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ORIGINAL RESEARCH

Comparative Effectiveness of Rosuvastatin Versus Atorvastatin in Acute Ischemic Stroke Treatment

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BACKGROUND: Research specifically addressing the efficacy of rosuvastatin versus atorvastatin in patients with ischemic stroke is insufficient. Using a large stroke registry, we investigated whether 2 commonly used statins, rosuvastatin and atorvastatin, differ in their effectiveness in reducing the risk of vascular events in patients with acute ischemic stroke.

METHODS: We analyzed data from a nationwide stroke registry in South Korea between January 2011 and April 2022. Patients with acute ischemic stroke within 7 days of onset who were prescribed either atorvastatin or rosuvastatin at discharge were included. The primary outcome was a composite of recurrent stroke (either hemorrhagic or ischemic), myocardial infarction, and all-cause mortality within 1 year.

RESULTS: A total of 43 512 patients (age, 69.2±12.5 years; male, 59.8%) were analyzed in this study. Atorvastatin was used in 84.8% (n=36 903), and rosuvastatin was used in 15.2% (n=6609). The 1-year cumulative event rate of the composite of recurrent stroke, myocardial infarction, and all-cause mortality was significantly lower in the rosuvastatin group than in the atorvastatin group (9.7% [95% CI, 9.0–10.5] versus 10.7% [95% CI, 10.4–11.0]; *P*=0.049). Cox proportional hazards analysis revealed that rosuvastatin, compared with atorvastatin, was significantly associated with less risk of 1-year composite of recurrent stroke, myocardial infarction, and all-cause mortality, with an absolute risk reduction of 1% [95% CI, −1.8 to −0.2] and a relative risk reduction of 11% (hazard ratio, 0.89 [95% CI, 0.82–0.97]). However, there were discrepancies in the statistical significance of the results between the propensity score matching and stabilized inverse probability of treatment weighting analysis.

CONCLUSIONS: The results of this analysis of a large cohort of patients with ischemic stroke suggested that, compared with atorvastatin, rosuvastatin was significantly associated with a reduced risk of a 1-year composite of recurrent stroke, myocardial infarction, and all-cause mortality in patients with acute ischemic stroke. However, in real clinical practice, rosuvastatin is used less than one-fifth as frequently as atorvastatin in patients with acute ischemic stroke. This study serves as a hypothesis-generating function.

Key Words: acute isc hemic stroke ■ atorvastatin ■ rosuvastatin

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CLINICAL PERSPECTIVE

What Is New?

- In patients with acute ischemic stroke, compared with atorvastatin, rosuvastatin was associated with reducing the risk of the 1-year composite of recurrent stroke, myocardial infarction, and all-cause mortality by 11% and all-cause mortality by 19%.
- In South Korea, atorvastatin is prescribed for patients with acute ischemic stroke at more than 5 times the frequency of rosuvastatin, reflecting a significant preference for atorvastatin in real-world practice.

What Are the Clinical Implications?

- Rosuvastatin is associated with improved 1-year composite of stroke, myocardial infarction, and all-cause mortality, compared with atorvastatin in patients with acute ischemic stroke, highlighting the need for further investigation through randomized controlled trials.
- Clinicians are encouraged to consider efficacy, patient-specific factors, and treatment goals when choosing between rosuvastatin and atorvastatin for patients with acute ischemic stroke.

Nonstandard Abbreviations and Acronyms

IPTW	stabilized inverse probability of treatment weighting
NIHSS	National Institute of Health Stroke Scale
PS	propensity score
PSM	propensity score matching

For secondary prevention after ischemic stroke, especially when poststroke low-density lipoprotein cholesterol (LDL-C) levels exceed 100 mg/dL, 80 mg atorvastatin is indicated based on findings from the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial.[1,2] However, unlike the American Heart Association/American Stroke Association guidelines, the European Stroke Organization guidelines and Korean dyslipidemia guidelines did not specify the use of particular statins like atorvastatin.[3,4]

Recent studies of patients with atherosclerotic cardiovascular diseases have demonstrated that moderate-intensity rosuvastatin (10 mg) plus ezetimibe (10 mg) treatment was not inferior to high-intensity rosuvastatin (20 mg) monotherapy.[5] In addition, previous comparative studies revealed that compared with atorvastatin or other statins, rosuvastatin exhibited a superior LDL-C lowering effect,[6,7] but it did not significantly reduce the risk of vascular events.[8] But these studies did not focus on patients with ischemic stroke. Research specifically addressing the use of rosuvastatin in patients with stroke remains insufficient. As a result, atorvastatin seems to be commonly preferred for secondary prevention in the acute phase of ischemic stroke.

Therefore, using a large stroke registry, we aimed to investigate whether 2 commonly used statins, rosuvastatin and atorvastatin, differ in their effectiveness in reducing the risk of vascular events in patients with acute ischemic stroke. In addition, we explored whether the effects of the 2 statins varied or remained consistent when outcomes were stratified by statin treatment intensity, stroke subtypes, admission LDL-C levels, or prior statin use.

METHODS

Subjects

In this study, data from the CRCS-K (Clinical Research Center for Stroke-Korea) registry, a nationwide collection of consecutive patients with acute stroke or transient ischemic attack admitted to 18 academic hospitals in South Korea, were analyzed. Comprehensive methodological details about the CRCS-K registry have been previously documented.[9,10] We identified patients who experienced acute cerebrovascular events and were thus admitted to the included hospitals between January 2011 and April 2022 (n=99 791). The study involved 12 out of 18 hospitals that prospectively collected data on brand-name statins. We enrolled patients who experienced acute ischemic stroke within 7 days of onset and who were prescribed either atorvastatin or rosuvastatin at discharge. Those with uncommon stroke cause (other etiology subtype) and those lacking information on statin names upon admission were excluded. A detailed patient selection flow chart is shown in Figure S1.

