Research Article

Rosuvastatin Monotherapy Versus Rosuvastatin/Ezetimibe Combination Therapy on Insulin Sensitivity, Vascular Inflammation, and Lipid Profile In Patients With Type 2 Diabetes Mellitus: A Randomised Controlled Trial

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is characterised by insulin resistance, atherogenic dyslipidaemia, and chronic low-grade inflammation, collectively elevating atherosclerotic cardiovascular disease (ASCVD) risk. Statins are the cornerstone of lipid-lowering therapy in T2DM; however, the potential of rosuvastatin/ezetimibe combination therapy to provide additional cardiometabolic benefits beyond lipid lowering remains incompletely characterised.

Methods: A prospective, open-label, parallel-group randomised controlled trial was conducted at a tertiary care centre in Tamil Nadu, India. Ninety statin-naive adults with T2DM and dyslipidaemia were randomised 1:1 to rosuvastatin 10 mg monotherapy (Group I) or rosuvastatin 5 mg plus ezetimibe 10 mg combination therapy (Group II) once daily for 12 weeks. Primary outcomes were changes in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), high-sensitivity C-reactive protein (hsCRP), and LDL cholesterol from baseline to week 12. Secondary outcomes included changes in fasting insulin, HDL cholesterol, triglycerides, fasting blood sugar (FBS), and glycated haemoglobin (HbA1c).

Results: Both groups were comparable at baseline. Combination therapy produced significantly greater reductions in LDL cholesterol (mean change: −27.2 mg/dL vs −19.2 mg/dL; p = 0.02), HOMA-IR (−1.01 vs −0.49; p = 0.002), and hsCRP (−0.41 mg/L vs −0.20 mg/L; p = 0.01) compared with monotherapy. HDL cholesterol increased more in Group II (45.6 ± 6.8 vs 43.5 ± 6.4 mg/dL; p = 0.03), and triglyceride reduction was also greater (p = 0.04). Fasting insulin declined significantly in Group II (p = 0.03). Although both groups demonstrated significant within-group reductions in FBS and HbA1c, the intergroup difference in HbA1c was not statistically significant (p = 0.21).

Conclusions: Rosuvastatin/ezetimibe combination therapy demonstrated superior efficacy over rosuvastatin monotherapy in improving lipid parameters, reducing insulin resistance, and attenuating systemic inflammation in patients with T2DM and dyslipidaemia. hese findings suggest that rosuvastatin/ezetimibe combination therapy may offer additional cardiometabolic benefits compared with rosuvastatin monotherapy in patients with T2DM and dyslipidaemia.

Trial Registration: Clinical Trials Registry of India: CTRI/2025/11/097905.

Keywords: Type 2 diabetes mellitus; rosuvastatin; ezetimibe; dyslipidaemia; insulin resistance; HOMA-IR; high-sensitivity C-reactive protein; combination therapy; randomised controlled trial.

Introduction

Type 2 diabetes mellitus (T2DM) has emerged as one of the foremost public health challenges of the 21st century, affecting approximately 537 million adults worldwide and projected to rise to 783 million by 2045 [1]. India bears a disproportionate share of this burden, with over 77 million individuals living with the condition [2]. Beyond glycaemic dysregulation, T2DM is characterised by a constellation of interconnected metabolic abnormalities — including atherogenic dyslipidaemia, insulin resistance, and chronic systemic inflammation — that collectively accelerate atherosclerotic cardiovascular disease (ASCVD), the leading cause of morbidity and mortality in this population [3].

Dyslipidaemia is a near-universal comorbidity in T2DM, occurring in 70–97% of affected individuals [4]. The hallmark lipid phenotype — elevated triglycerides, reduced high-density lipoprotein cholesterol (HDL-C), and an increased proportion of small dense low-density lipoprotein (LDL) particles — arises directly from hepatic overproduction of very low-density lipoprotein (VLDL) driven by insulin resistance [5]. This atherogenic triad, compounded by a pro-inflammatory and pro-thrombotic milieu, amplifies cardiovascular risk independently of conventional risk factors [6].

Insulin resistance, quantified in clinical research using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [7], is the central pathophysiological driver of both the metabolic and vascular complications of T2DM. In the insulin-resistant state, selective impairment of the phosphatidylinositol 3-kinase (PI3K) pathway in vascular endothelium reduces nitric oxide production,

promotes endothelial dysfunction, and shifts vascular homeostasis towards a pro-atherogenic phenotype [8]. Concurrently, chronic low-grade systemic inflammation, reflected by elevated high-sensitivity C-reactive protein (hsCRP), directly potentiates insulin resistance through serine phosphorylation of insulin receptor substrate-1 and contributes independently to cardiovascular risk [9].

Statins, as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, remain the cornerstone of lipid-lowering therapy in patients with T2DM and are endorsed by all major cardiovascular and diabetes guidelines [10]. Beyond their lipid-lowering action, statins exert pleiotropic effects including improvements in endothelial function, attenuation of vascular inflammation, and plaque stabilisation [10]. Rosuvastatin, a high-potency synthetic statin with a hydrophilic structure and marked hepatoselectivity, offers superior LDL-C reduction compared with other statins at equivalent doses and is particularly well-suited for managing the complex dyslipidaemia of T2DM [10].

