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Original Article

Effect and Safety of Rosuvastatin in Acute Ischemic Stroke

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Background and Purpose The benefit of statins in acute stroke remains uncertain. Statins may prevent stroke recurrence during the acute stage of stroke via pleiotropic effects. However, statins may increase the risk of intracerebral hemorrhage. We investigated the effect and safety of rosuvastatin in acute stroke patients.

Methods This randomized, double-blind, multi-center trial compared rosuvastatin 20 mg and placebo in statin-naïve stroke patients who underwent diffusion-weighted imaging (DWI) within 48 hours after symptom onset. The primary outcome was occurrence of new ischemic lesions on DWI at 5 or 14 days.

Results This trial was stopped early after randomization of 316 patients due to slow enrollment. Among 289 patients with at least one follow-up imaging, the frequency of new ischemic lesions on DWI was not different between groups (rosuvastatin: 27/137, 19.7% vs. placebo: 36/152, 23.6%) (relative risk 0.83, 95% confidence interval 0.53–1.30). Infarct volume growth at 5 days (log-transformed volume change, rosuvastatin: 0.2 ± 1.0 mm^3 vs. placebo: 0.3 ± 1.3 mm^3; P = 0.784) was not different, either. However, hemorrhagic infarction or parenchymal/subarachnoid hemorrhage on gradient-recalled echo magnetic resonance imaging occurred less frequently in the rosuvastatin group (6/137, 4.4%) than the placebo group (22/152, 14.5%, P = 0.007). Among 314 patients with at least one dose of study medication, progression or clinical recurrence of stroke tended to occur less frequently in the rosuvastatin group (1/155, 0.6% vs. 7/159, 4.4%, P = 0.067). Adverse events did not differ between groups.

Conclusions The efficacy of rosuvastatin in reducing recurrence in acute stroke was inconclusive. However, statin use was safe and reduced hemorrhagic transformation.

Keywords Stroke; Rosuvastatin; Statin; Diffusion-weighted imaging

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Introduction

Statins are effective in primary and secondary prevention of stroke.[1-3] Their long-term beneficial effects may be primarily mediated by their lipid-lowering effects. Statins may also work effectively in preventing recurrence or progression during the

acute stage of stroke because they have antithrombotic, anti-inflammatory, and anti-oxidative effects.[4-7]

Several observational studies have suggested that statin use before or during the acute stage of stroke was associated with better functional outcome and reduced mortality.[7-9] By contrast, intracerebral hemorrhage (ICH) developed more frequently in patients treated with high-dose statins during the subacute or chronic stage of ischemic stroke in large randomized trials.[2,10] Since the risk of hemorrhagic transformation is greater during the acute stage of stroke, statin treatment in acute stroke raises the concern of increased ICH risk. However, data from randomized trials are insufficient to establish whether statins are effective and safe in patients with acute ischemic stroke.[11] Furthermore, statins are not recommended in stroke guidelines as an agent with neuroprotective actions to improve outcome in acute stroke.[12] Therefore, we investigated the effect and safety of rosuvastatin in acute ischemic stroke patients.

Methods

This double-blind, placebo-controlled, randomized, multicenter study was approved by the Ministry of Food and Drug Safety, Korea, and the institutional review board at each study center. Written informed consent was obtained from each patient. This trial (Effects of very early use of rosuvastatin in preventing recurrence of ischemic stroke [EUREKA]) was registered on ClinicalTrials.gov (NCT01364220).

Study population

We enrolled patients over 20 years old diagnosed with acute ischemic stroke on diffusion-weighted imaging (DWI) within 48 hours after symptom onset who had been untreated with a statin for the previous 3 months. Patients also should show any degree of stenosis on the relevant artery of infarction on DWI. Patients with hemorrhagic stroke, history of symptomatic hemorrhagic stroke, high-risk cardiac sources of embolism, or stroke of other determined etiology were excluded. Other exclusion criteria are described in Supplementary data.

The modified intention-to-treat population consisted of patients who underwent a baseline magnetic resonance imaging (MRI), had triglyceride (TG) < 500 mg/dL, low-density lipoprotein cholesterol < 190 mg/dL, and took at least one dose of study medication. The per-protocol (PP) population consisted of patients who completed scheduled MRIs without a major protocol violation.

Randomization, blinding, and interventions

Patients were randomized 1:1 to receive either rosuvastatin or placebo. Permutated-block randomization with a block size of 4 was generated by an independent clinical trials center (Severance Hospital, Yonsei University Health System, Seoul, Korea). After patients were screened and completed enrollment, drugs were assigned a unique study number, selected sequentially from the central randomization list that corresponded to the treatment pack, and allocated in a double-blind manner. The drug was administered within 18 hours after baseline MRI and then daily during the 14-day treatment period. Patients received either one 20-mg tablet or a placebo tablet, once daily.