The data used in this study are available upon reasonable request following the submission of a legitimate academic research proposal to be assessed by the CRCS-K steering committee.

Ethics Statement

Clinical information was collected from the CRCS-K registry with approval from the local institutional review boards of all participating centers. A waiver of informed consent was provided because of study subject anonymity and minimal risk to the participants.

Data Collection

Demographic, clinical, imaging, and laboratory information was prospectively collected. Information on

statin dosage and brand names was not comprehensively collected, as it was an optional entry in the registry. When data on statin dosage and brand name were available, statin treatment intensity was categorized as high or low to moderate. High-intensity statin therapy was defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg,[11] and other dosages were classified as low-to-moderate-intensity statin treatments. Additionally, the use of nonstatin lipid-lowering agents such as ezetimibe was documented if available. Ischemic stroke subtypes were classified using the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) criteria and refined with additional data from modern imaging studies.[12,13]

Outcomes

Vascular events were prospectively observed during hospitalization and during a 3-month and 1-year follow-up period after the qualifying event via routine clinic visits or telephone interviews performed by dedicated nurses or physicians with a predefined protocol. To ensure the accuracy of the outcome captured and to minimize interinterviewer discrepancy, a set of uniform structured questionnaires was used by trained personnel. The primary vascular outcome within 1 year was a composite of recurrent stroke (either hemorrhagic or ischemic), myocardial infarction (MI) and all-cause mortality. The secondary vascular outcomes were the individual outcomes of (1) all-cause mortality, (2) recurrent stroke (either ischemic or hemorrhagic), (3) MI, and (4) hemorrhagic stroke. Detailed definitions of the vascular outcome events and methods of outcome capture used in the current study are described in previous reports.[9,10]

Statistical Analysis

The frequency (percentage), mean±SD, or median (interquartile range) was reported depending on the variable type. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test, and continuous variables were analyzed using Student's *t* test or the Wilcoxon rank-sum test, as appropriate. The following parameters had missing data for which median values were substituted: white blood cell count (0.1% of the data were missing), creatinine (0.1%), initial random glucose (0.5%), platelet count (0.1%), height (2.2%), and body weight (1.1%).

Primary analysis was performed with Cox proportional hazard models using adjustment for variables that were predetermined based on their influence on outcomes and treatment groups (including age; male sex; prestroke disability status; body mass index; National Institute of Health Stroke Scale [NIHSS] score; history of stroke, coronary artery disease, hypertension, diabetes, atrial fibrillation, and prior statin use; LDL-C, systolic blood pressure, and glucose levels; TOAST subtypes; and reperfusion therapy status). Comparisons of cumulative 1-year event rates between the 2 groups were performed using z-tests, based on estimates derived from Cox proportional hazards regression model.

Propensity score (PS) matching (PSM) and stabilized inverse probability of treatment weighting (IPTW) were used as supportive strategies to adjust for baseline imbalances. To generate comparable groups, 36 variables were used to calculate the PS. PS was estimated using multiple logistic regression analysis with 36 variables included as main effects only. PSM was conducted with 1:1 matching on the logit of the PS, applying a caliper width of 0.2.[14] Matching was performed without replacement, excluding patients who could not be matched within the specific caliper. Survival curves were constructed using Kaplan–Meier estimates, and 1-year cumulative event rates were compared using the log-rank test. To evaluate the effects of rosuvastatin compared with those of atorvastatin and other covariates on various outcomes, hazard ratios (HRs) and 95% CIs were estimated using Cox regression models with robust SEs. An absolute standardized difference of <0.1 for each baseline covariate was considered to indicate a minimal and acceptable imbalance between the 2 groups. In predefined subgroup analyses, we explored differences in outcomes for the following parameters: age (≥75 or <75 years old), sex (male or female), TOAST subtypes, LDL-C on admission (<70 mg/dL, 70–100 mg/dL or >100 mg/dL), prior statin use (prior use versus naïve use), and NIHSS scores. For sensitivity analysis, among only patients with information on statin dose, comparative analysis of the effects of rosuvastatin and atorvastatin in the high-intensity and low-intensity groups was performed.

Two-sided *P* values <0.05 were considered to indicate statistical significance. Given the known insensitivity of interaction testing, evidence of heterogeneity was considered present with *P* values ≤0.10. Statistical analyses were performed with R software using the "rms" package (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

General Characteristics

A total of 43 512 patients (mean age; 69.2±12.5 years; 59.8% men) met the eligibility criteria and were included in this study. The median NIHSS score was 3 (interquartile range, 1–7). The mean LDL-C level on admission was 108.9±38.3 mg/dL. Atorvastatin was used in 84.8% (n=36 903) of patients, and rosuvastatin was used in 15.2% (n=6609) of patients. Nonstatin

lipid-lowering agents were used in 2.5% of patients, with rosuvastatin and atorvastatin having usage rates of 8.9% and 1.4%, respectively.

