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ORIGINAL RESEARCH

Statin Treatment in Patients With Stroke With Low-Density Lipoprotein Cholesterol Levels Below 70 mg/dL

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BACKGROUND: It is unclear whether statin treatment could reduce the risk of early vascular events when baseline low-density lipoprotein cholesterol (LDL-C) levels are already low, at <70 mg/dL, at the time of the index stroke.

METHODS AND RESULTS: This study was an analysis of a prospective, multicenter, nationwide registry of consecutive patients with first-ever acute ischemic stroke with baseline low-density lipoprotein cholesterol levels <70 mg/dL and without statin pretreatment. An inverse probabilities of treatment weights method was applied to control for imbalances in baseline characteristics. The primary outcome was a composite of stroke (either hemorrhagic or ischemic), myocardial infarction, and all-cause death within 3 months. A total of 2850 patients (age, 69.5±13.4 years; men, 63.5%) were analyzed for this study. In-hospital statin treatment was used for 74.2% of patients. The primary composite outcome within 3 months occurred in 21.5% of patients in the nonstatin group and 6.7% of patients in the statin group (P<0.001), but the rates of stroke (2.65% versus 2.33%), hemorrhagic stroke (0.16% versus 0.10%), and myocardial infarction (0.73% versus 0.19%) were not significantly different between the 2 groups. After inverse probability of treatment weighting analysis, the primary composite outcome was significantly reduced in patients with statin therapy (weighted hazard ratio [HR], 0.54 [95% CI, 0.42–0.69]). However, statin treatment did not increase the risk of hemorrhagic stroke (weighted HR, 1.11 [95% CI, 0.10–12.28]).

CONCLUSIONS: Approximately three-quarters of the patients with first-ever ischemic stroke with baseline low-density lipoprotein cholesterol levels <70 mg/dL received in-hospital statin treatment. Statin treatment, compared with no statin treatment, was significantly associated with a reduced risk of the 3-month primary composite outcomes and all-cause death but did not alter the rate of stroke recurrence.

Key Words: acute ischemic stroke ■ early vascular outcomes ■ LDL-C ■ statin

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CLINICAL PERSPECTIVE

What Is New?

- In this study of registry patients in Korea with first-ever ischemic stroke and low-density lipoprotein cholesterol levels <70 mg/dL at admission, approximately three-quarters of the patients received in-hospital statin treatment.
- Early statin treatment was associated with a reduced risk of 3-month composite vascular events and all-cause death but did not alter the risk of stroke recurrence in patients with first-ever ischemic stroke with low-density lipoprotein cholesterol levels <70 mg/dL at admission.

What Are the Clinical Implications?

- Initiation of statin treatment when baseline low-density lipoprotein cholesterol levels are already low, at <70 mg/dL, at the time of index stroke may reduce the risk of early vascular events.

Nonstandard Abbreviations and Acronyms

CRCS-K	Clinical Research Center for Stroke–Korea
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
NIHSS	National Institutes of Health Stroke Scale
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
TOAST	Trial of Org 10 172 in Acute Stroke Treatment
TST	Treat Stroke to Target

Elevated low-density lipoprotein cholesterol (LDL-C) levels increase the risk of stroke and vascular events. Lipid-lowering therapy using statins could reduce the risk of stroke recurrence and vascular events. A meta-analysis of 26 statin trials demonstrated that further reductions in LDL-C levels definitely further reduced the risk of vascular events, which was consistent across baseline LDL-C levels.[1] Most of the trials have enrolled patients with cardiovascular disease, but only a small proportion of patients had acute ischemic stroke and low baseline levels of LDL-C (<70 mg/dL).[1,2] Moreover, conflicting results have been reported in previous studies,[3] which revealed no evidence of the benefit of further LDL-C reduction in patients with baseline LDL-C levels <66 mg/dL or more intensive LDL-C lowering (versus less intensive LDL-C lowering) in patients with baseline LDL-C levels <100 mg/dL.[4,5]

For secondary prevention of ischemic stroke, high-intensity statins, such as atorvastatin 80 mg, reduce the risk of recurrent stroke in patients with acute ischemic stroke with initial LDL-C levels >100 mg/dL.[6,7] A target LDL-C level <70 mg/dL is recommended to reduce the risk of vascular events in acute ischemic stroke.[8] However, an issue that still needs further research is whether statin treatment could reduce the risk of early vascular events when baseline LDL-C levels are already low, at <70 mg/dL, at the time of index stroke. In a recent prospective study, a significant association between lower LDL-C levels and a higher risk of intracerebral hemorrhage was observed when LDL-C levels were <70 mg/dL.[9] These factors may cause physicians to be reluctant to use statins in patients with acute ischemic stroke with low LDL-C levels at baseline.