Sample size

We hypothesized that, compared to placebo, rosuvastatin would reduce the occurrence of new ischemic lesions on MRI by 30%. To test our hypothesis, assuming a type I error of 5% and a power of 80%, sample sizes were calculated as 260 in each group. The proportion in the rosuvastatin group was assumed to be 0.40 under the null hypothesis and 0.28 under the alternative hypothesis, based on a previous study that recognized new ischemic lesions on DWI in 34%-47.4% of patients during the first week after baseline DWI taken within 24 hours after symptom onset.[13,14] The test statistic used was the 2-sided Fisher's exact test. Assuming a drop-out rate of 5%, the total number of patients needed was 547.

Imaging protocol

To be eligible, patients underwent DWI, fluid attenuated inversion recovery, gradient-recalled echo (GRE), and magnetic resonance (MR) angiography that included both the circle of Willis and neck vessels at baseline using a 1.5 T or 3.0 T MR scanner. Computed tomography (CT) angiography was also allowed. The follow-up imaging schedule included DWI, GRE, and fluid attenuated inversion recovery at 5 ± 1 days and 14 ± 2 days using the same MR scanner. The images were saved in Digital Imaging and Communications in Medicine (DICOM) format and sent to the independent clinical trials center for review of adequacy and analyses.

Adjudication of images

Two stroke neurologists blinded to clinical and group information reviewed angiographic images and determined the presence of relevant artery stenosis in ischemic lesions on DWI. In cases of discrepancy between the reviewers, the decision was made by a third reviewer (a neuroradiologist). The reviewers also measured the degree of stenosis of the relevant

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artery based on methods used in the North American Symptomatic Carotid Endarterectomy Trial for extracranial arteries and the Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis trial for intracranial arteries[15,16] and categorized stenosis as ≥ 50% or < 50%.

Outcomes

Imaging outcomes were assessed by 2 reviewers blinded to clinical and group information. The primary outcome was occurrence of a new ischemic lesion on DWI or fluid attenuated inversion recovery at 5 or 14 days. The secondary outcomes were the volume change of ischemic lesions and the percent improvement in National Institute of Health Stroke Scale (NIHSS) at 5 days and 14 days. The safety outcome included adverse events, laboratory results, and the presence of any intracranial hemorrhagic transformation on GRE, which in-

