort is lower than the 31.1% reported in the Spanish TERESA study, which similarly evaluated patients on high-intensity statins [8]. However, it is crucial to note that even in the TERESA cohort, 71.7% of very high-risk patients failed to achieve their targets [8]. Data from Asian populations indicate similar challenges, with goal attainment rates ranging from approximately 20% to 39% [9,10,11]. These discrepancies are likely multifactorial, potentially driven by variations in baseline risk profiles, patient adherence, and the prevalence of comorbidities such as diabetes and obesity [11].

Combination therapy involving rosuvastatin and ezetimibe demonstrated the greatest reduction in LDL-C levels. This aligns robustly with evidence from clinical trials [12]. Despite the availability of potent regimens, a substantial proportion of patients failed to reach their LDL-C targets. This gap appears driven by clinical inertia, evidenced by the fact that nearly half of the uncontrolled patients were not titrated to maximum statin intensities. Failing to intensify therapy in these individuals prolongs their exposure to elevated ASCVD risk, violating the core preventive principle that 'time is plaque' [13] Literature indicates that early up-titration to high-intensity statins is independently associated with a lower risk of subsequent CV events compared to regimens that are not intensified. [14]

Current clinical guidelines strongly advocate for aggressive management. The 2019 ESC/EAS guidelines recommend stringent goals (e.g., <1.4 mmol/L for very high-risk patients) and explicitly endorse the proactive use of combination therapy [6]. Similarly, American College of Cardiology and the American Heart Association (ACC/AHA) guidelines emphasize achieving maximal tolerated statin intensity followed by the sequential addition of ezetimibe and Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors [4]. Beyond clinical outcomes, suboptimal lipid management imposes a severe economic burden. Projections estimate that enhancing LDL-C control specifically among high-risk patients with established ASCVD in Malaysia could yield a combined economic benefit of over 200 million MYR across a decade—comprising 72 million MYR in direct healthcare savings and 132.4 million MYR in productivity gains—while simultaneously saving over 32,000 life-years. [15]

In this retrospective analysis, medication adherence was proxied by the consistency of prescription refills documented within the 12-month follow-up window. Consequently, non-adherence cannot be excluded as a contributing factor to the suboptimal goal attainment observed in this cohort.

The findings of this study carry immediate implications for clinical practice in Malaysia. Given each doubling of the dose yields only a modest ~6% additional reduction in LDL-C [16, 17] and the superior performance of the rosuvastatin-ezetimibe combination observed in this cohort, clinical protocols should shift from a stepwise titration model to an 'upfront combination' strategy for high-risk patients. Initiating combination therapy at the outset could circumvent clinical inertia and achieve targets more rapidly.

Policy reforms are necessary to optimize national lipid management. Specifically, we recommend: (1) decentralizing prescribing privileges for ezetimibe and high-intensity statins to primary care levels to facilitate upfront combination therapy; and (2) re-evaluating the current MOH formulary listing for PCSK9 inhibitors to expand access for the high-risk group, ensuring a complete continuum of care for ASCVD prevention

Future research should focus on prospective studies evaluating major adverse CV (MACE) rather than surrogate lipid markers to confirm the long-term benefit of this strategy in the Malaysian population. Additionally, a formal pharmacoeconomic analysis is needed to quantify the cost-effectiveness of widening access to generic high-intensity statins at the primary care level.

However, this study has limitations inherent to its retrospective design. Despite statistical adjustments, the analysis remains susceptible to potential confounding variables and selection bias. The reliance on electronic medical records limited our ability to capture certain granular data, such as precise medication adherence (beyond refill records), specific justifications for treatment modifications, and detailed adverse event profiles. Additionally, as this study was conducted at a single public-funded hospital in Malaysia, the findings may not be fully generalisable to other healthcare settings or populations. Consequently, these results should be interpreted with caution, particularly regarding the precise magnitude of treatment effects.

Conclusion

In conclusion, this study reinforces the concerning reality of a significant and persistent gap between guideline-recommended LDL-C targets and the levels achieved by patients in routine clinical practice, particularly those at the highest cardiovascular risk.

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Author contributions
D.G., L.J.S., and C.S.J. were involved in the initial proposal development. L.JS. oversaw the data acquisition for the study. D.G. primarily conducted the data analysis. All three authors (D.G., L.J.S., and C.S.J.) contributed to the preparation, editing, and final review of the manuscript.

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Conflict of interest
The investigators declare no conflict of interest.