Despite robust statin therapy, a substantial proportion of patients with T2DM fail to achieve guideline-recommended LDL-C targets, necessitating intensification of lipid-lowering treatment [10]. Ezetimibe, a selective inhibitor of the Niemann-Pick C1-Like 1 protein mediating intestinal cholesterol absorption, provides an LDL-C-lowering mechanism entirely distinct from and complementary to statin action. Evidence from the landmark IMPROVE-IT and RACING trials has established that statin/ezetimibe combination therapy achieves superior lipid target attainment with a favourable tolerability profile compared to high-intensity statin monotherapy [11,12].

While the lipid-lowering superiority of combination therapy is well established, its effects on insulin sensitivity and systemic inflammation in patients with T2DM remain a subject of ongoing investigation. The available evidence is heterogeneous, with some studies suggesting potential insulin-sensitising and anti-inflammatory benefits of combination therapy, while others report neutral or conflicting effects. This therapeutic uncertainty is clinically important: in a population already characterised by both insulin resistance and chronic inflammation, a lipid-lowering strategy that simultaneously addresses these pathophysiological mediators of cardiovascular risk would offer substantial advantages.

The present study was therefore designed to compare the effects of rosuvastatin 10 mg monotherapy with rosuvastatin 5 mg/ezetimibe 10 mg combination therapy on insulin sensitivity (HOMA-IR), vascular inflammation (hsCRP), and the complete lipid profile in patients with T2DM and dyslipidaemia over a 12-week treatment period.

Methods

Study Design and Setting

This was a prospective, open-label, parallel-group, randomised controlled trial conducted at the Department of General Medicine, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India — a tertiary care academic medical centre. The study was designed to evaluate the comparative effects of rosuvastatin monotherapy and rosuvastatin/ezetimibe combination therapy on insulin sensitivity, vascular inflammation, and lipoprotein response over a 12-week treatment period. The trial was self-funded by the principal investigator and conducted in accordance with the principles of the Declaration of Helsinki [13] and applicable Good Clinical Practice guidelines. The study commenced in September 2024 with an 18-month planned duration.

Ethics Approval and Trial Registration

Institutional Ethics Committee (IEC) approval was obtained prior to study initiation (Ethics Clearance Number: SRMIEC-ST0924-1797; Reg. No.: EC/NEW/INST/2022/2933; IEC meeting date: 04 September 2024; approval letter issued: 04 December 2024), SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur. The trial was prospectively registered with the Clinical Trials Registry of India (CTRI/2025/11/097905) in accordance with national regulatory requirements.

Participants

Adults aged over 18 years with an established diagnosis of T2DM — confirmed by HbA1c 6.5–9.0%, fasting blood glucose > 126 mg/dL, or random blood glucose > 200 mg/dL with symptoms of hyperglycaemia [14] — and with LDL-C > 100 mg/dL at screening were considered eligible [10]. All participants were required to be statin-naive and insulin-naive (no therapy in the preceding three months), to have serum AST and ALT within 1.5 times the upper limit of normal, and to provide written informed consent.

Patients were excluded if they had: known hypersensitivity to statins or ezetimibe; familial hypercholesterolaemia; chronic kidney disease stage IIIb or worse (eGFR < 45 mL/min/1.73 m^2); established heart failure of any functional class; known coronary artery disease (prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting); history of stroke or transient ischaemic attack; or current pregnancy or lactation.

All participants were provided with a written Patient Information Sheet in English and Tamil. Confidentiality was maintained throughout; participants were identified by unique study numbers in all documents and databases.

Sample Size

The sample size was calculated based on the primary outcome of change in HOMA-IR from baseline to 12 weeks. An expected reduction of 1.5 HOMA-IR units in the combination therapy group versus 0.5 units in the monotherapy group was assumed, based on prior literature [7]. Using a two-sample means formula with a two-sided alpha of 0.05, 80% power, and a pooled standard deviation of 2.0, the calculated per-group requirement was 63 participants. Accounting for an anticipated 15% dropout rate, the target recruitment was set at 45 participants per group, yielding a total sample size of 90.

Randomisation and Allocation Concealment

Eligible participants who provided written informed consent were randomised in a 1:1 ratio to one of two treatment groups. The random allocation sequence was generated using a computer-generated random number sequence prior to study commencement. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes. Upon enrolment, the next sequential envelope was opened to determine group assignment. The personnel responsible for enrolling participants were the same individuals who opened the envelopes; however, the sequence was generated independently by a separate investigator not involved in participant enrolment or outcome assessment. Simple randomisation without blocking or stratification was employed. The random sequence was generated using computer-based random number generation.

Blinding

This trial was conducted as an open-label study. Neither participants nor treating clinicians were blinded to treatment allocation. Laboratory analyses were performed on coded samples, and the laboratory technicians processing samples were unaware of group assignments. Objective biochemical endpoints were used as primary and secondary outcome measures to mitigate the risk of assessment bias inherent to the open-label design.

Interventions

Participants randomised to Group I (monotherapy) received rosuvastatin 10 mg orally once daily at bedtime. Participants randomised to Group II (combination therapy) received rosuvastatin 5 mg plus ezetimibe 10 mg orally once daily at bedtime. Both regimens were administered for 12 weeks. All participants continued their pre-existing oral hypoglycaemic medications without modification unless clinically indicated. Standard counselling on dietary modifications (reduced saturated fat intake, increased dietary fibre, moderated carbohydrate intake) and physical activity (at least 150 minutes of moderate-intensity exercise per week) [15] was provided uniformly to all participants at baseline. Medication adherence was assessed at the 12-week follow-up visit by pill counting and structured participant interview.