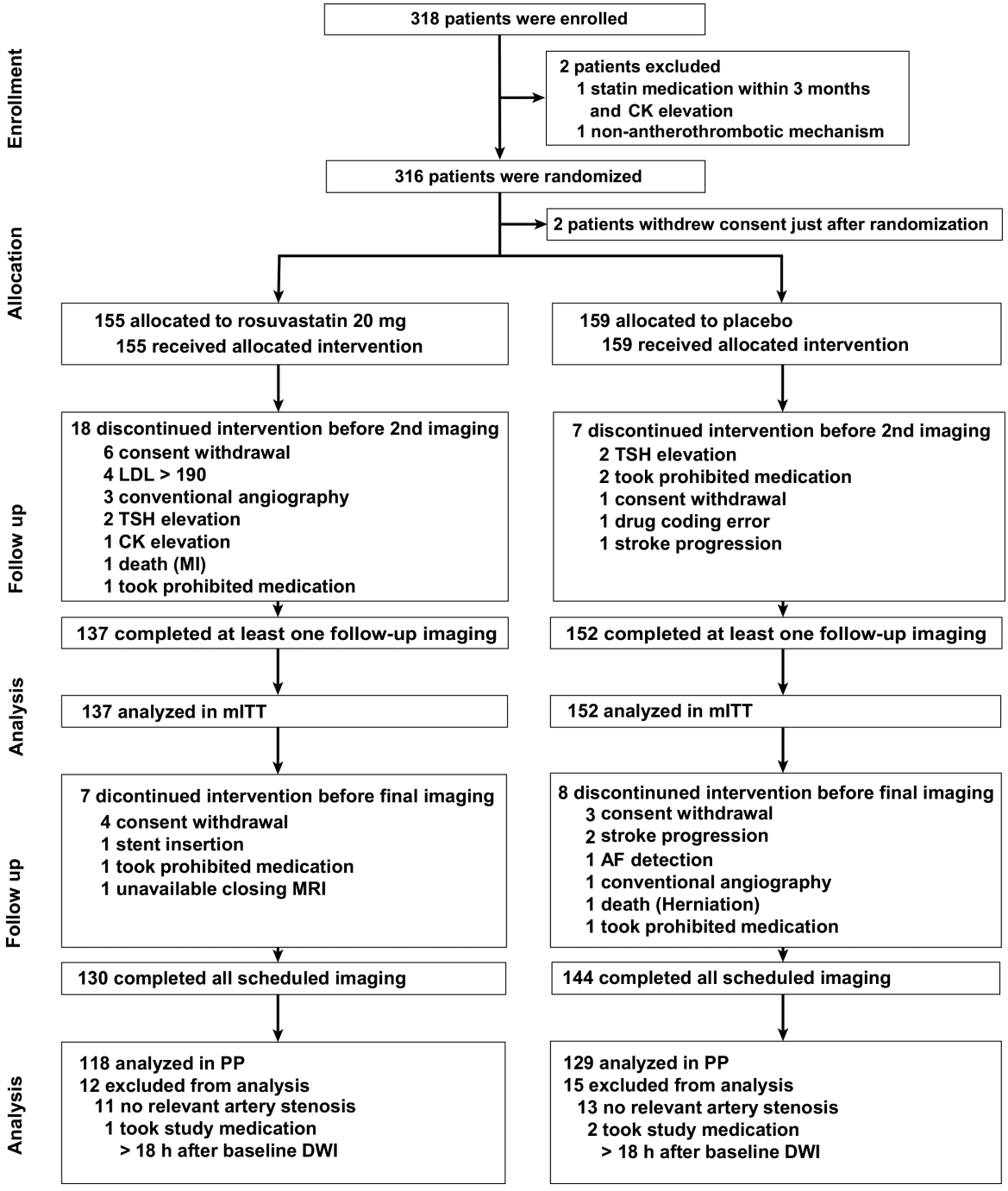

Figure 1. Trial profile. CK, creatine kinase; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone; mITT, modified intention-to-treat population; MRI, magnetic resonance imaging; PP, per-protocol population; DWI, diffusion-weighted imaging.

cluded hemorrhagic infarction (HI) and parenchymal hemorrhage based on European Cooperative Acute Stroke Study definitions.[17] In case of a discrepancy in the presence of new lesions or hemorrhagic transformation, conclusions were reached by consensus. The volume of infarctions was measured on DWI in a semi-automatic manner using Xelis software (Infinitt, Seoul, Korea). The intraclass correlation coefficient between the reviewers for log-transformed volume measurements was 0.99. The percent improvement was defined as ([NIHSS at 5 days or 14 days – NIHSS at baseline]/NIHSS at baseline) × 100.[18]

Details of the conduction of study are provided in Supplemental data.

Statistical analysis

The efficacy outcome was compared based on the modified intention-to-treat and PP population. Safety was assessed in all patients who took at least one dose of study medication. We used the χ^2 test with continuity correction to compare the occurrence of newly developed DWI lesion, the independent sample t test to compare the percent improvement in NIHSS, and the mixed-effect model to compare the change in log-transformed DWI lesion volume between the rosuvastatin and placebo groups. The χ^2 test or Fisher's exact test was performed to compare safety outcomes. Statistical analyses were performed using SAS statistical software, version 9.2 (SAS institute Inc., Cary, NC). Data are presented as number (%) or mean ± standard deviation. Two-sided *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 28 centers in Korea participated in this study, and 25 centers enrolled at least 1 patient. Among 318 patients enrolled, 316 patients met inclusion criteria and were randomized, and 314 took at least one dose of study medication (155 in the rosuvastatin group and 159 in the placebo group). Among them, the primary outcome was assessed in 289 patients (Figure 1). Baseline demographic characteristics were similar between the groups except total cholesterol and low-density lipoprotein cholesterol levels, which were higher in the rosuvastatin group (Table 1, Supplemental Table 1). Characteristics of the patients whose primary outcome was not assessed are provided in as a Supplemental Table 2.

Efficacy outcomes

Efficacy was compared in the modified intention-to-treat

Table 1. Baseline characteristics of the rosuvastatin and placebo groups

	Rosuvastatin (n=155)	Placebo (n=159)	*P* value
Demographics			
Sex (male)	87 (56.1)	101 (63.5)	0.222
Age (year)	65.4±12.3	64.6±11.3	0.564
Body mass index (kg/m^2)	23.8±3.1	24.1±3.0	0.417
Abdominal circumference (cm)	86.2±9.4	87.2±9.3	0.388
Past history			
Hypertension	104 (67.0)	102 (64.1)	0.667
Diabetes mellitus	50 (32.2)	51 (32.0)	1.000
Hypercholesterolemia	24 (15.4)	26 (16.3)	0.955
Smoking	72 (46.4)	67 (42.1)	0.512
Coronary artery occlusive disease	1 (0.6)	4 (2.5)	0.371
Peripheral artery occlusive disease	2 (1.2)	0 (0.0)	0.243
Previous stroke	16 (10.3)	13 (8.1)	0.644
Concomitant medication			
Antihypertensive	67 (43.2)	73 (45.9)	0.715
Antiplatelet			0.677
Aspirin	39 (25.1)	39 (24.5)	
Clopidogrel	9 (5.8)	10 (6.2)	
Aspirin and clopidogrel	88 (56.7)	92 (57.8)	
Aspirin and cilostazol	5 (3.2)	9 (5.6)	
Aspirin, clopidogrel, and cilostazol	14 (9.0)	9 (5.6)	
Anticoagulant	0 (0.0)	1 (0.6)	1.000
Lipid-lowering drug (other than statin)	2 (1.2)	1 (0.6)	0.619
Diabetes mellitus drug	34 (21.9)	35 (22.0)	1.000
Nonsteroidal anti-inflammatory drug	8 (5.1)	13 (8.1)	0.399
Intravenous tissue plasminogen activator	4 (2.5)	5 (3.1)	1.000
Log-transformed baseline diffusion-weighted imaging volume (mm^3)	6.7±1.9	6.8±2.0	0.761
Baseline National Institute of Health Stroke Scale	3 [1-6]	3 [2-5.3]	0.713
Degree of stenosis			0.703
No stenosis	12 (7.7)	12 (8.8)	
<50%	52 (36.4)	56 (38.6)	
50%-99%	47 (32.9)	53 (36.6)	
Occlusion	44 (30.8)	36 (24.8)	
Lab			
White blood cells (×10^3/μL)	7.96±89.2	7.48±84.3	0.929
Neutrophils (×10^3/μL)	6.24±1.6	6.13±1.74	0.616
Hemoglobin (g/dL)	14±1.6	14±1.6	0.823
Hematocrit (%)	41±4.5	41.1±4.4	0.817
Platelet count (×10^3/μL)	246.3±60.3	240.1±65.5	0.296
Blood urea nitrogen (mg/dL)	15.1±5.2	15.5±5.6	0.575
Creatinine (mg/dL)	0.83±0.208	0.865±0.253	0.244
Fasting glucose (mg/dL)	131.2±57.8	136.8±57.1	0.256
Albumin (g/dL)	4.1±0.34	4.14±0.36	0.302
Uric acid (mg/dL)	5.06±1.36	5.06±1.53	0.770
high sensitivity C-reactive protein (mg/dL)	2.517±7.111	2.114±6.794	0.491
Uric acid (mg/dL)	5.06±1.36	5.06±1.53	0.770
high sensitivity C-reactive protein (mg/dL)	2.517±7.111	2.114±6.794	0.491