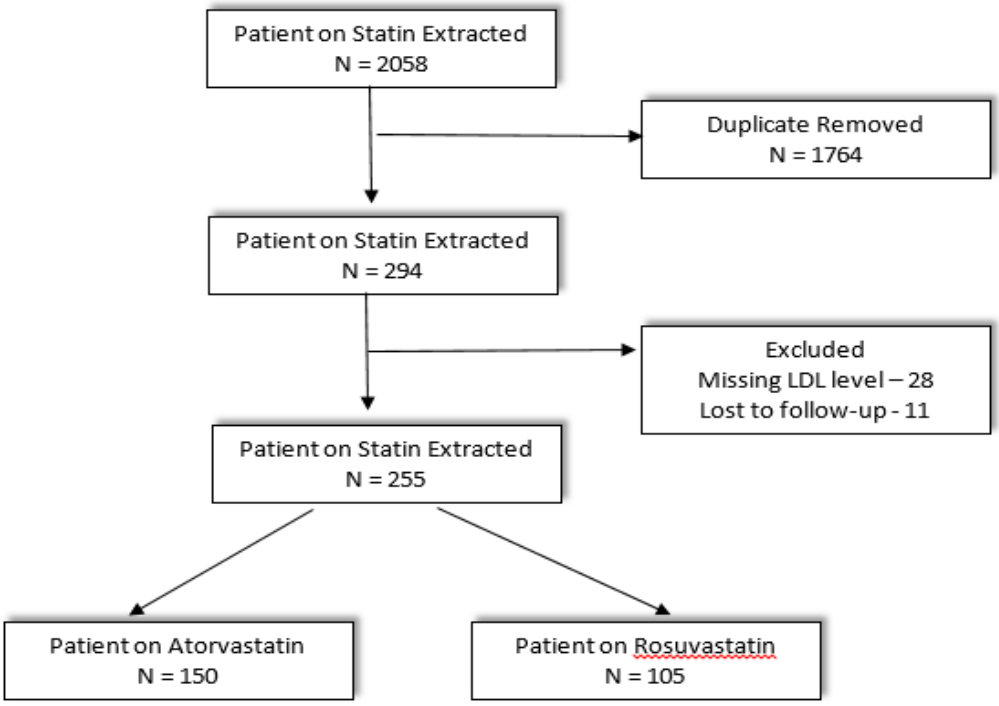

Figure 1. Study sample flow diagram

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants, Stratified by Statin Group.

	Atorvastatin	Rosuvastatin	Atorvastatin + Ezetimibe	Rosuvastatin + Ezetimibe	*P*-value
Age, in years	62.9 (10.6)	62.8 (12.5)	63.2 (11.3)	64.4 (11.9)	0.902
Gender,					
Male	16 (12.1)	33 (25.0)	66 (50.0)	17 (12.9)	0.020
Female	19 (15.4)	22 (17.9)	49 (39.8)	33 (26.8)	
Ethnicity					
Malay	16 (13.0)	13 (10.6)	64 (52.0)	30 (24.4)	< 0.001
Chinese	7 (9.9)	30 (42.3)	27 (38.0)	7 (9.9)	
Indian	12 (19.3)	12 (19.3)	24 (39.3)	13 (21.3)	
Presence of ASCVD	20 (10.2)	41 (21.1)	93 (47.9)	40 (20.6)	0.032
Presence of Diabetes	20 (13.8)	36 (24.8)	57 (39.3)	32 (22.1)	0.158
CV Risk					
Very High	23 (11.6)	41 (20.7)	93 (47.0)	41 (20.7)	0.520
High	5 (17.9)	5 (17.9)	12 (42.9)	6 (21.4)	
Moderate	3 (25.0)	3 (25.0)	5 (41.7)	1 (8.3)	
Low	4 (23.5)	6 (35.3)	5 (29.4)	2 (11.8)	
Baseline LDL-C	2.68 (1.11)	2.53 (1.09)	3.25 (1.17)	3.92 (1.99)	<0.001

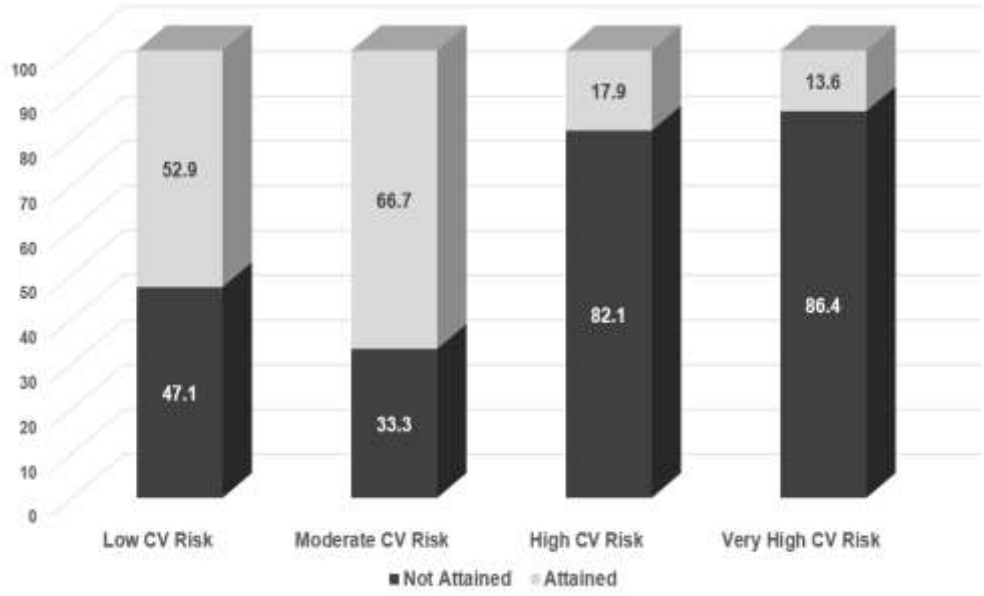

Figure 2. Distribution of attainment of low-density lipoprotein-c by cardiovascular risk