Outcome Measures

The primary outcomes were: (1) change in HOMA-IR from baseline to 12 weeks [7]; (2) change in hsCRP from baseline to 12 weeks; and (3) change in LDL cholesterol from baseline to 12 weeks [10].

Secondary outcomes included: changes in fasting serum insulin; changes in total cholesterol, HDL-C, and triglycerides; changes in fasting blood sugar (FBS) and HbA1c; proportion of participants achieving LDL-C reduction > 50%; proportion achieving LDL-C < 70 mg/dL [10]; and incidence of adverse events.

Clinical and Laboratory Assessments

Assessments were performed at baseline (Visit 1) and at 12 weeks (Visit 2, ±1 week). At each visit, a detailed clinical history, physical examination, and anthropometric measurements (height, weight, BMI) were recorded. Blood samples were collected following an overnight fast of 8–10 hours. Laboratory parameters assessed at both visits included: fasting lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides); fasting blood glucose; post-prandial blood glucose; HbA1c; fasting serum insulin; and hsCRP. Baseline assessments additionally included complete blood count, renal function tests, liver function tests, and urine examination. LDL-C was calculated using the Friedewald formula when triglycerides were below 400 mg/dL [16]. All laboratory analyses were performed using standardised, quality-controlled instruments at the SRM Medical College Hospital laboratory. Internal quality control samples were included in each analytical batch.

HOMA-IR was calculated using the formula: HOMA-IR = (Fasting Insulin [µIU/mL] × Fasting Glucose [mg/dL]) / 405 [7].

Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY) and GraphPad Prism version 9.0. A two-tailed p-value < 0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation (SD); categorical variables as frequencies and percentages. Intergroup comparisons of continuous variables were performed using independent samples t-test for normally distributed data and the Mann-Whitney U test for non-parametric data. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Within-group comparisons from baseline to follow-up were performed using the paired t-test or Wilcoxon signed-rank test. Effect sizes were calculated using Cohen's d. Pearson or Spearman correlation coefficients were used for correlation analyses. Prespecified subgroup analyses were conducted

based on age, sex, baseline HbA1c, LDL-C, HOMA-IR, and BMI. No missing data were observed during the study period; therefore, imputation methods were not required. The safety analysis included all participants who received at least one dose of study medication.

Patient and public involvement: Patients were not involved in the design, conduct, or reporting of this study. The findings will be disseminated to participants through the treating clinicians on request.

This manuscript has been prepared in accordance with the CONSORT 2010 reporting guidelines for randomized controlled trials.

Results

Participant Flow and Recruitment

A total of 90 participants with T2DM and dyslipidaemia were enrolled and randomly allocated: 45 to Group I (rosuvastatin 10 mg monotherapy) and 45 to Group II (rosuvastatin 5 mg/ezetimibe 10 mg combination therapy). All 90 randomised participants received at least one dose of the assigned study medication. The 12-week follow-up assessments were completed by all 90 participants; no withdrawals, dropouts, or protocol deviations requiring exclusion were recorded during the study period. All 90 participants were therefore included in both the intention-to-treat and per-protocol analyses. The study flow is presented in accordance with CONSORT 2010 guidelines.

