

Moderate-Intensity Rosuvastatin Plus Ezetimibe Versus High-Intensity Rosuvastatin for Target Low-Density Lipoprotein Cholesterol Goal Achievement in Patients With Recent Ischemic Stroke: A Randomized Controlled Trial

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Background and Purpose Moderate-intensity statin plus ezetimibe versus high-intensity statin alone may provide a greater low-density lipoprotein cholesterol (LDL-C) reduction in patients with recent ischemic stroke.

Methods This randomized, open-label, controlled trial assigned patients with recent ischemic stroke <90 days to rosuvastatin/ezetimibe 10/10 mg once daily (ROS10/EZT10) or to rosuvastatin 20 mg once daily (ROS20). The primary endpoint was LDL-C reduction $\geq 50\%$ from baseline at 90 days. Key secondary endpoints were LDL-C <70 mg/dL and multiple lipid goal achievement, and composite of major vascular events.

Results Of 584 randomized, 530 were included in the modified intention-to-treat analysis. The baseline LDL-C level was 130.2 ± 34.7 mg/dL in the ROS10/EZT10 group and 131.0 ± 33.9 mg/dL in the ROS20 group. The primary endpoint was achieved in 198 patients (72.5%) in the ROS10/EZT10 group and 148 (57.6%) in the ROS20 group (odds ratio [95% confidence interval], 1.944 [1.352–2.795]; $P=0.0003$). LDL-C level <70 mg/dL was achieved in 80.2% and 65.4% in the ROS10/EZT10 and ROS20 groups ($P=0.0001$). Multiple lipid goal achievement rate was 71.1% and 53.7% in the ROS10/EZT10 and ROS20 groups ($P<0.0001$). Major vascular events occurred in 1 patient in the ROS10/EZT10 group and 9 in the ROS20 group ($P=0.0091$). The adverse event rates did not differ between the two groups.

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Conclusion Moderate-intensity rosuvastatin plus ezetimibe was superior to high-intensity rosuvastatin alone for intensive LDL-C reduction in patients with recent ischemic stroke. With the combination therapy, more than 70% of patients achieved LDL-C reduction $\geq 50\%$ and 80% had an LDL-C < 70 mg/dL at 90 days.

Keywords Stroke; LDL cholesterol; Rosuvastatin; Ezetimibe; Target goal

Introduction

In patients with ischemic stroke or transient ischemic attack due to atherosclerosis or having concomitant atherosclerotic diseases, intensive low-density lipoprotein cholesterol (LDL-C) lowering is recommended to reduce the risk of subsequent vascular events. In meta-analyses, the benefit of stroke prevention was greater as the magnitude of LDL-C reduction was larger and the achieved LDL-C level was lower.^{1,2} For secondary stroke prevention, guidelines recommend LDL-C reduction of $\geq 50\%$ from baseline or a target LDL-C goal of < 70 mg/dL.^{3,4}

As a first-line strategy for intensive LDL-C lowering, high-intensity statins are generally recommended. However, high-intensity statins as compared to moderate- or low-intensity statins increase the risks of diabetes, hepatic dysfunction, and myopathy.⁵⁻⁷ Furthermore, the additional reduction in LDL-C with increasing statin dose is limited, only 5% to 7% absolute reduction with doubling the dose of statins.⁸

Non-statin lipid-lowering therapies added to statins were effective for preventing cardiovascular events, and the benefit was likely driven by further LDL-C lowering.⁹⁻¹² Ezetimibe inhibits intestinal cholesterol absorption by binding to the Niemann-Pick C1-like 1 (NPC1L1) protein.¹³ When added to statins, ezetimibe resulted in a substantial LDL-C reduction, and the reduction appeared greater than that achieved with doubling statin dose.^{8,14,15} For patients with recent ischemic stroke, there has been no randomized trial that compared moderate-intensity statin plus ezetimibe and high-intensity statin for LDL-C reduction.

We conducted the ROSuvastatin plus Ezetimibe Treatment for Target LDL-C goal Achievement in patients with recent ischemic Stroke (ROSETTA-Stroke) trial to evaluate moderate-intensity rosuvastatin plus ezetimibe, as compared with high-intensity rosuvastatin alone for target LDL-C goal achievement in patients with recent ischemic stroke of atherosclerotic origin or having concomitant atherosclerotic cardiovascular diseases.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Trial design

In this multicenter, randomized, open-label, parallel-group trial conducted at 13 sites in South Korea, we compared rosuvastatin 10 mg plus ezetimibe 10 mg once daily (ROS10/EZT10) and rosuvastatin 20 mg alone once daily (ROS20) for target LDL-C goal achievement in patients with recent ischemic stroke. In Korea, rosuvastatin 40 mg has not been approved, and accordingly we selected the dose of 20 mg as a high-intensity rosuvastatin and 10 mg as a moderate-intensity rosuvastatin.¹⁶

This was an investigator-initiated trial and funded by Hanmi Pharm. Co., Ltd. The sponsor participated in the trial design and provided study medications, but it had no role in the conduct of the trial, data collection and analysis, and writing and submitting the manuscript for publication. All the data were collected by the site investigators, and were monitored and maintained by an independent research organization contracted by the principal investigator affiliated academic institution. All the authors vouch for the completeness and accuracy of the data and the fidelity of the trial to the protocol. The principal investigator and independent statisticians had full access to and vouch for the data and analysis. The trial was approved by local institutional review boards. Enrolled patients or their legally authorized representatives provided written informed consent. The trial is registered with ClinicalTrials.gov (NCT03993236).