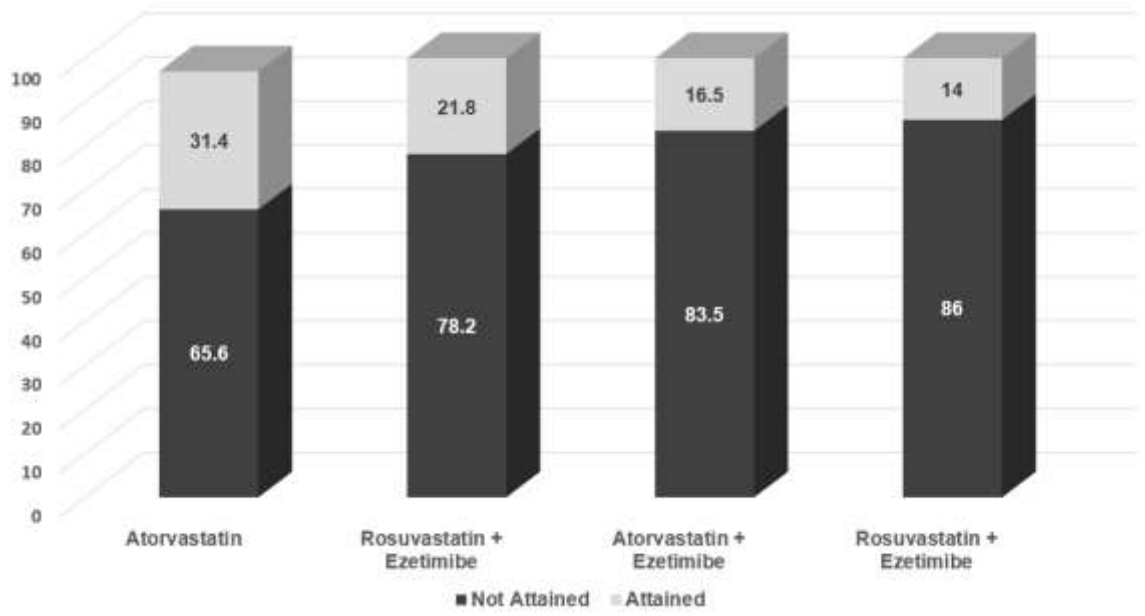

Figure 3. Distribution of attainment of low-density lipoprotein-c by statin group

Table 2. Association of cardiovascular risk and statin intensity

Baseline CV Risk	Moderate Intensity Statin	High Intensity Statin
Low CV Risk	8 (47.1%)	9 (52.9%)
Moderate CV Risk	2 (16.7)	10 (83.3%)
High CV Risk	4 (14.3%)	24 (85.7%)
Very High CV Risk	41 (16.1%)	214 (83.9%)

Note. Fisher's exact test was used due to small expected cell counts (p = 0.01); CV = Cardiovascular

Table 3. Tukey HSD post hoc comparisons for LDL reduction

Comparison	Mean Difference	95% CI	p-value
Rosuvastatin + Ezetimibe vs Atorvastatin	0.65	0.01, 1.30	0.045
Rosuvastatin + Ezetimibe vs Atorvastatin + Ezetimibe	0.59	0.09, 1.08	0.013
Rosuvastatin + Ezetimibe vs Rosuvastatin	0.64	0.07, 1.21	0.021
Rosuvastatin vs Atorvastatin	0.01	−0.62, 0.65	1.000
Rosuvastatin vs Atorvastatin + Ezetimibe	-0.05	-0.53, 0.43	0.992
Atorvastatin vs Atorvastatin + Ezetimibe	−0.07	−0.63, 0.50	0.990

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Appendix 1

Cardiovascular Risk Category	LDL-C Treatment Goal	Clinical Description
Very High Risk	**<1.4 mmol/L (<55 mg/dL)** *AND* ≥ 50% reduction from baseline	Documented ASCVD (clinical or imaging) Diabetes (DM) with target organ damage Severe CKD (eGFR <30) Calculated SCORE risk ≤10% Familial Hypercholesterolaemia (FH) with ASCVD
High Risk	**<1.8 mmol/L (<70 mg/dL)** *AND* ≥ 50% reduction from baseline	Markedly elevated single risk factor (e.g., TC >8 mmol/L) Diabetes (DM) without target organ damage (duration ≥10 years) Moderate CKD (eGFR 30–59 Calculated SCORE risk ≥ 5% and <10% FH without other major risk factors
Moderate Risk	**<2.6 mmol/L (<100 mg/dL)**	Young patients (T1DM <35y; T2DM <50y) with DM <10 years duration Calculated SCORE risk ≥1% and <5%
Low Risk	**<3.0 mmol/L (<116 mg/dL)**	Calculated SCORE risk <1%