Therefore, we investigated whether early statin treatment could reduce the risk of early vascular events in patients with first-ever ischemic stroke with baseline LDL-C levels <70 mg/dL.

METHODS

Subjects

This study was a retrospective analysis of a prospective, multicenter, nationwide registry of consecutive patients with acute stroke or transient ischemic attack admitted to 17 academic hospitals in South Korea: the Clinical Research Center for Stroke–Korea (CRCS-K) registry. Detailed methodologic information about the CRCS-K registry has been reported previously.[10,11] We identified patients in the CRCS-K data set of patients with acute ischemic stroke admitted between January 2011 and July 2020. We included patients with acute ischemic stroke (within 7 days of onset), including patients who were lesion positive with symptoms lasting <24 hours and baseline LDL-C levels <70 mg/dL. Patients with stroke of other determined or undetermined cause, those without information on fasting lipid profiles at admission, those with a history of symptomatic atherothrombotic diseases, including stroke, transient ischemic attack, coronary artery diseases, or peripheral artery diseases, and those with prior statin treatment were excluded. A detailed patient selection flowchart is shown in Figure S1.

Ethics Statement

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

Data Collection

Demographic, clinical, imaging, and laboratory data were prospectively collected (Data S1). Ischemic stroke subtypes were classified according to the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) criteria and refined to incorporate additional information from modern imaging studies. A magnetic resonance imaging–based diagnostic algorithm for acute ischemic subtype classification was used to assign the TOAST classifications. Lipid profiles, including LDL-C, non–high-density lipoprotein cholesterol, and triglyceride levels, were obtained during the first fasting period following admission.

Treatment

The patients in the study were treated following the stroke guidelines established by the American Heart Association/American Stroke Association and the Korean Stroke Society.[6,12] The decision to use antiplatelet and anticoagulant medications was made on the basis of appropriate indications. Additionally, statin therapy was started during their hospital stay and continued afterwards.

Outcomes

The primary outcome of the study was a composite of stroke (either hemorrhagic or ischemic), myocardial infarction (MI), and all-cause death within 3 months. Secondary outcomes were the occurrence of the following individual events within 3 months: (1) all types of stroke, (2) MI, (3) all-cause death, and (4) hemorrhagic stroke.

Statistical Analysis

The details of the statistical analysis are described in Data S1. In brief, to minimize confounding and residual selection bias in observational treatment comparisons (statin versus no statin), a propensity score weighting method was applied to control for imbalances in various baseline characteristics across the 2 groups. In this study, a propensity score was applied using binary logistic regression, and the corresponding inverse probabilities of treatment weights were estimated by the inverse of propensity score or inverse of 1—propensity score. Survival curves were constructed using weighted Kaplan–Meier estimates and compared using inverse probability of treatment weighting log-rank tests. For individual secondary outcomes, the probability of outcome occurrence at 3 months was estimated and compared using the cumulative incidence function with death as a competing risk and Gray's test for stroke, MI, and hemorrhagic stroke. In multivariable analysis for each secondary outcome (stroke, MI, and hemorrhagic stroke), the Fine and Gray subdistribution hazard model was used to account for competing death events.[13] In predefined subgroup analyses, we explored differences in outcomes for the following parameters: age (≥75 or <75 years old); sex (male or female); National Institutes of Health Stroke Scale (NIHSS) scores (0–4 or >4); large-artery steno-occlusion; TOAST subtypes; and body mass index (<25 kg/m^2 or ≥25 kg/m^2).

For post hoc analysis, we explored the nonlinear associations of initial LDL-C levels as a continuous variable and the risks of the composite outcome events using Cox proportional hazards models with restricted cubic splines.

An absolute standardized difference of <0.1 for each baseline covariate was assumed as a minimal and acceptable imbalance between the 2 groups. All reported *P* values were 2-sided, and a *P* value <0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

General Characteristics

A total of 2850 patients (mean age, 69.5±13.4; men, 63.5%) met the eligibility criteria and were included in the analysis. The median NIHSS score was 4 (interquartile range, 2–11). The mean LDL-C level on admission was 56.6±11.2 mg/dL, and in-hospital statin treatment was administered to 74.2% of the study subjects. Regarding stroke subtypes, 39.7% of patients had the large-artery atherosclerosis subtype, 19.1% had the small-vessel occlusion subtype, and 41.2% had the cardioembolism subtype. The demographic and clinical characteristics of the 3 groups are shown in Table 1. Compared with the no-statin treatment group, the statin treatment group was more likely to have lower NIHSS scores, the large-artery atherosclerosis subtype, hypertension, diabetes, and dyslipidemia and less likely to have the cardioembolism subtype, atrial fibrillation, large-artery occlusion, and higher lipid profile levels. After inverse probability of treatment weighting, the distributions of the baseline characteristics were fairly well balanced; the absolute standardized differences after inverse probability of treatment weighting were within the margin of 0.1 for all covariates (Table S1).