Study population

Patients were eligible for enrollment if they were 19 years or older; they had recent ischemic stroke within 90 days confirmed by diffusion-weighted imaging; statin therapy was indicated according to the recommendations of the 2014 American Heart Association/American Stroke Association guidelines;¹⁷ they had not taken statins within 4 weeks before the index stroke; and the baseline LDL-C level was measured after onset of the index stroke. Prior to randomization, administration of non-study statins immediately after acute stroke hospitalization according to each institution's practice protocol was allowed. In this case, the baseline LDL-C level should be measured within 3 days of initiating non-study statins, and the randomization and initiation of study medications should be completed within 7 days of the baseline LDL-C level measurement. Detailed inclusion and exclusion cri-

teria are provided in Supplementary Table 1.

Randomization, intervention, and follow-up

Eligible patients were randomly assigned, in a 1:1 ratio, to receive, once daily, either rosuvastatin 10 mg plus ezetimibe 10 mg (ROS10/EZT10 group) or rosuvastatin 20 mg alone (ROS20 group). Randomization was stratified by centers and baseline LDL-C levels (<100 mg/dL vs. \geq 100 mg/dL), using an interactive web response system. All patients received the standard secondary stroke prevention therapy recommended by current practice guidelines. Concomitant use of additional lipid-lowering agents (non-study statins, fibrates, or omega-3 fatty acids) was not allowed during the trial.

Patients were scheduled for follow-up visits at 30 days and at 90 days after the enrollment. Unscheduled visits were made as needed. Major vascular events (including recurrent stroke, coronary event, or vascular death) and adverse events were collected during the follow-up. Lipid profiles and laboratory tests for monitoring adverse events were measured at the 90-day follow-up visit. For patients who withdrew during the trial, we recommended to measure lipid profiles at the time of withdrawal, which were used for endpoint analysis if available.

Endpoints

The primary endpoint was the proportion of patients who achieved a target LDL-C goal, defined as LDL-C reduction of \geq 50% from baseline. We selected the LDL-C reduction of \geq 50% as a target goal, which was widely recommended by the guidelines when we designed this trial.¹⁶

Secondary endpoints included (1) proportion of patients achieving LDL-C level <70 mg/dL, (2) proportion of patients with LDL-C reduction \geq 50% or achieved LDL-C level <70 mg/dL, (3) the absolute and percentage changes in LDL-C level, (4) proportion of patients achieving multiple lipid goals of total cholesterol <200 mg/dL, LDL-C <70 mg/dL, and triglyceride <150 mg/dL,¹⁸ (5) composite of major vascular events including stroke (ischemic or hemorrhagic), coronary event (myocardial infarction or coronary revascularization), or vascular death, (6) all cause of death, (7) new onset diabetes, (8) fatigue assessed by the Fatigue Severity Scale,¹⁹ (9) rhabdomyolysis, and (10) significant liver enzyme elevation (alanine aminotransferase or aspartate aminotransferase elevation >3 times from baseline).

Safety endpoints included any adverse event, treatment-emergent adverse event (TEAE), any serious adverse event, and serious TEAE. TEAEs were defined as adverse events for which a causal relationship with study medications could not be excluded. Serious events included those that (1) resulted in death or were life-threatening, (2) required or prolonged hospitalization, (3) re-

sulted in persistent or significant disability/incapacity, (4) caused a congenital anomaly/birth defect, or (5) resulted in the development of drug dependency/abuse or significant medical events.

Sample size calculation and statistical analysis

This trial was designed to detect the superiority of rosuvastatin 10 mg plus ezetimibe 10 mg once daily over rosuvastatin 20 mg once daily for achieving LDL-C reduction \geq 50% from baseline. Based on the prior study findings,²⁰ the sample size was calculated by assuming that the primary endpoint rate would be 82% in the ROS10/EZT10 group and 72% in the ROS20 group. Under two-sided significance level of 5%, a total of 554 patients (277 patients per group) were needed to ensure 80% of power of detecting 10% of absolute difference in the primary endpoint rate using the chi-square test. Assuming a 5% dropout rate, a total of 584 patients (292 patients per group) was planned to enroll. Given that lipid-lowering with statins and ezetimibe are approved and widely used in daily clinical practice, neither an independent data safety monitoring board was organized, nor interim analysis was planned.

The primary and secondary endpoints were assessed in the modified intent-to-treat (ITT) population, which included patients who were randomized, received at least 1 dose of study medications, and completed follow-up LDL-C level measurement. For patients who withdrew during the trial after initiation of study medications, but their LDL-C levels were measured at the time of withdrawal, they were included in the modified ITT population. Per-protocol (PP) analysis was additionally conducted, which included patients who had no major protocol violation, took >80% of the assigned study medications, and did not take non-study lipid-lowering agents after enrollment among the modified ITT population. Adverse events were assessed in the safety population, which included all patients who were randomized and received at least 1 dose of study medications.

The primary endpoint was analyzed using the chi-square test. Additionally, an adjusted analysis was planned if there were significant differences in the baseline characteristics with biological plausibility, but no such variable was found. For the baseline LDL-C levels, we predetermined that they would not be adjusted even if there was a significant imbalance between the two groups because randomization was stratified by the baseline LDL-C levels (<100 mg/dL vs. \geq 100 mg/dL). Secondary and safety endpoints were analyzed, using the chi-square test, Fisher's exact test, Student's t-test, or Mann-Whitney U-test as indicated in the statistical analysis plan (SAP). All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Cary, NC, USA), and a two-sided *P*-value <0.05 was considered significant. All analyses were pre-planned in the SAP and performed by two

independent statisticians who were blinded to the treatment allocation.