The demographic and clinical characteristics of the patients in the statin groups are shown in Table 1. Compared with the atorvastatin group, the rosuvastatin

Table 1. General Characteristics of the Subjects

	All patients	Atorvastatin	Rosuvastatin	*P* value*
No.	43512	36903	6609	
Age, y	69.2±12.5	69.2±12.5	69.7±12.8	0.01
Male sex	26001 (59.8)	21992 (59.6)	4009 (60.7)	0.10
Body mass index	23.8±3.5	23.8±3.5	23.8±3.6	0.47
Prestroke modified Rankin Scale score, 0–1	37963 (87.2)	32383 (87.8)	5580 (84.4)	<0.001
National Institutes of Health Stroke Scale score, med (interquartile range)	3 (1–7)	3 (1–7)	3 (1–6)	<0.001
History of transient ischemic attack	742 (1.7)	635 (1.7)	107 (1.6)	0.56
History of stroke	8817 (20.3)	7274 (19.7)	1543 (23.3)	<0.001
History of peripheral artery disease	292 (0.7)	255 (0.7)	37 (0.6)	0.23
History of coronary artery disease	3771 (8.7)	3146 (8.5)	625 (9.5)	0.01
Hypertension	29112 (66.9)	24562 (66.6)	4550 (68.8)	<0.001
Diabetes	14798 (34.0)	12426 (33.7)	2372 (35.9)	<0.001
Dyslipidemia	15175 (34.9)	12656 (34.3)	2519 (38.1)	<0.001
Current smoking	10500 (24.1)	9010 (24.4)	1490 (22.5)	0.001
Atrial fibrillation	8489 (19.5)	7214 (19.5)	1275 (19.3)	0.63
Prior medication				
Antiplatelet	11950 (27.5)	9879 (26.8)	2071 (31.3)	<0.001
Antihypertensive	22142 (50.9)	18639 (50.5)	3503 (53.0)	<0.001
Statin	9329 (21.4)	7292 (19.8)	2037 (30.8)	<0.001
Antidiabetic	10815 (24.9)	9086 (24.6)	1729 (26.2)	0.01
Laboratory finding				
White blood cell count	8.2±2.9	8.2±2.9	8.0±2.9	<0.001
Blood urea nitrogen	17.5±8.6	17.5±8.6	17.5±8.4	0.72
Creatinine	1.00±0.80	1.01±0.81	0.97±0.76	<0.001
Hemoglobin	13.6±2.0	13.6±2.0	13.6±2.0	0.09
Glucose	146.2±63.5	145.6±63.3	149.5±64.5	<0.001
Platelet count	231.7±70.6	232.0±70.9	229.9±68.7	0.02
Low-density lipoprotein-cholesterol	108.9±38.3	109.6±38.1	105.2±39.2	<0.001
Systolic blood pressure	147.1±27.8	146.1±27.7	152.4±27.7	<0.001
Trial of Org 10172 in Acute Stroke Treatment subtype				<0.001
Large artery atherosclerosis	16412 (37.7)	13976 (37.9)	2436 (36.9)	
Small vessel occlusion	8151 (18.7)	6609 (17.9)	1542 (23.3)	
Cardioembolic	8401 (19.3)	7087 (19.2)	1314 (19.9)	
Undetermined	10548 (24.2)	9231 (25.0)	1317 (19.9)	
Reperfusion therapy				<0.001
No	36635 (84.2)	30820 (83.5)	5815 (88.0)	
IVT	3801 (8.7)	3343 (9.1)	458 (6.9)	
EVT	1579 (3.6)	1410 (3.8)	169 (2.6)	
IVT+EVT	1497 (3.4)	1330 (3.6)	167 (2.5)	
Antidiabetics, at discharge	11479 (26.4)	9560 (25.9)	1919 (29.0)	<0.001
Antihypertensives, at discharge	20010 (46.0)	16740 (45.4)	3270 (49.5)	<0.001

EVT indicates endovascular thrombectomy; and IVT, intravenous thrombolysis.
**P* value was determined by the Pearson chi-square test, Student's *t* test, or Wilcoxon rank-sum test, as appropriate.

group was more likely to be older and have a history of stroke, coronary artery disease, hypertension, diabetes, dyslipidemia, prior antiplatelet use, prior antihypertensive use, prior antidiabetic use, prior statin use, small vessel occlusion subtype, cardioembolic subtype, in-hospital antidiabetic treatment, and in-hospital antihypertensive treatment. After PSM and IPTW, the distributions of the baseline characteristics were fairly well balanced; the absolute standardized differences after PSM and IPTW were within the margin of 0.1 for all covariates (Tables S1 and S2 and Figures S2 and S3).

Outcomes

The mean follow-up duration was 338±77 days (median, 365 [362–365] days), with 89.6% of patients completing 1 year of follow-up. The primary composite outcome of recurrent stroke (ischemic and hemorrhagic), MI, and all-cause mortality occurred in 4375 patients, and the 1-year cumulative event rate was 10.5%. For individual components of vascular outcomes, the 1-year cumulative event rates were 4.4% for recurrent stroke, 6.8% for all-cause mortality, and 0.3% for MI. Hemorrhagic stroke occurred in 0.4% of patients. According to the unadjusted analysis, the 1-year cumulative event rate of the composite of recurrent stroke, MI, and all-cause mortality was significantly lower in the rosuvastatin group than in the atorvastatin group (9.7% [95% CI, 9.0–10.5] versus 10.7% [95% CI, 10.4–11.0], risk difference 1.0% [95% CI, 0.2–1.8], P=0.049). All-cause mortality was significantly lower in the rosuvastatin group than in the atorvastatin group (5.9% [95% CI, 5.3–6.5] versus 7.0% [95% CI, 6.7–7.2], risk difference 1.1% [95% CI, 0.5–1.8], P=0.002). However, for recurrent stroke, MI, and hemorrhagic stroke outcomes, there were no differences between the rosuvastatin group and the atorvastatin group (Table 2).