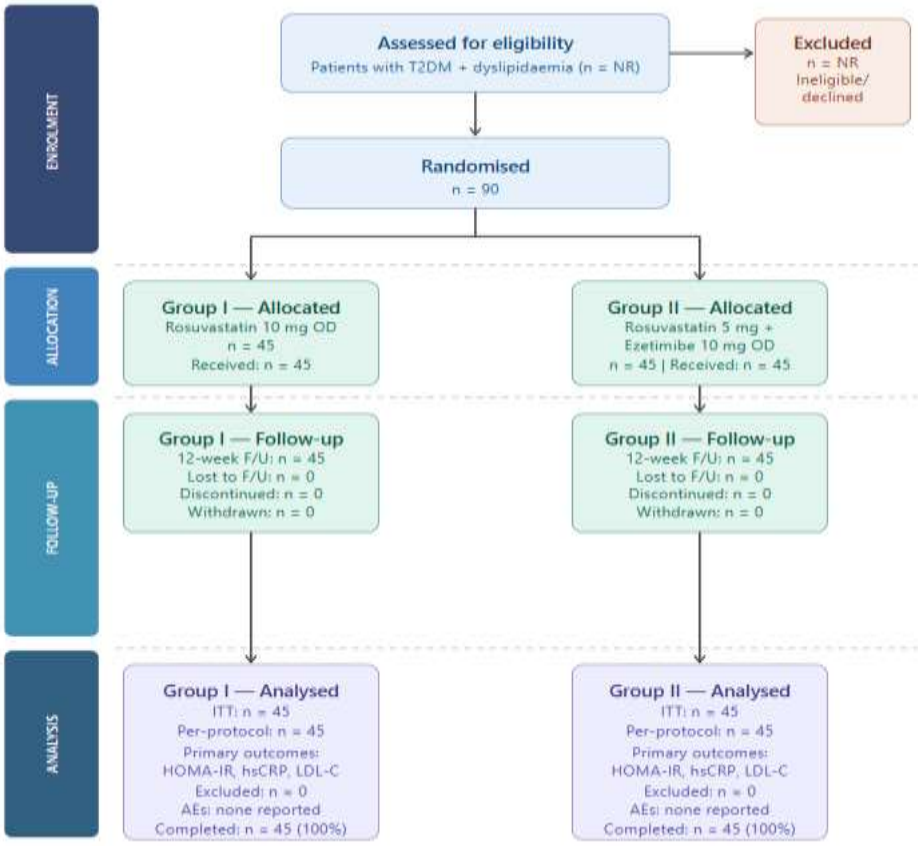

Figure 1. CONSORT flow diagram showing participant enrolment, randomisation, follow-up, and analysis. Group I: rosuvastatin 10 mg monotherapy; Group II: rosuvastatin 5 mg + ezetimibe 10 mg combination therapy.

Baseline Characteristics

The two groups were well matched at baseline across all demographic and biochemical parameters (Table 1). The mean age was 43.2 ± 9.1 years in Group I and 42.7 ± 8.7 years in Group II (p = 0.78). Group I comprised 26 males (57.8%) and 19 females (42.2%); Group II comprised 25 males (55.6%) and 20 females (44.4%); the gender distribution did not differ significantly between groups (p = 0.84). Mean fasting blood sugar, HbA1c, LDL-C, HDL-C, triglycerides, fasting insulin, hsCRP, and HOMA-IR were all comparable at baseline, with no statistically significant intergroup difference for any parameter (all p > 0.05). This baseline equivalence supports the attribution of post-treatment differences to the interventions under study.

Table 1. Baseline Demographic and Biochemical Characteristics of Study Participants

Parameter	Group I (Rosuvastatin 10 mg) n = 45	Group II (Rosuvastatin 5 mg + Ezetimibe 10 mg) n = 45	p-value
Age (years), mean ± SD	43.2 ± 9.1	42.7 ± 8.7	0.78
Sex: Male, n (%)	26 (57.8%)	25 (55.6%)	0.84
Sex: Female, n (%)	19 (42.2%)	20 (44.4%)	
Fasting Blood Sugar (mg/dL), mean ± SD	142.6 ± 28.4	143.8 ± 29.1	0.82
HbA1c (%), mean ± SD	7.92 ± 0.74	7.86 ± 0.68	0.67
LDL Cholesterol (mg/dL), mean ± SD	134.6 ± 32.5	135.8 ± 30.8	0.89
HDL Cholesterol (mg/dL), mean ± SD	41.8 ± 6.7	42.1 ± 7.0	0.84
Triglycerides (mg/dL), mean ± SD	186.7 ± 41.6	189.4 ± 39.8	0.76
Fasting Insulin (µIU/mL), mean ± SD	14.2 ± 3.5	14.1 ± 3.7	0.91
hsCRP (mg/L), mean ± SD	0.86 ± 0.44	0.91 ± 0.46	0.62
HOMA-IR, mean ± SD	3.98 ± 1.02	4.05 ± 1.05	0.76

SD: standard deviation; HbA1c: glycated haemoglobin; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; hsCRP: high-sensitivity C-reactive protein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. p-values from independent samples t-test (continuous) or chi-square test (categorical).

Primary Outcomes

The primary outcomes are summarised in Table 2. Combination therapy produced significantly greater improvements in all three primary endpoints.

Insulin Resistance (HOMA-IR): HOMA-IR decreased from 3.98 ± 1.02 to 3.48 ± 0.94 in Group I (mean change: −0.49) and from 4.05 ± 1.05 to 3.03 ± 0.86 in Group II (mean change: −1.01). The intergroup difference was highly significant (p = 0.002), indicating superior insulin-sensitising efficacy of combination therapy.

Vascular Inflammation (hsCRP): hsCRP decreased from 0.86 ± 0.44 to 0.66 ± 0.38 mg/L in Group I (mean change: −0.20 mg/L) and from 0.91 ± 0.46 to 0.50 ± 0.30 mg/L in Group II (mean change: −0.41 mg/L). The reduction was significantly greater in Group II (p = 0.01).

LDL Cholesterol: Post-treatment LDL-C was 115.4 ± 28.1 mg/dL in Group I and 108.6 ± 25.7 mg/dL in Group II, representing mean reductions of −19.2 mg/dL and −27.2 mg/dL respectively. The intergroup difference was statistically significant (p = 0.02), confirming superior LDL-C lowering with combination therapy.

Table 2. Primary and Secondary Outcome Measures: Baseline, Post-Treatment Values, and Mean Change Scores

Parameter	Group I Baseline mean ± SD	Group I Post-Tx mean ± SD	Group II Baseline mean ± SD	Group II Post-Tx mean ± SD	Intergroup p-value*
PRIMARY OUTCOMES					
HOMA-IR	3.98 ± 1.02	3.48 ± 0.94	4.05 ± 1.05	3.03 ± 0.86	0.002
hsCRP (mg/L)	0.86 ± 0.44	0.66 ± 0.38	0.91 ± 0.46	0.50 ± 0.30	0.01
LDL-C (mg/dL)	134.6 ± 32.5	115.4 ± 28.1	135.8 ± 30.8	108.6 ± 25.7	0.02
SECONDARY OUTCOMES					
FBS (mg/dL)	142.6 ± 28.4	122.1 ± 24.3	143.8 ± 29.1	120.9 ± 22.6	0.04
HbA1c (%)	7.92 ± 0.74	7.49 ± 0.70	7.86 ± 0.68	7.45 ± 0.63	0.21
HDL-C (mg/dL)	41.8 ± 6.7	43.5 ± 6.4	42.1 ± 7.0	45.6 ± 6.8	0.03
Triglycerides (mg/dL)	186.7 ± 41.6	156.1 ± 38.2	189.4 ± 39.8	157.6 ± 35.4	0.04
Fasting Insulin (µIU/mL)	14.2 ± 3.5	14.0 ± 3.2	14.1 ± 3.7	13.6 ± 3.0	0.03