Results

Patients

Between September 9, 2019, and September 27, 2021, 584 patients were randomized (295 to the ROS10/EZT10 group and 289 to the ROS20 group). After randomization, 2 patients in the ROS20 group did not take any study medication, and 52 (22 in the ROS10/EZT10 group and 30 in the ROS20 group) did not undergo follow-up LDL-C measurements. Therefore, 530 patients (273 in the ROS10/EZT10 group and 257 in the ROS20 group) were included in the modified ITT population. Of the modified ITT population, 31 patients took less than 80% of study medications or received other lipid-lowering agents, and 499 patients (262 in the ROS10/EZT10 group and 237 in the ROS20 group) were included in the PP population. The safety population included 582 patients (295 in the ROS10/EZT10 group and 287 in the ROS20 group) (Figure 1).

Baseline demographics and clinical characteristics were well balanced between the two groups (Table 1). The mean LDL-C level at baseline was 130.2 mg/dL in the ROS10/EZT10 group and 131.0 mg/dL in the ROS20 group. In each group, the median interval from the index ischemic stroke onset to randomization was 4 days, and the median National Institutes of Health Stroke Scale (NIHSS) score at randomization was 2. Before randomization, 193

patients (70.7%) in the ROS10/EZT10 group and 188 (73.2%) in the ROS20 group received non-study statins immediately after acute stroke hospitalization. The proportion of patients taking non-study statins before randomization and the average dose (converted to atorvastatin equivalent dose) did not differ between the two groups. The interval from initiating non-study statins to randomization was 3.0 ± 1.7 days in the ROS10/EZT10 group and 3.1 ± 1.6 days in the ROS20 group ($P=0.8958$) (Table 1 and Supplementary Table 2).

The follow-up LDL-C levels were obtained at 90 days in 516 patients (266 in the ROS10/EZT10 group and 250 in the ROS20 group). In 14 (7 in each group) patients, the follow-up LDL-C levels were measured at the time of withdrawal, and these values were used for the endpoint analysis.

Endpoints

The primary endpoint of LDL-C reduction $\geq 50\%$ from baseline was achieved in 198 patients (72.5%) in the ROS10/EZT10 group and 148 (57.6%) in the ROS20 group of the modified ITT population, and the difference was significant (odds ratio [95% confidence interval], 1.944 [1.352–2.795]; $P=0.0003$) (Table 2). Of secondary endpoints regarding lipid profiles, the ROS10/EZT10 group compared to the ROS20 group had higher proportions of patients with the achieved LDL-C level < 70 mg/dL (80.2% vs. 65.4%; OR [95% CI], 2.148 [1.450–3.184]; $P=0.0001$), LDL-C reduction $\geq 50\%$ or the achieved LDL-C < 70 mg/dL (84.2% vs. 73.2%; OR [95% CI], 1.963 [1.281–3.008]; $P=0.0018$), and multiple lipid goal

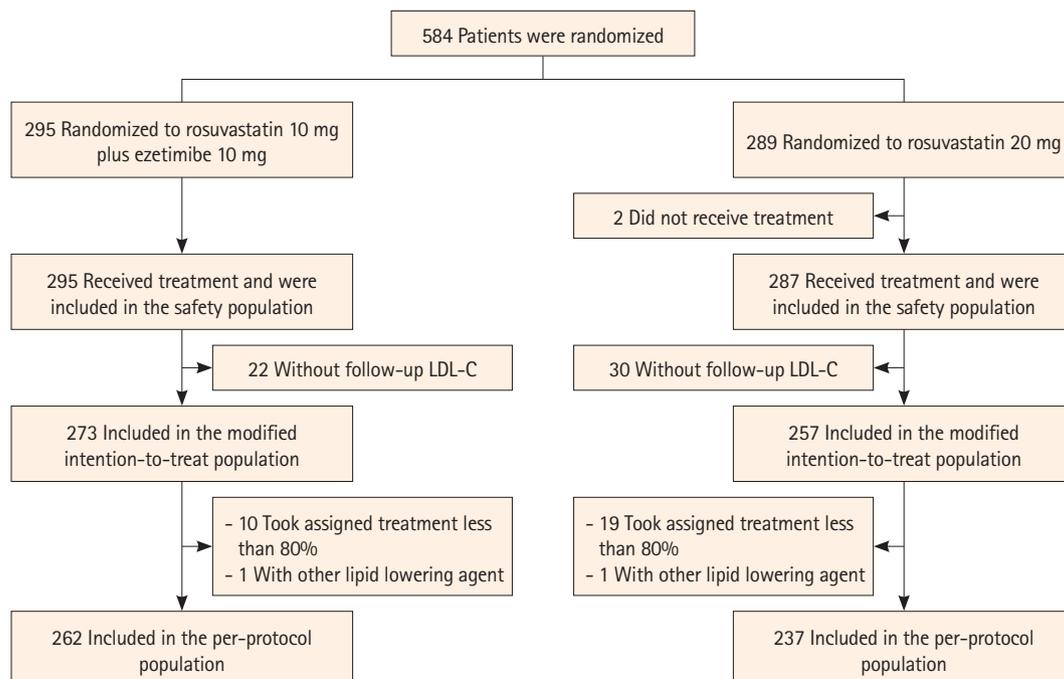


Figure 1. Trial flow. LDL-C, low-density lipoprotein cholesterol.