Outcomes

The mean follow-up duration was 91.3±19.9 days, with 97.5% of patients completing 3 months of follow-up. The primary composite outcome of stroke (ischemic

Table 1. General Characteristics of the Subjects According to Statin Treatment

	Total	No statin	Statin	*P* value
No.	2850	735	2115	
Age, y	69.5±13.4	70.1±13.9	69.3±13.2	0.166
Sex, male, n (%)	1810 (63.5)	448 (61.0)	1362 (64.4)	0.095
Weight, kg	60.8±11.5	59.1±11.7	61.4±11.4	<0.001
Height, cm	162.8±8.9	162.5±8.8	162.9±9.0	0.317
Body mass index	22.9±3.5	22.3±3.7	23.1±3.4	<0.001
Arrival, n (%)				0.001
Within 24 h	1916 (67.2)	529 (72.0)	1387 (65.6)	
>24 h	934 (32.8)	206 (28.0)	728 (34.4)	
Prestroke modified Rankin Scale 0–1, n (%)	2490 (87.4)	630 (85.7)	1860 (87.9)	0.117
Baseline NIHSS score, median (IQR)	4 (2–11)	6 (2–15)	4 (1–9)	<0.001
TOAST, n (%)				<0.001
Large-artery atherosclerosis	1132 (39.7)	229 (31.2)	903 (42.7)	
Small-vessel occlusion	543 (19.1)	106 (14.4)	437 (20.7)	
Cardioembolism	1175 (41.2)	400 (54.4)	775 (36.6)	
Medical history and risk factors, n (%)				
Hypertension	1802 (63.2)	437 (59.5)	1365 (64.5)	0.014
Diabetes	1047 (36.7)	240 (32.7)	807 (38.2)	0.008
Dyslipidemia	276 (9.7)	37 (5.0)	239 (11.3)	<0.001
Smoking				<0.001
Never	1812 (63.6)	481 (65.4)	1331 (62.9)	
Current	658 (23.1)	134 (18.2)	524 (24.8)	
Ex-smoker	261 (9.2)	81 (11.0)	180 (8.5)	
Recent	119 (4.2)	39 (5.3)	80 (3.8)	
Atrial fibrillation	952 (33.4)	325 (44.2)	627 (29.6)	<0.001
Prior antiplatelet use	518 (18.2)	128 (17.4)	390 (18.4)	0.535
Prior anticoagulant use	147 (5.2)	50 (6.8)	97 (4.6)	0.019
Prior antihypertension use	1416 (49.7)	336 (45.7)	1080 (51.1)	0.012
Prior antidiabetic use	832 (29.2)	180 (24.5)	652 (30.8)	0.001
Large artery steno-occlusion, n (%)				<0.001
No stenosis	1238 (43.4)	328 (44.6)	910 (43.0)	
Mild stenosis (<50%)	196 (6.9)	32 (4.4)	164 (7.8)	
Significant stenosis (>50%)	497 (17.4)	81 (11.0)	416 (19.7)	
Occlusion	919 (32.2)	294 (40.0)	625 (29.6)	
Laboratory findings				
White blood cell count	8.2±3.6	8.5±4.4	8.0±3.2	0.007
Platelet count	217.2±84.7	212.0±85.5	218.9±84.4	0.058
Creatinine	1.10±1.17	1.20±1.40	1.07±1.08	0.016
Glucose	147.8±67.6	149.3±75.7	147.3±64.5	0.528
Total cholesterol	119.7±25.0	116.2±23.5	120.9±25.4	<0.001
Triglyceride	104.7±92.8	97.6±84.3	107.2±95.5	0.010
HDL-C	43.2±14.8	41.4±14.7	43.8±14.8	<0.001
Non–HDL-C	76.6±22.5	74.8±20.2	77.2±23.2	0.008
LDL-C	56.6±11.2	54.8±12.5	57.2±10.6	<0.001
Systolic blood pressure	141.0±26.4	138.2±27.0	142.0±26.1	<0.001
Discharge treatment, n (%)				
Antidiabetic	691 (24.2)	110 (15.0)	581 (27.5)	<0.001
Antihypertension	1088 (38.2)	198 (26.9)	890 (42.1)	<0.001

P value by Pearson chi-square test, Student's *t* test, or Wilcoxon rank-sum test as appropriate. HDL-C indicates high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10 172 in Acute Stroke Treatment.

and hemorrhagic), MI, and all-cause death occurred in 292 patients, and its 3-month cumulative event rate was 10.5%. For individual components of the composite, the 3-month cumulative event rates were 2.4% for stroke, 0.3% for MI, and 8.6% for all-cause death. Hemorrhagic stroke occurred in 0.1% of patients.