In the adjusted analysis, the composite of recurrent stroke, MI, and all-cause mortality within 1 year were significantly different between the rosuvastatin group and the atorvastatin group, with an absolute difference of 1.0% (95% CI, 0.2–1.8) and a relative risk reduction of 11% (Tables 2 and 3). All-cause mortality within 1 year significantly differed between the 2 groups (5.8% [95% CI, 5.2–6.3] in the rosuvastatin group versus 7.0% [95% CI, 6.7–7.2] in the atorvastatin group, P<0.001). However, no differences were observed for the individual outcomes of recurrent stroke, MI, or hemorrhagic stroke. Similar results were observed in the PSM analysis. The composite of recurrent stroke, MI, all-cause mortality within 1 year significantly differed between the 2 groups in the PSM analysis but not in the IPTW analysis. All-cause mortality within 1 year was significantly lower in the rosuvastatin group than in the atorvastatin group (5.9% [95% CI, 5.3–6.5] versus 7.6% [95% CI, 7.0–8.3] in PSM analysis and

Table 2. One-Year Outcome Event Rates (%, 95% CI) Between the Rosuvastatin Group and the Atorvastatin Group

	Crude*				Adjusted				PSM				IPTW			
	Rosuvastatin	Atorvastatin	Risk difference (95% CI)	P value†	Rosuvastatin	Atorvastatin	Risk difference (95% CI)	P value‡	Rosuvastatin	Atorvastatin	Risk difference	P value§	Rosuvastatin	Atorvastatin	Risk difference (95% CI)	P value‖
Primary outcomes	9.7 (9.0 to 10.5)	10.7 (10.4 to 11.0)	−1.0 (−1.8 to −0.2)	0.049	9.7 (9.0–10.4)	10.7 (10.4 to 11.0)	−1.0 (−1.8 to −0.2)	0.01	9.7 (9.0 to 10.5)	11.5 (10.7 to 12.3)	−1.8 (−2.9 to −0.7)	<0.001	10.0 (9.2 to 10.8)	10.7 (10.3 to 11.0)	−0.7 (−1.6 to 0.2)	0.23
Secondary outcomes																
Stroke	4.3 (3.8 to 4.8)	4.4 (4.2 to 4.6)	−0.1 (−0.7 to −0.5)	0.90	4.2 (3.7 to 4.7)	4.4 (4.2 to 4.7)	−0.2 (−0.7 to 0.3)	0.35	4.3 (3.8 to 4.8)	4.7 (4.1 to 5.2)	−0.4 (−1.1 to 0.3)	0.48	4.5 (3.9 to 5.0)	4.4 (4.2 to 4.7)	0.1 (−0.5 to 0.7)	0.67
All-cause mortality	5.9 (5.3 to 6.5)	7.0 (6.7 to 7.2)	−1.1 (−1.8 to −0.5)	0.002	5.8 (5.2 to 6.3)	7.0 (6.7 to 7.2)	−1.2 (−0.3 to −0.6)	<0.001	5.9 (5.3 to 6.5)	7.6 (7.0 to 8.3)	−1.7 (−2.6 to −0.8)	<0.001	6.1 (5.4 to 6.7)	6.9 (6.7 to 7.2)	−0.8 (−1.5 to −0.1)	0.02
Myocardial infarction	0.3 (0.2 to 0.5)	0.3 (0.3 to 0.4)	0.0 (−0.2 to 0.2)	0.77	0.3 (0.2 to 0.4)	0.4 (0.3 to 0.4)	−0.1 (−0.3 to 0.1)	0.36	0.3 (0.2 to 0.5)	0.3 (0.2 to 0.5)	0.0 (−0.2 to 0.2)	0.61	0.3 (0.2 to 0.5)	0.3 (0.3 to 0.4)	0.0 (−0.2 to 0.2)	0.95
Hemorrhagic stroke	0.3 (0.1 to 0.4)	0.4 (0.3 to 0.4)	−0.1 (−0.2 to 0.1)	0.42	0.3 (0.2 to 0.5)	0.4 (0.3 to 0.4)	−0.1 (−0.3 to 0.1)	0.75	0.3 (0.1 to 0.4)	0.3 (0.2 to 0.5)	0.0 (−0.2 to 0.2)	0.61	0.3 (0.2 to 0.5)	0.4 (0.3 to 0.4)	−0.1 (−0.3 to 0.1)	0.93

IPTW indicates stabilized inverse probability of treatment weighting; and PSM, propensity score matching.
*Based on Kaplan–Meier estimates.
†P value was determined by the log-rank test.
‡Based on the Cox model (adjusted: age, male sex, prestroke modified Rankin Scale score 0–1, body mass index, National Institutes of Health Stroke Scale score, history of stroke, history of coronary artery disease, hypertension, diabetes, atrial fibrillation, prior statin use, low-density lipoprotein cholesterol, systolic blood pressure, glucose, Trial of Org 10 172 in Acute Stroke Treatment, and reperfusion therapy).
§P value was determined by stratified log-rank test.
‖P value by weighted log-rank test.

Table 3. Associations of Rosuvastatin and Atorvastatin With 1-Year Outcomes

	Univariate analysis		Multivariate analysis		PSM		Stabilized IPTW	
	HR (95% CI)	*P* value*	HR (95% CI)	*P* value*	HR (95% CI)	*P* value†	HR (95% CI)	*P* value‡
Primary outcome	0.92 (0.84–1.00)	0.049	0.89 (0.82–0.97)	0.01	0.85 (0.77–0.95)	0.004	0.95 (0.86–1.04)	0.24
Secondary outcomes								
Stroke	0.99 (0.87–1.13)	0.90	0.94 (0.82–1.07)	0.35	0.94 (0.80–1.11)	0.46	1.03 (0.89–1.19)	0.69
All-cause mortality	0.84 (0.75–0.94)	0.002	0.81 (0.72–0.91)	<0.001	0.77 (0.67–0.88)	<0.001	0.87 (0.77–0.99)	0.03
Myocardial infarction	0.93 (0.57–1.51)	0.77	0.92 (0.56–1.51)	0.75	0.88 (0.47–1.64)	0.68	0.98 (0.51–1.86)	0.95
Hemorrhagic stroke	0.81 (0.49–1.35)	0.42	0.79 (0.47–1.31)	0.36	0.93 (0.50–1.72)	0.81	1.02 (0.60–1.72)	0.95