Values are number (%), mean±standard deviation, or median [interquartile range].

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population (137 patients in the rosuvastatin group and 152 patients in the placebo group). New ischemic lesions on DWI were observed less frequently in the rosuvastatin group (27 patients [19.7%]) than in the placebo group (36 patients [23.6%]), but the difference was not statistically significant (absolute difference 3.9%, relative risk [RR] 0.83, 95% confidence interval [CI] 0.53-1.30, $P=0.500$) (Figure 2A). Infarction volumes on DWI increased at 5 days and then decreased at 14 days in both groups. Infarct volume growth at 5 days (log-transformed volume change, rosuvastatin: 0.2 ± 1.0 mm^3 vs. placebo: 0.3 ± 1.3 mm^3; $P=0.784$) and percent improvement in NIHSS (rosuvastatin vs. placebo: 36.6 ± 56.7 vs. 27.1 ± 90.8 at 5 days, $P=0.282$ and 51.4 ± 51.6 vs. 42.7 ± 91.5 at 14 days, $P=0.315$) were not different.

Safety outcomes

Of 314 patients, 3 in the placebo group (1.9%) and none in the rosuvastatin group demonstrated clinical recurrence of ischemic stroke ($P=0.248$). Progression or clinical recurrence of stroke was reported as a serious adverse event in 7 patients (4.4%) in the placebo group, but in only 1 patient (0.6%) in the rosuvastatin group ($P=0.067$). The frequency of adverse events did not differ between the groups (Table 2).

On GRE, HI was observed in 6 patients at baseline (5/155 [3.2%] in the rosuvastatin and 1/159 [0.65] in the placebo groups). Occurrence of any new intracranial hemorrhagic transformation (HI, parenchymal hemorrhage, or subarachnoid hemorrhage) or aggravation of pre-existing HI1 at baseline (defined as conversion to HI2 or parenchymal hemorrhage) was assessed in 289 patients with available GRE at 5 or 14 days. Any new HI was observed less frequently in the rosuvastatin group (6/137, 4.4%) than in the placebo group (22/152, 14.5%) ($P=0.007$). In the rosuvastatin group, 1 patient developed parenchymal hemorrhage ($P=0.478$), and 1 patient developed focal cortical subarachnoid hemorrhage on GRE ($P=0.478$), both of whom were asymptomatic (Table 3).

Post-hoc subgroup analysis

We compared the occurrence of a new ischemic lesion on DWI in patients with relevant artery stenosis ≥50%. New