Table 1. Baseline characteristics of the modified intention-to-treat population

	ROS10/EZT10 (n=273)	ROS20 (n=257)	P
Age (yr)	63.9±11.9	63.7±11.9	0.8124
Male sex	207 (75.8)	180 (70.0)	0.1337
Onset to randomization (day)	4.8±4.3	4.4±3.1	0.1869
NIHSS at randomization	2.0 [1.0–4.0]	2.0 [1.0–4.0]	0.0580
Body-mass index (kg/m ²)	23.9±3.2	24.5±3.6	0.0523
Systolic blood pressure (mm Hg)	142.9±19.4	140.3±23.3	0.1649
Diastolic blood pressure (mm Hg)	82.5±12.2	82.5±13.5	0.9826
Vascular risk factors			
Hypertension	169 (61.9)	154 (59.9)	0.6401
Diabetes	83 (30.4)	73 (28.4)	0.6139
Current smoking	110 (40.3)	106 (41.2)	0.8236
Coronary heart disease	11 (4.0)	9 (3.5)	0.7502
Prior stroke history	14 (5.1)	18 (7.0)	0.3649
Lipid profiles (mg/dL)			
Low-density lipoprotein cholesterol	130.2±34.7	131.0±33.9	0.7777
Total cholesterol	194.3±37.7	196.5±39.2	0.5191
Triglyceride	141.4±74.0	138.4±80.7	0.2033
High-density lipoprotein cholesterol	45.4±11.8	46.3±11.3	0.3791
Glucose (mg/dL)	130.4±43.1	113.3±25.2	0.1021
Glycated hemoglobin (%)	6.4±1.6	6.3±1.4	0.5385
Non-study statin use after hospitalization before randomization	193 (70.7)	188 (73.2)	0.5297

Data are presented as mean±standard deviation, n (%), or median [interquartile range].

NIHSS, National Institutes of Health Stroke Scale.

achievement (71.1% vs. 53.7%; OR [95% CI], 2.117 [1.479–3.030]; $P < 0.0001$). The absolute LDL-C reduction was greater in the ROS10/EZT10 group than in the ROS20 group (72.7 mg/dL vs. 64.7 mg/dL; $P = 0.0111$), and accordingly the achieved LDL-C level was lower in the ROS10/EZT10 group than in the ROS20 group (57.4±24.6 mg/dL vs. 66.3±26.2 mg/dL; $P < 0.0001$) (Supplementary Table 3).

Major vascular events occurred in 1 patient (0.4%) in the ROS10/EZT10 group and 9 (3.5%) in the ROS20 group (OR [95% CI], 0.101 [0.013–0.805]; $P = 0.0091$). Of the 10 major vascular events, 7 were recurrent ischemic strokes and 3 were coronary events. Death occurred in 1 patient (sudden cardiac death) in the ROS20 group. There was no rhabdomyolysis during the trial. The two groups did not differ in the incidences of new onset diabetes and significant liver enzyme elevation, and the Fatigue Severity Scale. The results of the PP population analyses were consistent with those of the modified ITT population analyses (Supplementary Table 4).

Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were comparable between the two groups at baseline (Table 1). At follow-up, the total cholesterol level was lower in the ROS10/EZT10 group than in the ROS20 group. However, the 90-day high-density lipoprotein cholesterol and triglyceride levels did not differ between the two groups (Supplementary Table 3).

Of the modified ITT population, 14 patients (4 in the ROS10/EZT10 group and 10 in the ROS20 group) discontinued study medications transiently or permanently between the 1st follow-up visit (at day 30) and the final visit (at day 90). Analysis excluding these patients showed consistent results regarding LDL-C related endpoints (Supplementary Table 5). Additional analysis excluding 22 patients (8 in the ROS10/EZT10 group and 14 in the ROS20 group) who transiently or permanently discontinued study medications at any point during the trial also showed similar results (Supplementary Table 6).

Subgroup analyses were not prespecified, but were undertaken in a *post-hoc* manner. For the primary endpoint, treatment effects were consistent across major subgroups of age (<64 vs. ≥64), sex, baseline LDL-C level (<100 mg/dL vs. ≥100 mg/dL), hypertension, diabetes, and smoking (Figure 2).

Adverse events

In the safety population, there were no significant differences between the ROS10/EZT10 and ROS20 groups in the rates of any adverse event (36.9% vs. 36.9%; $P = 0.9969$), any TEAE (4.7% vs. 3.5%; $P = 0.3814$), any serious adverse event (7.5% vs. 7.7%; $P = 0.9244$), and serious TEAE (0% vs. 0%; $P > 0.9999$) (Table 3). Details of any serious adverse events and TEAE according to individual organs are described in Supplementary Tables 7 and 8. For muscle-related adverse events, there was no clinically significant myopathy. Myalgia occurred in 5 patients (2.3%) in the ROS10/EZT10 group and 3 (1.4%) in the ROS20 group ($P = 0.5000$). Of these, myalgia in 6 patients (3 in each group) was considered as TEAEs.