Adjusted variables: age, male sex, prestroke modified Rankin Scale score 0–1, body mass index, National Institutes of Health Stroke Scale score, history of stroke, history of coronary artery disease, hypertension, diabetes, atrial fibrillation, prior statin use, Clow-density lipoprotein cholesterol, systolic blood pressure, glucose, Trial of Org 10 172 in Acute Stroke Treatment, and reperfusion therapy. HR indicates hazard ratio; IPTW, stabilized inverse probability of treatment weighting; PH, proportional hazards; and PSM, propensity score matching.

*Cox's PH regression.

†Cox's PH regression with robust SEs to account for clustering in matched pairs.

‡Weighted Cox's PH regression with robust SEs.

6.1% [95% CI, 5.4–6.7] versus 6.9% [95% CI, 6.7–7.2] in IPTW analysis). The Kaplan–Meier cumulative incidence plots of the composite of recurrent stroke, MI, and all-cause mortality, recurrent stroke, and all-cause mortality (Figures 1A, 1B, and 1C) showed that the outcome differences between treatment groups mainly occurred 3 months after stroke onset. Also, adjusted and matched/weighted Kaplan–Meier plots are shown in Figures S4 and S5.

Subgroup Analysis

In the 4 predefined subgroup analyses, there was significant heterogeneity regarding the composite of recurrent stroke, MI, and all-cause mortality among the NIHSS score subgroups (Figure 2 and Table S3). Greater associations of reducing the risk of the composite of recurrent stroke, MI, and all-cause mortality were suggested for patients in the high NIHSS score subgroup (NIHSS >10; HR, 0.67 [95% CI, 0.55–0.81]; $P_{interaction}$=0.02).

Sensitivity Analysis

The sensitivity analysis revealed that 74.7% (n=32 499) of patients had available information on statin dose. Among them, 58.2% of patients received high-intensity statin therapy, and 41.8% of patients received low-to-moderate-intensity statin therapy. Rosuvastatin was prescribed as a high-intensity statin in 52.3% of patients, compared with 58.7% for atorvastatin (Tables S4 through S6). The outcome events within 1 year are presented in Table S7, and the associations of rosuvastatin with atorvastatin for 1-year vascular outcomes are shown in Table S8. The effectiveness of rosuvastatin versus atorvastatin according to the statin-intensity groups is presented in Table 4. There was no interaction effect between statin group and statin treatment intensity on the 1-year primary outcome; there was a consistent association of lower risk of the 1-year composite of recurrent stroke, MI, and all-cause mortality for rosuvastatin (versus atorvastatin) in the high-intensity statin group (adjusted HR, 0.82 [95% CI, 0.68–0.98]) and in the low-to-moderate-intensity statin group (HR, 0.86 [95% CI, 0.71–1.04]).

DISCUSSION

In an analysis of more than 43 000 patients with acute ischemic stroke treated with statins, we found that rosuvastatin, compared with atorvastatin, was associated with reducing the risk of the 1-year composite of recurrent stroke, MI, and all-cause mortality by 11% and all-cause mortality by 19%. However, in real clinical practice, rosuvastatin is used less than one-fifth as frequently as atorvastatin in patients with acute ischemic stroke. Our study, the first to compare the effectiveness of rosuvastatin versus atorvastatin in acute ischemic stroke from real-world data, suggests the need for future prospective comparative clinical studies of statins.

In this study, we observed that for real-world practice in South Korea, atorvastatin was used >5 times more frequently than rosuvastatin in patients with acute ischemic stroke. This might be attributed to recommendations in guidelines from the American Heart Association/American Stroke Association endorsing atorvastatin 80 mg or results from studies such as the SPARCL trial.[1,2] Although the European Stroke Organization and Korean dyslipidemia guidelines recommend using statins and setting target LDL-C levels to reduce the risk of atherosclerotic cardiovascular diseases,[3,4] they did not specify the use of particular statins like atorvastatin. Therefore, it seems that