*

Intergroup p-value from independent samples t-test comparing post-treatment values between groups. Post-Tx: post-treatment at 12 weeks; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; FBS: fasting blood sugar; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol.

Secondary Outcomes

All secondary outcomes are presented in Table 2. Fasting blood sugar declined significantly in both groups, with a greater reduction in Group II (120.9 ± 22.6 mg/dL vs 122.1 ± 24.3 mg/dL; p = 0.04). HbA1c decreased from 7.92 ± 0.74% to 7.49 ± 0.70% in Group I, and from 7.86 ± 0.68% to 7.45 ± 0.63% in Group II; however, the intergroup difference was not statistically significant (p = 0.21). HDL-C was higher in Group II at follow-up (45.6 ± 6.8 vs 43.5 ± 6.4 mg/dL; p = 0.03), and triglyceride reduction was also significantly greater in Group II (p = 0.04). Fasting insulin declined to a greater extent in Group II (p = 0.03), consistent with the HOMA-IR findings.

Within-Group Changes and Mean Change Score Comparison

Within-group paired t-test analysis demonstrated statistically significant improvements from baseline to 12 weeks in both treatment groups across all key metabolic parameters (Table 3). However, the magnitude of within-group improvement was consistently greater in Group II, as confirmed by the mean change score analysis. Group II demonstrated significantly larger changes than Group I for HOMA-IR (−1.01 vs −0.49; p = 0.002), hsCRP (−0.41 vs −0.20 mg/L; p = 0.01), LDL-C (−27.2 vs −19.2 mg/dL; p = 0.02), and FBS (−21.0 vs −20.5 mg/dL; p = 0.04). The intergroup difference in HbA1c change was not significant (p = 0.21).

Table 3. Within-Group Statistical Significance (Paired t-test) and Mean Change Score Comparison Between Groups

Parameter	Group I Within-group p-value	Group II Within-group p-value	Mean Change Group I	Mean Change Group II (Intergroup p-value)
FBS (mg/dL)	0.001	< 0.001	−20.5	−21.0 (p = 0.04)
HbA1c (%)	0.002	< 0.001	−0.43	−0.40 (p = 0.21)
LDL-C (mg/dL)	0.003	< 0.001	−19.2	−27.2 (p = 0.02)
hsCRP (mg/L)	0.01	< 0.001	−0.20	−0.41 (p = 0.01)
HOMA-IR	0.005	< 0.001	−0.49	−1.01 (p = 0.002)

FBS: fasting blood sugar; HbA1c: glycated haemoglobin; LDL-C: LDL cholesterol; hsCRP: high-sensitivity C-reactive protein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. Intergroup p-value from independent samples t-test comparing mean change scores.