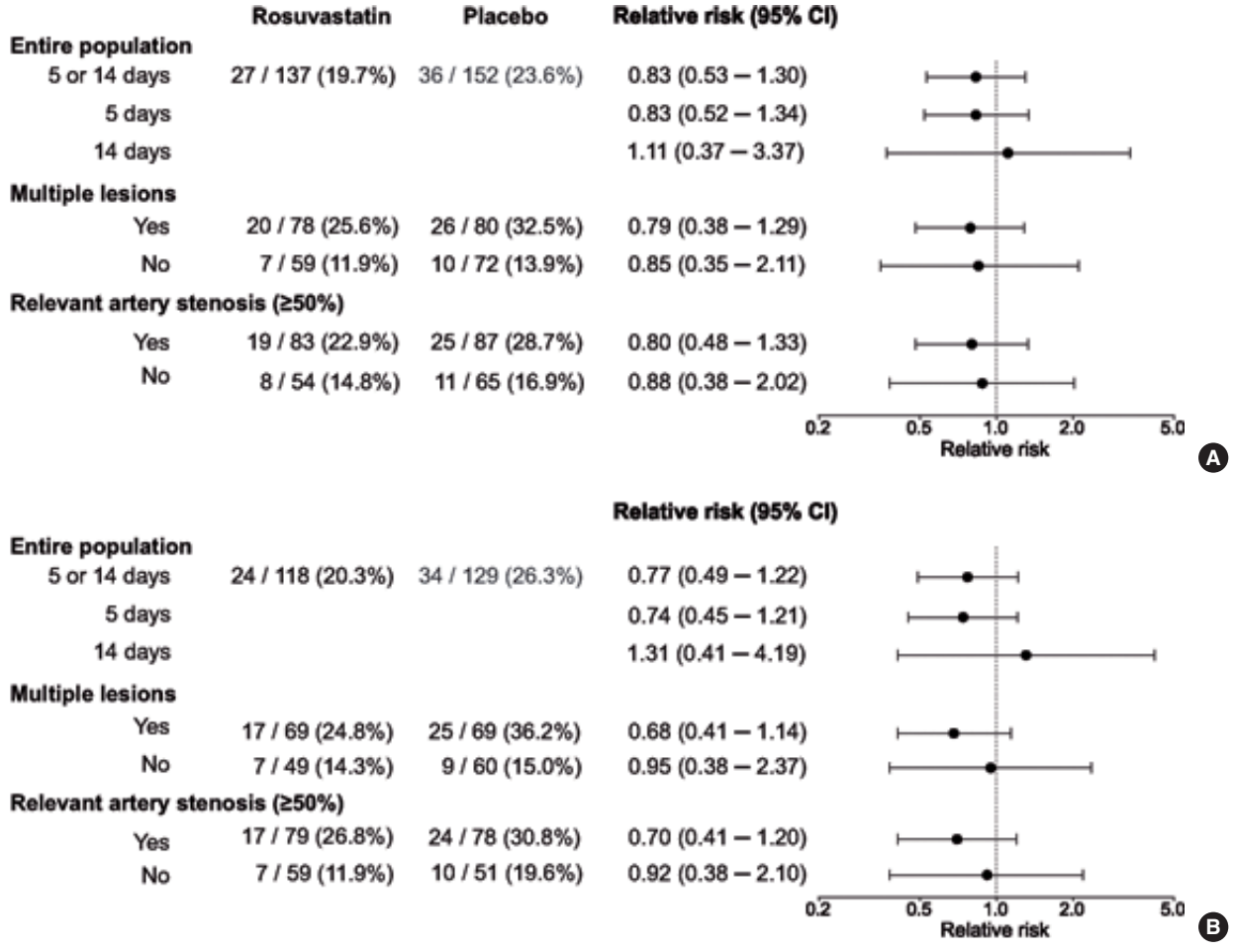

Figure 2. New ischemic lesions on diffusion-weighted imaging in the modified intention-to-treat population (A) and per-protocol population (B).

Table 2. Adverse events

	Rosuvastatin (n=155)	Placebo (n=159)	*P* value
Any AE	88 (56.8)	87 (54.7)	0.800
Any SAE	4 (2.6)	8 (5.0)	0.379
SAE in nervous system	2 (1.3)	8 (5.0)	0.104
Progression or clinical recurrence of stroke*	1 (0.6)	7 (4.4)	0.067
Brain herniation	0 (0.0)	1 (0.6)	1.000
Intracerebral hemorrhage	1 (0.6)	0 (0.0)	0.494
SAE in cardiac system	2 (1.2)	1 (0.6)	0.619
Atrial fibrillation	1 (0.6)	0 (0.0)	0.494
Chest discomfort	0 (0.0)	1 (0.6)	1.000
Myocardial infarction	1 (0.6)	0 (0.0)	0.494
SAE in gastrointestinal system	0 (0.0)	1 (0.6)	1.000
Upper gastrointestinal bleeding	0 (0.0)	1 (0.6)	1.000
Any AE resulting in discontinuation of study drug	5 (2.1)	4 (1.9)	0.539
Any AE with incidence of ≥5%			
Constipation	13 (8.4)	15 (9.4)	0.726
Headache	9 (5.8)	15 (9.4)	0.319
Progression or clinical recurrence of stroke†	11 (7.1)	13 (8.2)	0.883
Coronary artery occlusive disease	16 (10.3)	12 (7.5)	0.506
Hypertension	12 (7.7)	14 (8.8)	0.891
Musculoskeletal AE			
Myalgia	3 (1.9)	4 (2.5)	1.000
Myopathy	0 (0.0)	0 (0.0)	1.000
Rhabdomyolysis	0 (0.0)	0 (0.0)	1.000
Laboratory values			
CK elevation >3×ULN	0 (0.0)	0 (0.0)	1.000
Aspartate aminotransferase or alanine aminotransferase elevation >3×ULN	0 (0.0)	0 (0.0)	1.000
Death	1 (0.4)	1 (0.5)	1.000

Values are number (%).
*Two patients with clinical recurrent stroke were included; †Three patients with clinical recurrent stroke (including two patients reported in SAE) were included.
AE, adverse event; SAE, serious adverse event; CK, creatine kinase; ULN, upper limit of the normal range.

ischemic lesions were found in 19 of 83 patients (22.9%) in the rosuvastatin group and 25 of 87 patients (28.7%) in the placebo group (RR, 0.80; 95% CI, 0.48-1.33; $P=0.387$). Twenty of 78 patients (25.6%) in the rosuvastatin group and 26 of 80 patients (32.5%) in the placebo group with multiple lesions on baseline DWI had new lesions (RR, 0.79; 95% CI, 0.48-1.29; $P=0.346$) (Figure 2A).