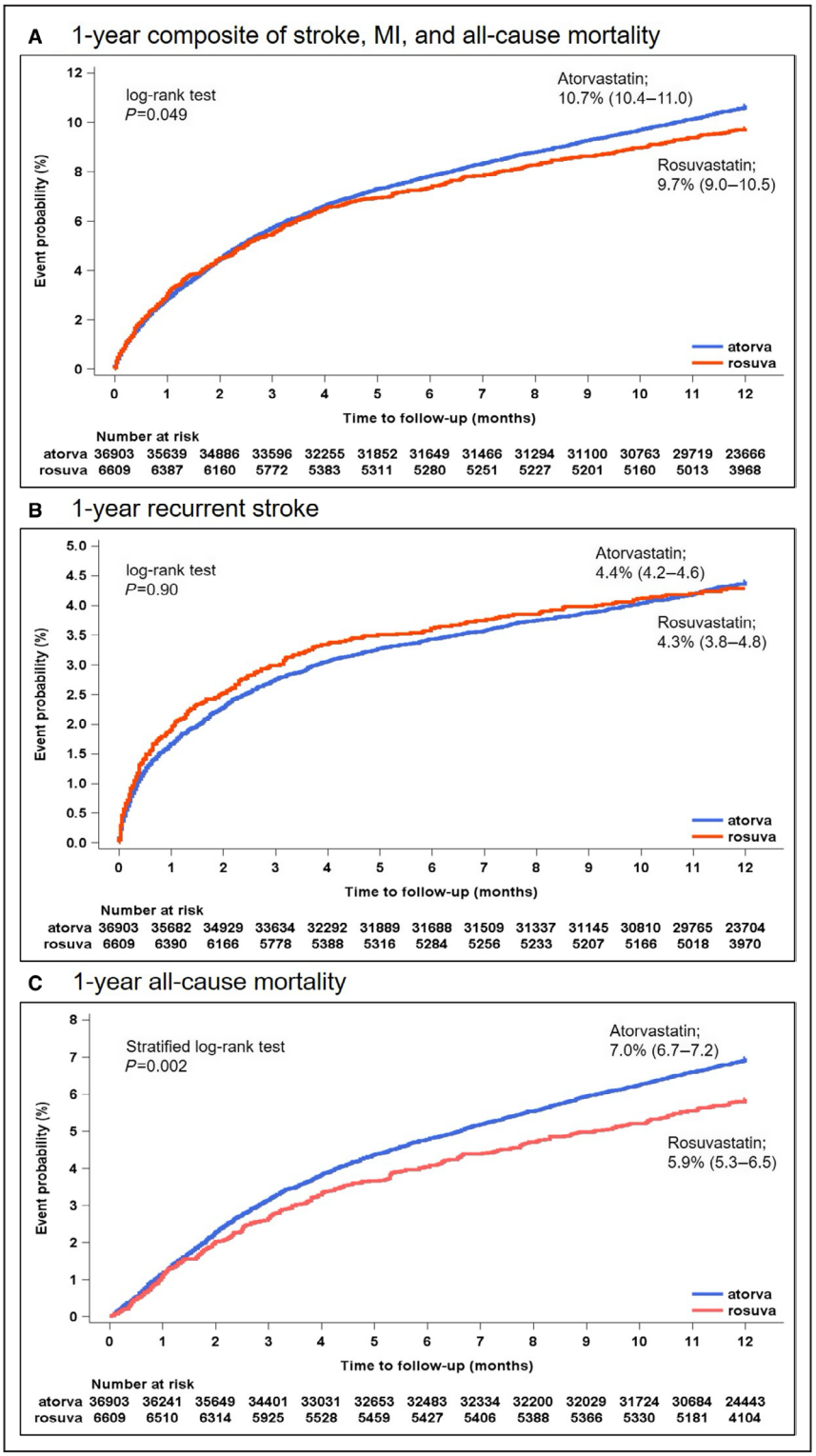

Figure 1. Kaplan–Meier plots for the 1-year composite of stroke, MI, and all-cause mortality (A), stroke (B), and all-cause mortality (C).
MI indicates myocardial infarction.

Korean stroke physicians generally follow the American Heart Association/American Stroke Association stroke guidelines.

Additionally, the scarcity of studies on rosuvastatin use in patients with stroke might contribute to its lower use. Previous comparative studies revealed that

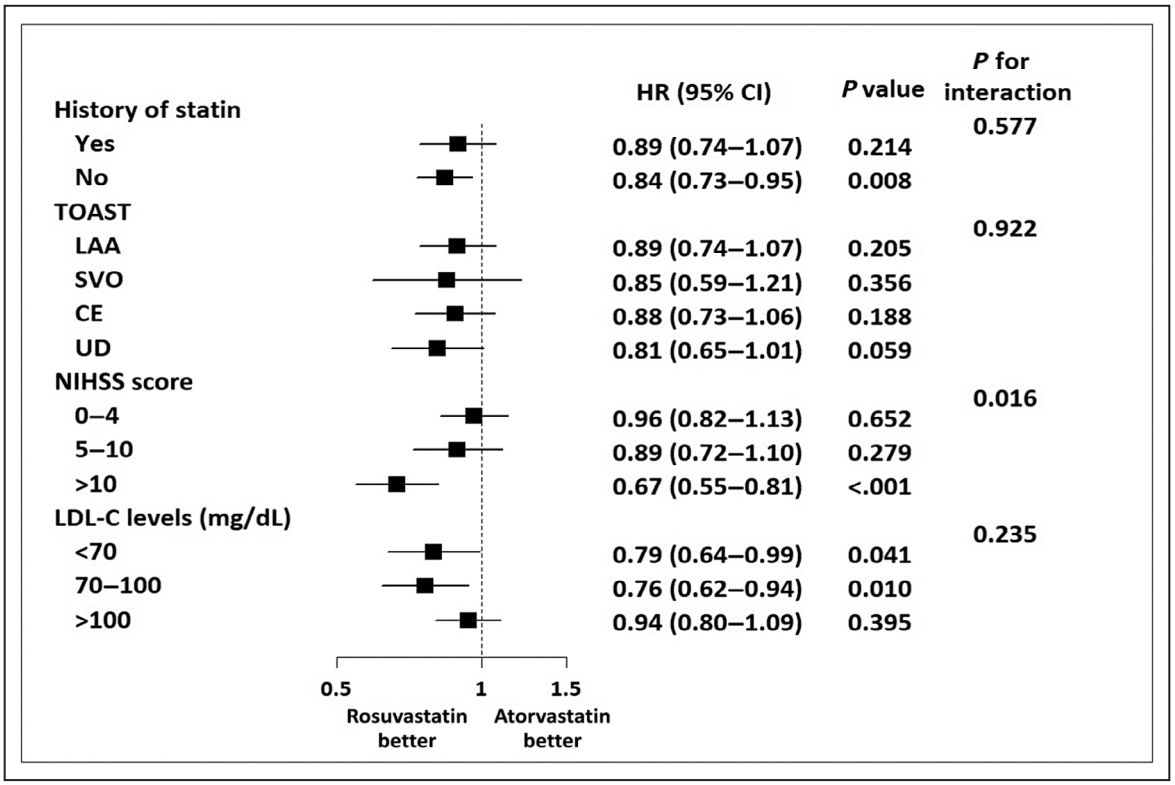

Figure 2. Subgroup analysis.
CE indicates cardioembolism; HR, hazard ratio; LAA, large artery atherosclerosis; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institute of Health Stroke Scale; SVO, small vessel occlusion; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; and UD, undetermined cause.