Figure 2. Changes in HOMA-IR from Baseline to 12 Weeks

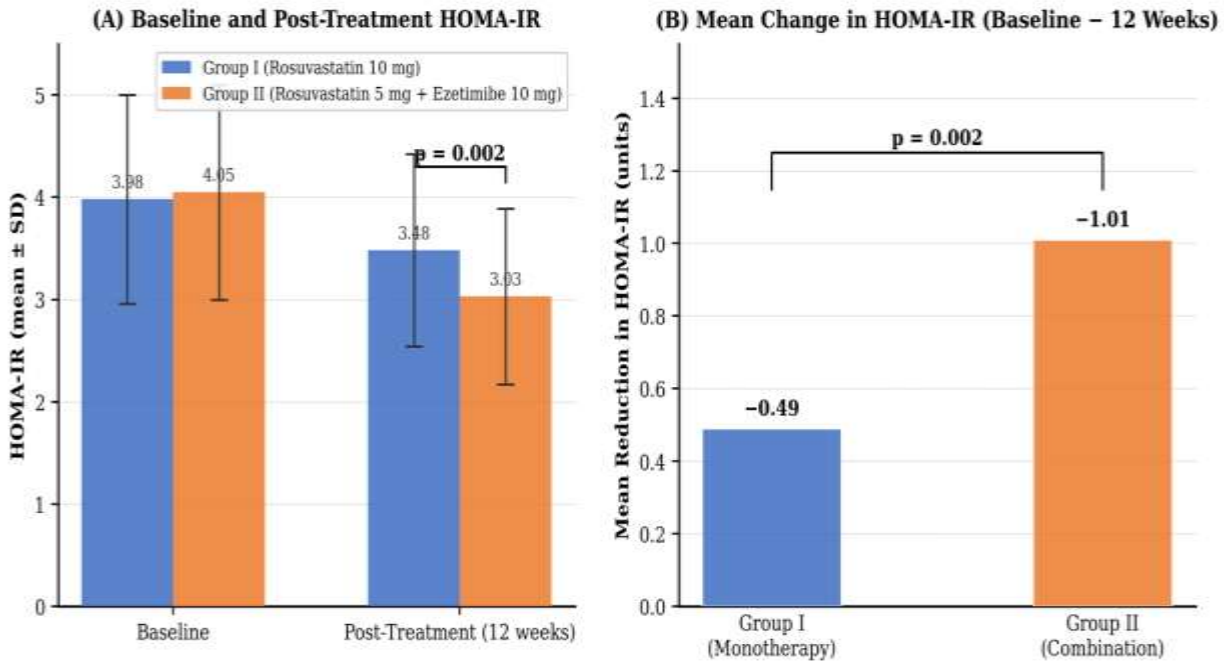

Figure 2. Comparison of mean change in HOMA-IR from baseline to 12 weeks between Group I (rosuvastatin 10 mg) and Group II (rosuvastatin 5 mg + ezetimibe 10 mg). Error bars represent standard deviation.

Figure 3. Changes in hsCRP from Baseline to 12 Weeks

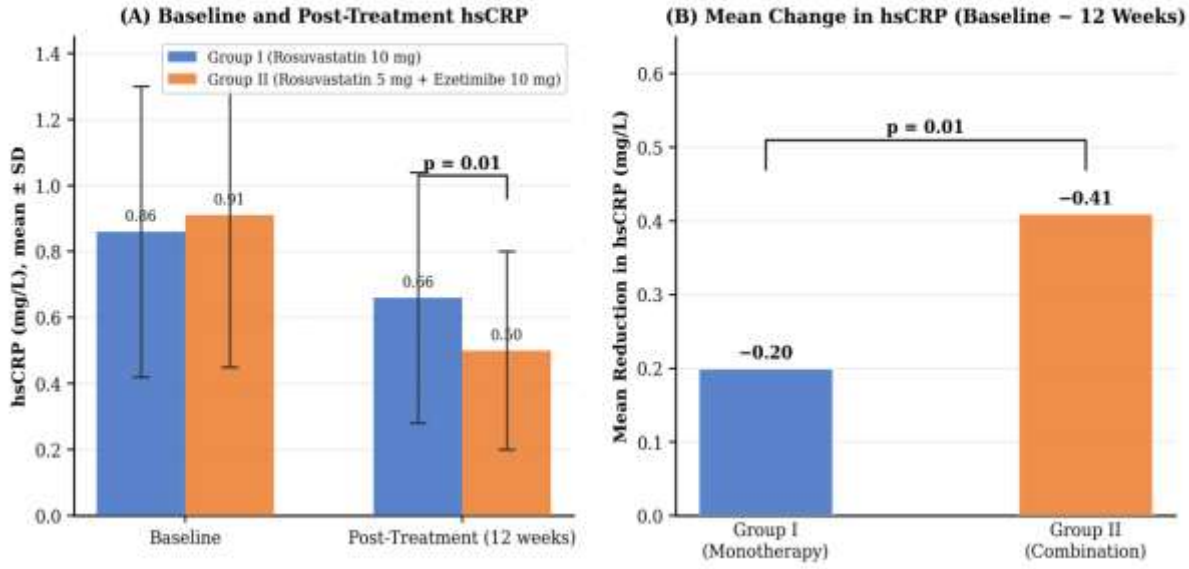

Figure 3. Comparison of mean change in hsCRP (mg/L) from baseline to 12 weeks between treatment groups.

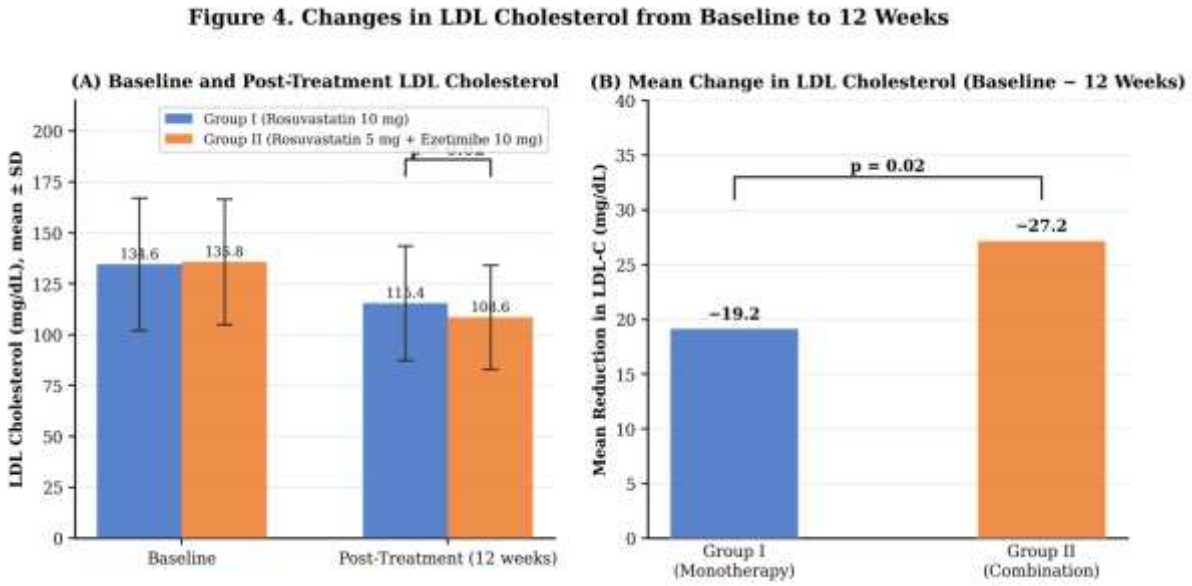

Figure 4. Comparison of mean change in LDL cholesterol (mg/dL) from baseline to 12 weeks between treatment groups.