Discussion

In this randomized trial, we found that the combination of moderate-intensity rosuvastatin 10 mg plus ezetimibe 10 mg was superior to high-intensity rosuvastatin 20 mg alone for LDL-C reduction in patients with recent ischemic stroke who initiated lipid-lowering therapy. With the combination therapy, more than 70% of patients achieved an LDL-C reduction ≥50% from baseline, and more than 80% had their LDL-C levels <70 mg/dL at 90 days. For every 100 patients indicated for LDL-C lowering, approximately additional 15 patients would achieve these target LDL-C goals

Table 2. Endpoints in the modified intent-to-treat population

Endpoints	ROS10/EZT10 (n=273)	ROS20 (n=257)	Odds ratio (95% confidence interval)	P
Primary endpoint				
LDL-C reduction ≥50%	198 (72.5)	148 (57.6)	1.944 (1.352–2.795)	0.0003
Secondary endpoints				
LDL-C <70 mg/dL	219 (80.2)	168 (65.4)	2.148 (1.450–3.184)	0.0001
LDL-C reduction ≥50% or LDL-C <70 mg/dL	230 (84.2)	188 (73.2)	1.963 (1.281–3.008)	0.0018
Absolute LDL-C reduction (mg/dL)	72.7±37.0	64.7±35.1		0.0111
LDL-C reduction percentage (%)	53.9±21.1	47.9±20.5		0.0010
Multiple lipid goal achievement	194 (71.1)	138 (53.7)	2.117 (1.479–3.030)	<0.0001
Major vascular events	1 (0.4)	9 (3.5)	0.101 (0.013–0.805)	0.0091
All death	0 (0.0)	1 (0.4)	0.469 (0.042–5.203)	0.4849
New onset diabetes	8 (4.3)	7 (3.8)	1.117 (0.397–3.147)	0.8334
Rhabdomyolysis	0 (0.0)	0 (0.0)		>0.9999
Fatigue Severity Scale	14.5±10.0	14.1±8.9		0.5755
Significant liver enzyme elevation*	5 (1.8)	1 (0.4)	4.776 (0.554–41.16)	0.2174

Data are presented as mean±standard deviation or n (%).

LDL-C, low-density lipoprotein cholesterol.

*Significant liver enzyme elevation: alanine aminotransferase or aspartate aminotransferase elevation >3 times from baseline.

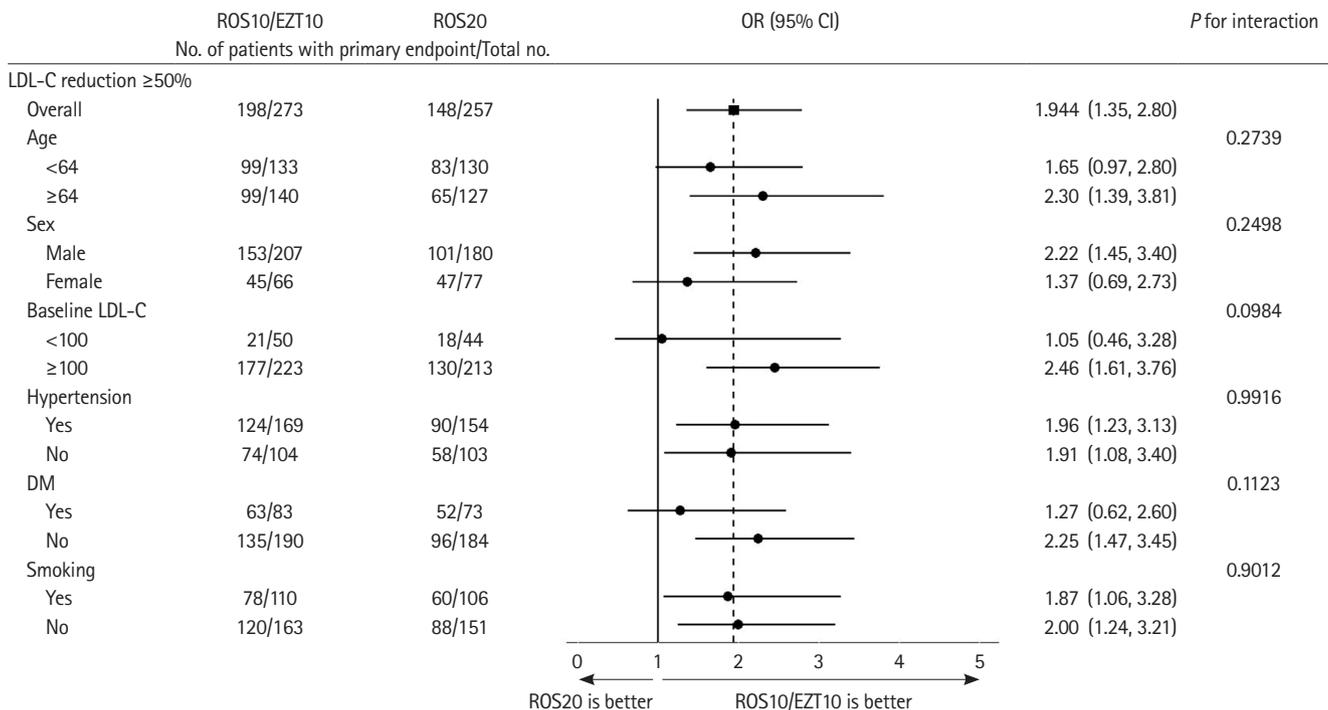


Figure 2. Subgroup analyses of primary endpoint, according to *post hoc* subgroups. LDL-C reduction ≥50% (the primary end point) at 90 days among patients in the ROS10/EZT10 group and in the ROS20 group, according to *post hoc* subgroups. LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus.

with the combination therapy as compared to rosuvastatin 20 mg alone. In addition, 71% of patients with the combination therapy achieved the multiple lipid goals, an absolute increase of about 17% as compared to that with rosuvastatin 20 mg alone.