compared with atorvastatin, rosuvastatin exhibited a superior LDL-C lowering effect,[6,7] but it did not significantly reduce the risk of vascular events.[8] In contrast, in our study, compared with atorvastatin, rosuvastatin was associated with an 11% relative risk reduction for the 1-year composite of recurrent stroke, MI, and all-cause mortality and 19% for the 1-year all-cause mortality. Particularly noteworthy was the finding that in the group receiving high-intensity treatment, there was still an 18% greater likelihood of reducing the risk of a 1-year composite of recurrent stroke, MI, and all-cause mortality. The difference in the risk of the primary composite outcome between 2 groups was primarily driven by all-cause mortality across all models, which was also evident from the Kaplan–Meier curves. These findings align with the results of a recent multidatabase cohort study, which showed that 6-year all-cause mortality was lower for rosuvastatin compared with atorvastatin. This difference has been partially attributed to the lower incidence of severe liver adverse effects associated with rosuvastatin.[15] The greater anti-inflammatory effect of rosuvastatin could also be beneficial for several disease states in noncardiac organs. It is well known that statins play a significant role in reducing mortality, beyond their LDL-C lowering effect.[16,17] As both atherothrombotic and nonatherothrombotic strokes were included for the study, the impact on mortality was likely accentuated. Based on the general characteristics presented in Table 1, rosuvastatin users were, on average, in slightly worse condition than atorvastatin users. Moreover, it is essential to note that our study focused on patients with acute-stage stroke, with only 70% providing dose information, and among them, 50% were receiving high-intensity statin treatments, distinguishing this finding from previous research.

However, we must acknowledge the possibility that the association observed between rosuvastatin use and reduced all-cause mortality may have arisen by chance, particularly given the retrospective nature of our study and the baseline differences between the 2 groups. Therefore, any apparent reduction in all-cause mortality should be interpreted cautiously and should not be considered as evidence of causation.

Our study revealed that rosuvastatin yielded consistent associations of reducing the risk of 1-year composite of recurrent stroke, MI, and all-cause mortality in subgroups for which the efficacy of statin therapy was unclear. Notably, favorable findings for rosuvastatin were observed in patients with LDL-C<100 mg/dL at admission (including <70 mg/dL), high NIHSS scores (>10), no prior statin use, and nonatherosclerotic stroke (undetermined cause, though the difference was

Table 4. Sensitivity Analysis of Patients With Information on Statin Dose and Subgroup Analysis According to Statin Treatment Intensity

	Univariate analysis			Multivariate analysis			PSM			IPTW (ATE weights)		
	HR (95% CI)	*P* value*	*P* value$_{interaction}$	HR (95% CI)	*P* value *	*P* value$_{interaction}$	HR (95% CI)	*P* value†	*P* value$_{interaction}$	HR (95% CI)	*P* value‡	*P* value$_{interaction}$
Primary outcome			0.70			0.70			0.57			0.95
High intensity	0.85 (0.70–1.02)	0.09		0.82 (0.68–0.98)	0.03		0.87 (0.68–1.11)	0.26		0.85 (0.69–1.05)	0.13	
Low-to-moderate intensity	0.90 (0.74–1.09)	0.26		0.86 (0.71–1.04)	0.12		0.96 (0.75–1.25)	0.78		0.84 (0.68–1.04)	0.12	
Stroke			0.15			0.26			0.64			0.34
High intensity	0.85 (0.64–1.12)	0.24		0.80 (0.60–1.06)	0.11		0.82 (0.57–1.18)	0.28		0.81 (0.59–1.11)	0.20	
Low-to-moderate intensity	1.14 (0.85–1.53)	0.39		1.00 (0.75–1.35)	0.98		0.92 (0.63–1.35)	0.68		1.01 (0.74–1.38)	0.96	
All-cause mortality			0.41			0.67			0.76			0.25
High intensity	0.81 (0.63–1.03)	0.09		0.77 (0.60–0.98)	0.04		0.85 (0.62–1.16)	0.30		0.85 (0.65–1.11)	0.23	
Low-to-moderate intensity	0.70 (0.54–0.90)	0.01		0.71 (0.55–0.92)	0.01		0.91 (0.64–1.28)	0.58		0.67 (0.50–0.90)	0.01	
Myocardial infarction			0.17			0.19			0.31			0.37
High intensity	0.73 (0.23–2.32)	0.59		0.69 (0.21–2.20)	0.53		0.77 (0.17–3.43)	0.73		0.99 (0.27–3.65)	0.99	
Low-to-moderate intensity	1.93 (0.91–4.10)	0.09		1.73 (0.81–3.70)	0.16		2.06 (0.62–6.80)	0.24		2.01 (0.90–4.51)	0.09	
Hemorrhagic stroke			0.56			0.54			0.54			0.20
High intensity	0.88 (0.32–2.44)	0.81		0.85 (0.31–2.36)	0.76		0.81 (0.22–3.03)	0.76		1.10 (0.39–3.13)	0.86	
Low-to-moderate intensity	0.53 (0.13–2.18)	0.38		0.49 (0.12–2.05)	0.33		0.42 (0.08–2.14)	0.29		0.35 (0.08–1.44)	0.15	