Safety and Tolerability

No serious adverse events were observed in either treatment group during the study period. Minor adverse effects, if any, were not systematically recorded. No participant required treatment discontinuation or dose modification. Serum liver transaminases and renal function tests remained within normal limits throughout the trial in all participants. No cases of myopathy, rhabdomyolysis, or new-onset diabetes mellitus were identified. The safety profile of both regimens was comparable, and the study was completed without any untoward pharmacological event.

Discussion

This randomised controlled trial compared the cardiometabolic effects of rosuvastatin 10 mg monotherapy with rosuvastatin 5 mg/ezetimibe 10 mg combination therapy over 12 weeks in patients with T2DM and dyslipidaemia. The principal findings were that combination therapy produced significantly greater improvements in insulin sensitivity (HOMA-IR), systemic inflammation (hsCRP), LDL-C lowering, HDL-C elevation, triglyceride reduction, and fasting blood sugar compared with monotherapy. The intergroup difference in HbA1c did not reach statistical significance. No adverse events of clinical concern were observed in either group. These findings suggest a potential advantage of combination therapy across multiple cardiometabolic parameters.

The finding of superior LDL-C lowering in the combination therapy group (−27.2 vs −19.2 mg/dL; p = 0.02) is consistent with the established mechanism and clinical evidence base for ezetimibe augmentation. A randomised trial of fixed-dose rosuvastatin/ezetimibe combinations demonstrated reductions in LDL-C of 56–63% compared with rosuvastatin alone, with particularly pronounced benefits in patients with diabetes or metabolic syndrome [17]. A subsequent phase III multicentre trial further confirmed the superiority of combination therapy in achieving LDL-C target attainment [18]. Additionally, a randomised comparison in patients with T2DM showed that rosuvastatin/ezetimibe achieved a 31% LDL-C reduction compared to 12% with rosuvastatin dose escalation [19]. The present findings align with these data and extend their relevance to the specific comparison of rosuvastatin 5 mg/ezetimibe 10 mg versus rosuvastatin 10 mg — a practically important comparison for clinicians

considering treatment intensification.

The superior HDL-C elevation and triglyceride reduction observed in Group II are particularly relevant given the atherogenic dyslipidaemia phenotype characteristic of T2DM. A head-to-head comparison of statins demonstrated that rosuvastatin achieves greater HDL-C increases than atorvastatin at equivalent doses [20], while a pooled analysis of over 21,000 subjects from 27 clinical trials confirmed that ezetimibe plus statin combination increases HDL-C and apolipoprotein A-I more effectively than statin monotherapy [21]. The additional triglyceride-lowering activity observed with combination therapy [19,22] is clinically meaningful in a population where hypertriglyceridaemia is an independent cardiovascular risk factor [5].

The most clinically impactful finding of this study was the markedly superior HOMA-IR reduction in Group II compared with Group I (−1.01 vs −0.49; p = 0.002). This result has substantive implications given that insulin resistance is both a central pathophysiological driver of T2DM progression and an independent predictor of cardiovascular events [7,8]. The mechanisms through which combination therapy may improve insulin sensitivity likely include multiple complementary pathways: the more pronounced LDL-C reduction may attenuate lipotoxicity in skeletal muscle and hepatocytes, thereby reducing lipid-induced impairment of insulin signalling; the concurrent reduction in systemic inflammation, reflected by the greater hsCRP decline, may alleviate inflammatory inhibition of the PI3K-Akt insulin signalling cascade [9]; and reduced VLDL-mediated lipid flux may improve peripheral insulin receptor responsiveness [5].

The literature on the effects of statin and statin/ezetimibe therapy on insulin sensitivity is heterogeneous. A comparative randomised study found that simvastatin, rosuvastatin, and simvastatin/ezetimibe all increased HOMA-IR to a comparable extent with no significant difference among treatment groups [23], while a 12-week trial in prediabetic subjects found that neither simvastatin nor ezetimibe, alone or in combination, affected insulin sensitivity [24]. In contrast, a meta-analysis of randomised controlled studies reported that statin/ezetimibe combination therapy reduced fasting blood glucose more significantly than statin monotherapy in diabetic patients without increasing adverse events [25]. The most directly comparable investigation found no additional effect of rosuvastatin/ezetimibe on insulin sensitivity overall; however, its subgroup analysis revealed significant HOMA-IR improvements in patients achieving ≥50% LDL-C reduction with combination therapy, suggesting that the magnitude of lipid lowering may mediate the insulin-sensitising benefit [26]. The present findings of a greater HOMA-IR reduction in Group II, alongside greater LDL-C lowering, are consistent with this mechanistic hypothesis.