Our findings are in accord with earlier studies. A prior meta-analysis showed that the LDL-C reduction was greater with add-

ing ezetimibe to ongoing statins (26.0% reduction from baseline) than with doubling the dose of ongoing statins (9.7% reduction).¹⁵ In the randomized comparison of efficacy and safety of lipid-lowering with statin monotherapy versus statin ezetimibe combination for high-risk cardiovascular disease (RACING) conducted in South Korea, 73% of patients receiving rosuvastatin 10 mg

Table 3. Adverse events in the safety population

Event	ROS10/EZT10 (n=295)	ROS20 (n=287)	P
Any adverse event	109 (36.9)	106 (36.9)	0.9969
TEAE	14 (4.7)	10 (3.5)	0.3814
Any serious adverse event	22 (7.5)	22 (7.7)	0.9244
Serious TEAE	0 (0)	0 (0)	>0.9999

Data are presented as n (%).

TEAE, treatment-emergent adverse event.

plus ezetimibe 10 mg and 55% of those receiving rosuvastatin 20 mg alone achieved an LDL-C level of <70 mg/dL at 1 year.²¹ The difference in the proportion (about 18%) between the 2 arms in RACING was quite comparable to that observed in our trial (about 15%). Both RACING and our trial would indicate that 7–8 out of 10 Korean patients with atherosclerotic diseases could achieve an LDL-C level of <70 mg/dL with rosuvastatin 10 mg plus ezetimibe 10 mg once daily.

In this trial, the clinical endpoints of major vascular events occurred significantly less in the ROS10/EZT10 group than in the ROS20 group. However, this trial was neither designed nor powered to detect the difference in the clinical endpoint. Given the short trial period and the magnitude of the achieved LDL-C level difference between the two groups, the clinical benefit observed in this study is highly likely due to by chance. Meta-analyses and a clinical trial indicated the greater benefit for secondary stroke prevention with greater LDL-C reduction or lower LDL-C levels achieved,^{1,2,22} and accordingly moderate-intensity rosuvastatin plus ezetimibe could be superior to high-intensity rosuvastatin to prevent vascular events. The RACING trial demonstrated that rosuvastatin 10 mg plus ezetimibe 10 mg was non-inferior to rosuvastatin 20 mg alone for the 3-year clinical composite outcome of major vascular events. The rate was slightly lower with the combination therapy (9.1%) than with rosuvastatin alone (9.9%).²¹ Therefore, both RACING and our trial suggest that rosuvastatin 10 mg plus ezetimibe 10 mg compared to rosuvastatin 20 mg alone was, at least, non-inferior for preventing vascular events, and was better for intensive LDL-C reduction. Clinical efficacy of statin plus ezetimibe combination therapy was further supported by a *post hoc* analysis of the Treat Stroke to Target (TST) trial.²³ In the lower LDL-C target group (LDL-C <70 mg/dL), the proportion of patients on combination therapy increased from <5% at baseline to >20% at 6 months and >50% at 3 years. The risk reduction of primary endpoint (major cardiovascular event) in the lower target group as compared with the higher target group (LDL-C 100±10 mg/dL) was significant during combination therapy, but not during statin monotherapy.

We observed a numerically higher incidence of alanine aminotransferase or aspartate aminotransferase elevation >3 times

from baseline in the ROS10/EZT10 group than in the ROS20 group. However, the incidence was low and did not significantly differ between the two groups. There was no case of clinically significant hepatic dysfunction. The low TEAE incidences and no case of serious TEAE in the two groups support the safety of the two treatments.

In this trial, we selected rosuvastatin 20 mg as a high-intensity statin strategy because rosuvastatin 40 mg has not been approved for clinical use in Korea. The 2013 American College of Cardiology/American Heart Association guidelines categorized rosuvastatin 20 mg as high-intensity statin.¹⁶ Studies have shown an increased risk of intracerebral hemorrhage with high-intensity statins, and the risk could be greater during the acute stage of ischemic stroke. However, in a randomized Korean trial involving 316 patients with acute ischemic stroke within 48 hours, the incidence of any intracranial hemorrhage detected on follow-up gradient-recalled echo magnetic resonance imaging at 14 days was not higher, but rather lower, in the rosuvastatin 20 mg group than in the placebo group.²⁴ In our study, patients were enrolled, on average, 4–5 days after acute ischemic stroke, and there was no hemorrhagic stroke during the follow-up. Therefore, both the combination therapy and high-intensity rosuvastatin appear safe in patients with acute ischemic stroke with regard to intracerebral hemorrhage.

Our study has several limitations. This was an open-label study, which was at risk of a reporting bias for clinical events. However, key endpoints were objective laboratory results, and independent statisticians blinded to the treatment allocation analyzed the data. We exclusively enrolled Korean patients. The response to lipid-lowering therapy could differ across ethnicities,²⁵ and thereby the generalizability of our findings might be limited. In addition, most of the included patients had a mild stroke, which could limit the applicability of our findings to patients with more severe strokes. Whether the greater LDL-C reduction with the combination therapy versus high-intensity rosuvastatin alone could be translated into better secondary stroke prevention remains unclear, which should be formally tested by a well-designed large trial.

Conclusions

The ROSETTA-Stroke trial showed that moderate-intensity rosuvastatin plus ezetimibe was superior to high-intensity rosuvastatin alone for intensive LDL-C lowering in patients with recent ischemic stroke who initiated lipid-lowering therapy. For every 100 patients treated with rosuvastatin 10 mg plus ezetimibe 10 mg once daily, almost 73 achieved LDL-C reduction ≥50%, and about 80 had an LDL-C level <70 mg/dL at 90 days.