PP Population

A total of 118 patients in the rosuvastatin group and 129 patients in the placebo group were included for the PP population (Figure 1). New ischemic lesions were found in 24 patients (20.3%) in the rosuvastatin group and 34 patients (26.3%) in the placebo group (RR 0.77; 95% CI, 0.49-1.22, $P=0.335$)

Table 3. Occurrence of intracranial hemorrhagic transformation on gradient-recalled echo (GRE)

	Rosuvastatin (n=137)	Placebo (n=152)	*P* value
HI1	2 (1.4)	15 (9.9)	0.002
HI2	2* (1.4)	7† (4.6)	0.177
PH1	1 (0.7)	0 (0.0)	0.478
PH2	0 (0.0)	0 (0.0)	
Radiological subarachnoid hemorrhage	1 (0.7)	0 (0.0)	0.478
Any hemorrhagic transformation	6 (4.3)	22 (14.5)	0.007

Values are number (%).
Hemorrhagic transformation was categorized into small petechial hemorrhagic infarction (HI1), confluent petechial HI (HI2), small parenchymal hemorrhage (PH1, <30% of infarct, mild mass effect), and large PH (PH2, >30% of infarct, marked mass effect).[17]
*including 1 patient who had HI-1 on baseline GRE and HI-2 on follow-up GRE.
†including 1 patient who had HI-1 on baseline GRE and HI-2 on follow-up GRE, 4 patients who had HI-1 on 5-day GRE and HI-2 on 14-day GRE.

(Figure 2B). In the subgroup with relevant artery stenosis ≥50%, new ischemic lesions were detected in 17 of 79 patients (21.5%) in the rosuvastatin group and 24 of 78 patients (30.8%) in the placebo group (RR, 0.70; 95% CI 0.41–1.20; $P=0.192$). In the subgroup with multiple lesions, new ischemic lesions were observed in 17 of 69 (24.8%) patients in the rosuvastatin group and 25 of 69 (36.2%) patients in the placebo group (RR 0.68; 95% CI, 0.41–1.14; $P=0.145$) (Figure 2B).

Discussion

This study was inconclusive to prove the hypothesis that rosuvastatin may effectively reduce early recurrence of new ischemic lesions, probably due to insufficient sample size. We could not include a sufficient number of patients because of slow enrollment. Despite insufficient evidence that use of a statin is effective or safe in acute ischemic stroke, investigators were reluctant to administer placebo, since statin use on discharge became a performance measure for primary stroke center certification.[19] However, a non-significant trend for less frequent appearance of new ischemic lesions on DWI or progression or clinical recurrence of stroke was observed in the rosuvastatin group. Thus, our findings support previous observational studies showing a benefit of statins in the acute stage of stroke.[7,8]

Previous randomized trials using statins in acute stroke included small numbers of patients and showed no clinical effect or even worse outcomes after statin treatment.[20-22] Serial MRIs were used to determine outcomes in this study. Defining clinical recurrence of stroke is sometimes difficult during the acute stage because pre-existing symptoms often fluctuate or progress. Many ischemic lesions that are recognized on

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DWI during the acute stage of stroke are clinically silent, but they are direct surrogate markers of recurrence. Ischemic injury progresses during the acute stage of infarctions[23] and may cause growth of infarct volume. By using MRI surrogate markers such as DWI and GRE, subclinical occurrence of ischemic and expansion of ischemic lesions as well as hemorrhagic outcomes might be assessed accurately.

In this study, new ischemic lesions in the placebo group developed less often than expectation which was assumed based on previous reports.[13,14] This might be partly ascribed to the high frequency of use with dual or triple antiplatelet agents (about 75%) in this study population. We hypothesized that the use of statins could reduce the risk of early recurrence of either symptomatic or asymptomatic ischemic lesions and expansion of ischemic lesions in acute stroke. This was because antithrombotic and anti-inflammatory effects of statins have been demonstrated in many experimental studies. Statins also play a beneficial role in stabilizing atherosclerotic plaques.[6,24] In the subgroup analysis of our trial, the RR reduction of new DWI lesion occurrence in the rosuvastatin group was greater in patients who were more likely to have had an atherothrombotic infarction, such as a 20% reduction in patients with relevant artery stenosis ≥ 50% and 21% reduction in those with multiple lesions in the territory of relevant artery stenosis. In the PP population (excluding patients without relevant artery stenosis after assessment), the difference was much greater. Although it is possible that statins are more effective in the prevention of stroke with an atherothrombotic mechanism, this hypothesis was inconclusive in our study.