Hazard ratio: rosuvastatin vs atorvastatin (ref). Adjusted variables: age, male sex, prestroke modified Rankin Scale score 0–1, body mass index, National Institutes of Health Stroke Scale score, history of stroke, history of coronary artery disease, hypertension, diabetes, atrial fibrillation, prior statin use, low-density lipoprotein cholesterol, systolic blood pressure, glucose, Trial of Org 10172 in Acute Stroke Treatment, reperfusion therapy, and statin treatment intensity (high vs low-to-moderate intensity). ATE indicates average treatment effect; HR, hazard ratio; IPTW, stabilized inverse probability of treatment weighting; PH, proportional hazards; and PSM, propensity score matching.

*Cox's PH regression.

†Cox's PH regression with robust SEs to account for clustering in matched pairs.

‡Weighted Cox's PH regression with robust SEs.

nonsignificant). The specific reasons for the differing effectiveness of rosuvastatin versus atorvastatin in these situations are not fully understood. However, a notable difference lies in their metabolic pathways. Although atorvastatin is extensively metabolized by CYP3A4, an enzyme found in the liver and gastrointestinal tract,[18] rosuvastatin is primarily metabolized by the CYP2C9 enzyme and is minimally affected by CYP3A4.[19] Consequently, rosuvastatin encounters fewer drug and food interactions compared with atorvastatin. Other possibility is the potentially stronger LDL-C-lowering effect of rosuvastatin than of atorvastatin, as suggested by previous studies.[8,20] Moreover, the lower the LDL-C level is, the lower the risk of atherosclerotic vascular events,[21] suggesting that rosuvastatin might be more favorable than atorvastatin. However, because we did not conduct LDL-C follow-ups and this was not a randomized study, establishing clear causation or effects was challenging.

The determination of statin type and intensity is important for the secondary prevention of atherosclerotic cardiovascular diseases, including stroke. In our study, even in patients with large artery atherosclerosis, high-intensity statin therapy was administered in 69% of patients after stroke among patients with available statin dose information (57% of patients with small vessel occlusion, and 48% of patients with cardioembolic stroke). These findings suggest a potential need for increased efforts in guideline implementation to enhance secondary stroke prevention in the future. European guidelines currently provide recommendations for targeting LDL-C levels without specifying a particular treatment intensity.[22] Additionally, a recent TST (Treat Stroke to Target) study indicated that achieving a target LDL-C<70 mg/dL in patients with stroke was more beneficial for secondary prevention.[23] Hence, reaching the LDL-C target after statin therapy may influence the results of study. Considering that patients with stroke may already be older, have a history of prior stroke (especially hemorrhagic stroke), or exhibit frailty, the practical use of high-intensity statin therapy in the real world for patients with stroke may not be common. Due to the heterogeneity of stroke, the appropriateness of high-intensity statin use in patients with the cardioembolism, undetermined cause, and small vessel occlusion subtypes remains questionable. Additionally, it is unclear whether high-intensity statin therapy is necessary when the LDL-C level is already <100 mg/dL or 70 mg/dL (in cases where the target LDL-C level has been reached) at the onset of the index stroke,[24] necessitating further investigation through prospective studies. Nevertheless, rosuvastatin appears to trend toward superiority over atorvastatin, even in subgroup analyses, which provides meaningful insight, suggesting its relevance in clinical considerations.

Our study has several limitations. First, selection bias regarding statin use is still a concern. Although we conducted supportive analyses, including PSM and IPTW, to rigorously adjust for confounding, the presence of unmeasured confounders cannot be ruled out. Additionally, although propensity-matched analysis showed significant results driven by all-cause mortality, the IPTW approach did not. Generally, PSM and IPTW yield similar results if the treatment selection process is similar. However, strong treatment-selection processes can cause biased estimations of the true marginal HR in both methods, even with a correctly specified PS model. Full matching tends to show less bias than IPTW in such cases.[25] These biases and method differences seem to arise from extreme weights, which are more pronounced in IPTW. Nevertheless, the discrepancy between the IPTW and PSM analyses suggests that our findings may not be conclusive. Second, information on follow-up LDL-C levels after statin treatment was unavailable. The partial collection of statin treatment intensity and the lack of monitoring for statin duration may have influenced the results. Nevertheless, the overall trends in the results may help mitigate the impact of these constraints. Third, safety outcomes were not analyzed. The use of statins has been associated with an increased risk of adverse effects such as new-onset diabetes, muscle symptoms, and neurocognitive decline.[26,27] Future prospective randomized trials are essential to address these concerns. Furthermore, our study, which was registry based and limited to Korean patients with stroke, has limitations in terms of generalizability and requires external validation for applicability to non-Korean patients. Therefore, this study serves as a hypothesis-generating function, not conclusive.

Conclusions

In conclusion, our analysis of a large cohort of patients with ischemic stroke suggested that, compared with atorvastatin, rosuvastatin was significantly associated with a reduced risk of a 1-year composite of recurrent stroke, MI, and all-cause mortality in patients with acute ischemic stroke. The favorable trend associated with rosuvastatin treatment was consistent across subgroups based on high-intensity statin therapy, ischemic stroke subtypes, baseline LDL-C levels, and prior statin use, demonstrating no treatment heterogeneity. However, due to the discrepant results between PSM and IPTW analyses, these findings should be interpreted with caution, as they may not be fully conclusive. Future prospective studies are needed to confirm our findings.

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Supplemental Material

Tables S1–S8
Figures S1–S5

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