Supplementary materials

Supplementary materials related to this article can be found online at <https://doi.org/10.5853/jos.2022.02957>.

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Conflicts of interest

K.- S. Hong, O. Y. Bang, J.-H. Park, J.-M. Jung, S.-H. Lee, T.-J. Song, H. S. Nam, H.-K. Park, K.-H. Jung, S. H. Heo, J. Koo, K.-H. Yu, K.-Y. Park, C. K. Kim, H.-K. Park, J. Lee, W.-K. Seo received research grants from Hanmi Pharm. Co., Ltd.

Author contribution

Conceptualization: KSH, OYB, HKP, WKS. Study design: KSH, OYB, HKP, WKS, JL (Juneyoung Lee). Methodology: KSH, OYB, HKP, WKS, JL (Juneyoung Lee). Data collection: all authors. Investigation: all authors. Statistical analysis: KSH, OYB, JL (Jiyeon Lee), JL (Juneyoung Lee). Writing—original draft: KSH, JL (Juneyoung Lee). Writing—review & editing: all authors. Funding acquisition: KSH, OYB. Approval of final manuscript: all authors.

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Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria	
1. Recent ischemic stroke that fulfills the following criteria	
1) Relevant acute ischemic stroke confirmed by diffusion-weighted imaging	
2) Randomization within 90 days after symptom onset	
2. Statin therapy indicated according to the 2014 American Heart Association/American Stroke Association guidelines, satisfying at least one of the following three criteria:	
1) Ischemic stroke due to arteriosclerosis and low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL	
2) Ischemic stroke due to arteriosclerosis and LDL-C < 100 mg/dL	
3) Associated atherosclerotic cardiovascular disease, requiring statin therapy	
3. No pre-stroke statin use within 28 days before the index ischemic stroke.	
4. Baseline LDL-C level measured after the index ischemic stroke, satisfying at least one of the following criteria:	
1) Baseline LDL-C level measured before initiating any statins after the index ischemic stroke	
2) For patients who received non-study statins immediately after hospitalization before the study enrollment, the baseline LDL-C should be measured within 3 days of initiating non-study statins	
5. Randomization and initiation of study medications within 7 days of the baseline LDL-C measurement	
6. Age ≥ 19	
7. Written informed consent	
Exclusion criteria	
1. Planned vascular intervention before the end of trial	
2. Significant hepatic dysfunction (aspartate aminotransferase or alanine aminotransferase > 120 IU/L)	
3. Allergy or contraindication to rosuvastatin or ezetimibe	
4. Alcohol or drug addiction	
5. Pregnancy or breast-feeding	
6. Severe anemia: hemoglobin level < 10 g/dL for men and < 9 g/dL for women	
7. Bleeding diathesis: platelet count $< 100,000/\mu\text{L}$ or prothrombin time international normalized ratio (INR) > 1.7 (Note: patients who were taking oral anticoagulation and INR > 1.7 were eligible for enrollment)	
8. Inability or unwillingness to comply with study-related procedures	
9. Employees of the investigator or study center, with direct involvement in the current study	
10. Women unwilling to continue contraception during the study period	
11. Participation in other clinical trials within 3 months	
12. Malignancy or other serious medical conditions with a life expectancy < 6 months	
13. Treatment with protease inhibitors or cyclosporine	
14. Patients with severe renal impairment (creatinine clearance < 30 mL/min)	
15. Other reasons for ineligibility judged by investigators	

Supplementary Table 2. Non-study statin use before randomization

	ROS10/EZT10 (n=273)	ROS20 (n=257)	P
Non-study statin initiation to randomization (day)	3.0 \pm 1.7	3.1 \pm 1.6	0.8958
Non-study statin use before randomization after hospitalization	193 (70.7)	188 (73.2)	0.5297
Atorvastatin	120 (62.2)	115 (61.2)	
Rosuvastatin	73 (37.8)	73 (38.8)	
Statin dose (mg/dL)*	49.7 \pm 22.4	53.0 \pm 23.5	0.1694

Data are presented as mean \pm standard deviation or n (%).

*Statin dose: converted to atorvastatin-equivalent dose.

Supplementary Table 3. Lipid profiles at follow-up in the modified intention-to-treat population

	ROS10/EZT10 (n=273)	ROS20 (n=257)	P
LDL-C (mg/dL)	57.4±24.6	66.3±26.2	<0.0001
Total-C (mg/dL)	118.6±29.5	128.9±29.3	<0.0001
Triglyceride (mg/dL)	108.6±52.7	117.5±57.6	0.0933
HDL-C (mg/dL)	47.7±12.4	48.1±11.3	0.6184

Data are presented as mean±standard deviation.
LDL-C, low-density lipoprotein cholesterol; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol.