In this study, rosuvastatin 20 mg was safe in that there were no differences in the development of adverse events. Notably, the occurrence of HI on GRE was remarkably reduced in the rosuvastatin group. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial, atorvastatin 80 mg increased the risk of ICH (hazard ratio, 1.68; 95% CI 1.09-2.59),[2] and in the Heart Protection Study, simvastatin 40 mg was associated with approximately 2-fold increased risk of ICH in patients with prior stroke.[10] However, statin use was not associated with ICH in a large cohort study in patients with recent ischemic stroke,[25] and in a meta-analysis of primary and secondary prevention studies of statins.[26,27] Our findings suggest that statin use in the acute stage of stroke may protect against microvascular (capillary) damage and prevent HI. Matrix metalloproteinase-9 is a key proteinase that mediates HI by disrupting microvascular integrity.[28] Statins reduce expression of matrix metalloproteinase-9 in endothelial cells, astrocytes, and human plasma.[29,30] Thus, the protective effect of statins against occurrence of HI might be in part mediated by inhibiting matrix metalloproteinase-9.

This study has several limitations. First, this study did not include patients with cardioembolic sources and was conducted in one Asian country. Therefore, our results should be interpreted with caution. Second, the median NIHSS of the study population at screening was 3, which suggests that enrolled patients had rather milder stroke. Although we assessed the outcome in the subgroup with significant stenosis of the relevant artery, this might affect the outcome such as the frequency of progression or recurrence of stroke. Furthermore, the primary outcome of this trial was not clinical stroke recurrence, but imaging-based recurrent ischemic lesions. As a result, the data of clinical stroke recurrence was captured based on the investigators' reports of adverse events. Finally, this study was stopped early due to slow enrollment, which resulted in underpowered results.

In conclusion, by using MRI surrogate markers such as DWI and GRE, subclinical occurrence of ischemic as well as hemorrhagic outcomes may be assessed very sensitively and accurately with a relatively smaller sample size. Further studies are required to elucidate the potential benefit of statins in acute stroke patients to conclusively support the routine use of statins.

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SUPPLEMENTARY DATA

Exclusion criteria

The main exclusion criteria were hemorrhagic stroke or history of symptomatic hemorrhagic stroke; presence of high-risk potential cardiac sources of embolism or other determined etiology of stroke based on the Trial of Org 10,172 in Acute Stroke Treatment classification at the time of enrollment; known major hematologic, neoplastic, metabolic, gastrointestinal, or endocrine dysfunction; history of malignancy, except in subjects who had been disease-free >5 years or whose only malignancy has been basal or squamous cell skin carcinoma; life-threatening illness indicating that the subject is not expected to survive for at least 2 years; secondary causes of nephrotic syndrome and/or renal dysfunction (serum creatinine >2.0 mg/dL); uncontrolled hypertension defined as either a resting systolic blood pressure >185 mmHg or resting diastolic blood pressure >110 mmHg despite blood pressure lowering therapy; clinically significant heart disease likely to require coronary artery bypass surgery, cardiac transplantation, surgical repair, and/or valve replacement during the course of the study (within 14 days after enrollment); moderate or greater severity of congestive heart failure (New York Heart Association Class III or IV) or whose most recent determination of left ventricular ejection fraction was <0.35; triglyceride level >500 mg/dL; low-density lipoprotein (LDL) cholesterol level >190 mg/dL; creatine kinase >3 times the upper limit of normal range (ULN); aspartate aminotransferase, alanine aminotransferase, or bilirubin levels >3 times the ULN; thyroid stimulating hormone >1.5 times the ULN; modified Rankin scale score 4-6 before stroke; possible need for conventional angiography, intervention, or carotid artery surgery during the course of the study; known serious hypersensitivity reactions to HMG-CoA reductase inhibitors; and history of myopathy.

Conduct of study

The first patient was enrolled in August 2010, and the study was scheduled to complete enrollment in August 2012. However, in June 2013 the study was stopped early due to slow enrollment. All patient data were recorded on standardized data-collection forms by an investigator or coordinator who was unaware of study-group assignments. All data were subsequently entered into a web-based clinical data management system and managed by an independent data management service (ADM Korea Inc., Seoul, Korea).

Supplemental Table 1. Changes in lipid profiles before and after treatment

	Rosuvastatin (n=155)	Placebo (n=159)	*P* value
Total cholesterol			
Baseline	196.8±37.6	185.9±33.4	0.008
Closing	125.4±25.5	183.2±34.6	<0.001
Change	-69.2±34.2	-3.7±36.5	<0.001
HDL cholesterol			
Baseline	44.5±10.0	44.3±12.3	0.603
Closing	43.3±10.6	41.9±12.4	0.194
Change	-1.5±9.0	-2.2±12.1	0.477
LDL cholesterol			
Baseline	129.8±33.0	119.9±29.7	0.006
Closing	63±22.8	115.1±31.3	<0.001
Change	-63.9±30.4	-5.8±31.3	<0.001
Triglyceride			
Baseline	128.3±76.7	132.6±65.9	0.191
Closing	111.9±51.0	165±100	<0.001
Change	-20.7±73.2	29.2±86.1	<0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Supplemental Table 2. Characteristic of excluded patients from mITT