The significantly greater reduction in hsCRP in Group II (−0.41 vs −0.20 mg/L; p = 0.01) adds to the growing body of evidence that rosuvastatin/ezetimibe combination therapy provides anti-inflammatory benefits beyond those achievable with statin monotherapy alone. An early randomised trial demonstrated that ezetimibe/simvastatin reduced median hsCRP levels more than simvastatin monotherapy through mechanisms not fully explained by lipid changes alone, suggesting a direct anti-inflammatory contribution of ezetimibe [27]. This was corroborated by evidence that simvastatin/ezetimibe combination was superior to simvastatin alone in reducing inflammation markers, with a particularly pronounced effect in insulin-resistant patients [28] — a profile directly applicable to the present study population. Evidence from coronary intravascular imaging further demonstrated that ezetimibe/rosuvastatin combination reduced hsCRP, IL-6, and MMP-9 alongside significant reductions in coronary plaque burden and necrotic plaque composition [29]. Given the direct role of hsCRP in endothelial dysfunction and atherogenesis [9], the superior anti-inflammatory effect of combination therapy observed here translates into a plausible reduction in vascular risk beyond that achieved through lipid lowering alone.

The finding that HbA1c reduction did not differ significantly between groups (p = 0.21) merits consideration. Both groups demonstrated clinically meaningful within-group HbA1c reductions (−0.43% and −0.40%), but the absence of a significant intergroup difference likely reflects the relatively short study duration of 12 weeks. HbA1c integrates glycaemic control over the preceding 8–12 weeks; differential effects may require longer intervention periods to manifest. The significant intergroup difference in FBS (p = 0.04) suggests that combination therapy may produce earlier improvements in fasting glycaemia, which could potentially translate into differential HbA1c effects over a longer time horizon. A phase 4 randomised trial in patients with T2DM and high ASCVD risk demonstrated that rosuvastatin/ezetimibe combination improved beta-cell function without significantly affecting HbA1c at 12 weeks [30], which is consistent with the present observations.

The clinical translation of these surrogate findings is anchored by outcome data from major trials. The IMPROVE-IT trial demonstrated that adding ezetimibe to statin therapy significantly reduced cardiovascular events in patients with diabetes, with a 24% relative risk reduction in myocardial infarction and 39% in ischaemic stroke — benefits substantially greater than in non-diabetic patients [11]. The RACING trial established that moderate-intensity statin/ezetimibe combination therapy is non-inferior to high-intensity statin monotherapy for 3-year composite cardiovascular outcomes, while achieving higher rates of LDL-C < 70

mg/dL and lower rates of treatment discontinuation [12]. These outcome data, contextualised alongside the superior cardiometabolic improvements observed in the present study, collectively support combination therapy as a preferred intensification strategy in high-risk patients with T2DM.
However, these findings should be interpreted in the context of the study's sample size and short duration, and should not be extrapolated to long-term cardiovascular outcomes without further large-scale trials.

Several limitations must be acknowledged in interpreting these findings. First, the study was conducted at a single tertiary care centre, limiting generalisability to broader populations. Second, the 12-week follow-up was insufficient to assess long-term metabolic effects, cardiovascular outcomes, or the sustained impact on HbA1c. Third, the open-label design may introduce performance bias, although the use of objective biochemical endpoints mitigates this concern. Fourth, insulin sensitivity was measured using HOMA-IR rather than the gold-standard euglycaemic-hyperinsulinemic clamp technique; while HOMA-IR is extensively validated and widely used in clinical research [7], it provides a surrogate rather than a direct measure of insulin sensitivity. Fifth, the study was not powered to assess cardiovascular outcomes, which would require substantially larger sample sizes and extended follow-up. Finally, potential residual confounding from variations in dietary adherence and physical activity levels between participants cannot be entirely excluded despite standardised counselling.
Future research should focus on longer-duration, multi-centre randomised trials with comprehensive evaluation of insulin sensitivity using gold-standard methodology, alongside assessment of cardiovascular outcomes and quality of life endpoints. Investigation of the relationship between the magnitude of LDL-C reduction and the degree of improvement in insulin sensitivity and inflammation [26] would help to clarify the mechanistic underpinnings of combination therapy's cardiometabolic advantages.

Conclusions

In patients with type 2 diabetes mellitus and dyslipidaemia, rosuvastatin combined with ezetimibe was associated with greater improvements in lipid profile, insulin resistance, and systemic inflammation compared with rosuvastatin monotherapy over 12 weeks. While these findings indicate potential advantages of combination therapy, larger and longer-duration studies are required to confirm their impact on long-term cardiovascular outcomes.

Declarations

Ethics Approval and Consent to Participate

Ethical clearance was granted by the Institutional Ethics Committee of SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur (Ethics Clearance Number: SRMIEC-ST0924-1797; Reg. No.: EC/NEW/INST/2022/2933; dated 04 December 2024). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrolment.

Trial Registration

The trial was registered prospectively prior to patient enrolment with the Clinical Trials Registry of India: CTRI/2025/11/097905 (registered 24 November 2025).

Availability of Data and Materials

The datasets generated and analysed during the current study are not publicly available due to institutional data governance requirements but are available from the corresponding author on reasonable request, subject to appropriate data sharing agreements and ethical approvals.

Competing Interests

The authors declare that they have no competing interests. No pharmaceutical company or commercial entity had any role in the design, conduct, analysis, or reporting of this study.

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Authors' Contributions

VV: conceptualisation, study design, participant recruitment, data collection, statistical analysis, manuscript preparation. TAV: study supervision, critical review and revision of the manuscript. All authors read and approved the final manuscript.

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