Supplementary Table 4. End points in the per-protocol population

End points	ROS10/EZT10 (n=262)	ROS20 (n=237)	Odds ratio (95% confidence interval)	P
Primary end point				
LDL-C reduction ≥50%	193 (73.7)	140 (59.1)	1.938 (1.328–2.827)	0.0006
Secondary end points				
LDL-C <70 mg/dL	214 (81.7)	160 (67.5)	2.146 (1.417–3.248)	0.0003
LDL-C reduction ≥50% or LDL-C <70 mg/dL	225 (85.9)	180 (75.9)	1.926 (1.218–3.044)	0.0046
Absolute LDL-C reduction (mg/dL)	73.6±36.7	66.1±32.9	-	0.0174
LDL-C reduction percentage (%)	54.6±20.5	49.4±17.7	-	0.0025
Multiple lipid goal achievement	191 (72.9)	130 (54.9)	2.214 (1.524–3.217)	<0.0001
Major vascular events	1 (0.4)	9 (3.8)	0.097 (0.012–0.772)	0.0081
All death	0 (0)	1 (0.4)	0.508 (0.046–5.632)	0.2926
New onset diabetes	8 (4.4)	7 (4.1)	1.058 (0.375–2.984)	0.9145
Rhabdomyolysis	0 (0)	0 (0)	-	>0.9999
Fatigue Severity Scale	14.4±9.6	13.8±8.2	-	0.4610
Significant liver enzyme elevation*	5 (1.9)	0 (0)	5.535 (0.662–46.31)	0.0326

Data are presented as mean±standard deviation or n (%).
LDL-C, low-density lipoprotein cholesterol.
*Significant liver enzyme elevation: alanine aminotransferase or aspartate aminotransferase elevation >3 times from baseline.

Supplementary Table 5. LDL-C related endpoints after excluding patients who discontinued study medications transiently or permanently between the 1st follow-up visit (at day 30) and the final visit (at day 90)

Endpoints	ROS10/EZT10 (n=269)	ROS20 (n=247)	Odds ratio (95% confidence interval)	P
Primary endpoint				
LDL-C reduction ≥50%	197 (73.2)	143 (58.7)	1.925 (1.329–2.787)	0.0005
Secondary endpoints				
LDL-C <70 mg/dL	217 (80.7)	163 (66.0)	2.151 (1.440–3.212)	0.0002
LDL-C reduction ≥50% or LDL-C <70 mg/dL	228 (84.8)	183 (74.1)	1.945 (1.255–3.013)	0.0026
Absolute LDL-C reduction (mg/dL)	73.2±36.9	69.8±35.1	-	0.0236
LDL-C reduction percentage	54.2±21.0	48.9±19.6	-	0.0028

Data are presented as n (%) or mean±standard deviation.
LDL-C, low-density lipoprotein cholesterol.

Supplementary Table 6. LDL-C related endpoints after excluding patients who transiently or permanently discontinued study medications during the trial

Endpoints	ROS10/EZT10 (n=265)	ROS20 (n=243)	Odds ratio (95% confidence interval)	P
Primary endpoint				
LDL-C reduction \geq 50%	195 (73.6)	143 (58.9)	1.948 (1.340–2.831)	0.0004
Secondary endpoints				
LDL-C <70 mg/dL	213 (80.4)	160 (65.9)	2.125 (1.420–3.179)	0.0002
LDL-C reduction \geq 50% or LDL-C <70 mg/dL	224 (84.5)	180 (74.1)	1.912 (1.232–2.968)	0.0035
Absolute LDL-C reduction (mg/dL)	73.6 \pm 37.0	66.1 \pm 34.6	-	0.0175
LDL-C reduction percentage	54.4 \pm 21.0	48.8 \pm 19.6	-	0.0021

Data are presented as n (%) or mean \pm standard deviation.
LDL-C, low-density lipoprotein cholesterol.

Supplementary Table 7. Any serious adverse events by MedDRA body system in the safety population

Body system	Number (%) of patients		P
	ROS10/EZT10 (n=295)	ROS20 (n=287)	
Total	22 (7.5)	22 (7.7)	0.9244
Cardiac disorders	1 (0.3)	3 (1.0)	
Gastrointestinal disorders	3 (1.0)	1 (0.4)	
General disorders and administration site conditions	2 (0.7)	6 (2.1)	
Hepatobiliary disorders	3 (1.0)	0 (0.0)	
Infections and infestations	2 (0.7)	1 (0.4)	
Injury, poisoning and procedural complications	1 (0.3)	0 (0.0)	
Investigations	1 (0.3)	0 (0.0)	
Musculoskeletal and connective tissue disorders	1 (0.3)	0 (0.0)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.7)	1 (0.4)	
Nervous system disorders	6 (2.0)	10 (3.5)	
Psychiatric disorders	1 (0.3)	0 (0.0)	
Renal and urinary disorders	1 (0.3)	0 (0.0)	
Other vascular disorders	1 (0.3)	0 (0.0)	

Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 21.1 (<https://www.meddra.org/>) was used for coding.

Supplementary Table 8. TEAEs by MedDRA body system in the safety population

Body system	Number (%) of patients		P
	ROS10/EZT10 (n=295)	ROS20 (n=287)	
Total*	11 (3.7)	9 (3.1)	0.6946
Gastrointestinal disorders	1 (0.3)	0 (0)	
General disorders and administration site conditions	4 (1.4)	1 (0.4)	
Investigations	5 (1.7)	5 (1.7)	
Musculoskeletal and connective tissue disorders	3 (1.0)	3 (1.1)	

Medical Dictionary for Regulatory Activities (MedDRA) dictionary Version 21.1 (<https://www.meddra.org/>) was used for coding. For patients who experienced TEAEs in 2 or more organ system, each event was counted for each organ system. Therefore, in the ROS10/EZT10 group, the sum of each number (=1+4+5+3) is greater than the total number of 11.

TEAE, treatment-emergent adverse event.

*Total numbers indicate the number of patients who experienced TEAEs, which differ the values of event numbers presented in Table 3 because several patients had >1 TEAEs.