	Excluded from mITT (n=25)			Excluded from mITT (n=25)		
	Excluded from mITT (n=25)	Included in mITT (n=289)	*P*	Rosuvastatin 20 mg (n=18)	Placebo (n=7)	*P*
Demographics						
Sex (male)	14 (56.0)	174 (60.2)	0.842	9 (50.0)	5 (71.4)	0.407
Age (year)	67.4±11.8	64.8±11.8	0.299	65.7±11.1	71.7±13.4	0.260
Body mass index (kg/m^2)	23.2±3.3	24.0±3.0	0.184	23.4±3.1	22.5±3.7	0.551
Abdominal circumference (cm)	85.3±8.2	86.8±9.4	0.457	85.9±7.7	83.8±10.1	0.612
Past history						
Hypertension	19 (76.0)	187 (64.7)	0.357	13 (72.2)	6 (85.7)	0.627
Diabetes mellitus	12 (48.0)	89 (30.7)	0.123	9 (50.0)	3 (42.8)	1.000
Hypercholesterolemia	6 (24.0)	44 (15.2)	0.256	5 (27.7)	1 (14.2)	0.627
Smoking	17 (68.0)	158 (54.6)	0.281	12 (66.6)	5 (71.4)	1.000
Coronary artery occlusive disease	2 (8.0)	3 (1.0)	0.053	1 (5.5)	1 (14.2)	0.49
Peripheral artery occlusive disease	1 (4.0)	1 (0.3)	0.153	1 (5.5)	0 (0.0)	1.000
Previous stroke	6 (24.0)	23 (7.9)	0.019	4 (22.2)	2 (28.5)	1.000
Concomitant medication						
Antihypertensive	14 (56.0)	126 (43.5)	0.324	9 (50.0)	5 (71.4)	0.407
Antiplatelet			0.913			0.735
Aspirin	5 (20.0)	73 (25.2)		3 (16.6)	2 (28.5)	
Clopidogrel	2 (8.0)	17 (5.8)		1 (5.5)	1 (14.2)	
Aspirin and clopidogrel	16 (64.0)	164 (56.7)		12 (66.6)	4 (57.1)	
Aspirin and cilostazol	1 (4.0)	13 (4.4)		1 (5.5)	0 (0.0)	
Aspirin, clopidogrel, and cilostazol	1 (4.0)	22 (7.6)		1 (5.5)	0 (0.0)	
Anticoagulant	0 (0.0)	1 (0.3)	1.000	0 (0.0)	0 (0.0)	
Lipid-lowering drug (other than statin)	1 (4.0)	2 (0.6)	0.221	1 (5.5)	0 (0.0)	1.000
Diabetes mellitus drug	11 (44.0)	58 (20.0)	0.010	8 (44.4)	3 (42.8)	1.000
NSAID	3 (12.0)	18 (6.2)	0.228	2 (11.1)	1 (14.2)	1.000
Intravenous tPA	1 (4.0)	8 (2.7)	0.531	0 (0.0)	1 (14.2)	0.28
Baseline DWI volume (mm^3)	542.4 [203.5-4115.3]	710 [259.1-2803.6]	0.254	640.2 [223.7-4664.8]	221.5 [27.9-595.9]	0.049
Baseline NIHSS	4 [2-5]	3 [1-6]	0.206	3.5 [2-5]	4 [2-8]	0.544
Lab						
White blood cells (×10^3/μL)	7.898±2.436	7.982±2.325	0.896	8.248±2.74	6.997±1.075	0.296
Neutrophils (×10^3/μL)	60.664±10.556	61.921±17.159	0.242	61.1±10.686	59.543±10.96	0.743
Hemoglobin (g/dL)	13.480±1.720	14.018±1.590	0.098	13.461±1.716	13.529±1.867	0.936
Hematocrit (%)	39.416±4.776	41.158±4.424	0.054	39.656±5.024	38.8±4.369	0.737
Platelet count (×10^3/μL)	238.96±74.077	243.474±62.062	0.630	253.167±81.4	202.429±31.837	0.086
BUN (mg/dL)	16.108±5.354	15.236±5.38	0.387	15.444±4.93	17.814±6.41	0.388
Creatinine (mg/dL)	0.894±0.296	0.844±0.226	0.399	0.807±0.198	1.116±0.399	0.020
Fasting glucose (mg/dL)	137.656±60.42	133.711±57.247	0.728	131.411±47.397	153.714±88.428	0.556
Albumin (g/dL)	4.012±0.461	4.127±0.336	0.200	3.978±0.479	4.1±0.432	0.544
Uric acid (mg/dL)	5.146±1.616	5.052±1.429	0.812	4.831±1.609	5.957±1.427	0.088
hsCRP (mg/dL)	2.843±6.94	2.266±6.955	0.783	2.79±7.423	2.98±6.042	0.956

Values are number (%), mean±standard deviation, or median [interquartile range].
mITT, modified intention-to-treat; NSAID, indicates nonsteroidal anti-inflammatory drug; t-PA, tissue plasminogen activator; DWI, diffusion-weighted imaging; NIHSS, National Institute of Health Stroke Scale; hsCRP, high sensitivity C-reactive protein; BUN, blood urea nitrogen.