The primary composite outcome within 3 months occurred in 21.5% of patients in the no-statin group and 6.7% of patients in the statin group (P<0.001) (Table S2). All-cause death occurred significantly more frequently in the no-statin group (20.3%) than in the statin group (4.5%) (P<0.001), but the rates of stroke (2.65% versus 2.33%), hemorrhagic stroke (0.16% versus 0.10%), and MI (0.73% versus 0.19%) were not significantly different between the no-statin group and the statin group. After propensity analysis, weighted event rates at 3 months were similar to those in the unadjusted analysis, with significantly higher event rates of the primary outcome and all-cause death in the no-statin group (Table 2). The cumulative incidence curves are shown in Figure 1.

Statin treatment, compared with no statin treatment, was significantly associated with a reduction in the risk of the 3-month composite of stroke, MI, and all-cause death (crude hazard ratio [HR], 0.27 [95% CI, 0.22–0.35]). After the adjusted and inverse probability of treatment weighting analyses, the composite of stroke, MI, and all-cause death was significantly reduced in patients with statin therapy versus no statin therapy (adjusted HR, 0.42 [95% CI, 0.33–0.54]; and weighted HR, 0.54 [95% CI, 0.42–0.69]). However, statin treatment did not increase the risk of hemorrhagic stroke (crude HR, 0.58 [95% CI, 0.05–6.37]; and weighted HR, 1.11 [95% CI, 0.10–12.28]) (Table 3).

The weighted HR for the 3-month primary outcome is shown in Figure 2 when LDL-C was considered a continuous variable. In the no-statin group, lower LDL-C levels appear to have a higher HR for 3-month primary outcomes, but this was not the case in the statin group.

Subgroup Analysis

There were significant interactions between several subgroups, including NIHSS scores, large-artery steno-occlusion, and TOAST subtypes, and statin groups (Figure 3). In the subgroups with higher NIHSS scores (>4), large-artery occlusion, and the cardioembolism subtype on TOAST, substantial reductions in the primary outcome were observed with statin treatment.

DISCUSSION

In this analysis of >2800 patients with first-ever stroke with low LDL-C levels <70 mg/dL at baseline from a nationwide multicenter registry, approximately three-quarters of the patients received in-hospital statin treatment. Statin treatment, compared with no statin treatment, was significantly associated with a reduction in the risk of the 3-month primary composite outcomes and all-cause death but did not alter the rate of stroke recurrence. The results suggest that further research to address the effectiveness of lipid-lowering treatment would be warranted for patients with stroke with low LDL-C levels at baseline.

Our findings substantially expand the reported experience with statin treatment of patients with low LDL-C levels at baseline. Concordant with a previous study of acute myocardial infarction patients with a low LDL-C level of <70 mg/dL,[14] statin therapy reduced the weighted risk of composite stroke, MI, and all-cause death over 3 months by 45% in patients with acute ischemic stroke. In a meta-analysis of 26 lipid-lowering therapy trials, within the subset of patients starting with a mean LDL-C level of 66 mg/dL, further lowering of LDL-C beyond the lowest current targets was associated with a further reduced cardiovascular risk without offsetting safety risks.[15] The relative risk for major vascular events per 38.7 mg/dL reduction in LDL-C was 0.78 (95% CI, 0.65–0.94). The trials analyzed in the meta-analysis, however, involved nonstatin

Table 2. Event Rates at 3 Months According to Statin Treatment After Inverse Probability of Treatment Weighting

3-mo vascular events	No statin		Statin		P value†
	No. events/No. patients	Event rate at 3 mo, % (95% CI)*	No. events/No. patients	Event rate at 3 mo, % (95% CI)*	
Primary outcome	373/2897	13.13 (10.00–16.27)	213/2850	7.64 (6.46–8.82)	<0.001
Secondary outcome					
Stroke	59/2897	2.09 (1.00–4.36)	67/2850	2.37 (1.31–4.30)	0.692
All-cause death	343/2897	12.13 (9.09–15.17)	153/2850	5.51 (4.50–6.53)	<0.001
Myocardial infarction	11/2897	0.38 (0.09–1.55)	5/2850	0.18 (0.01–2.47)	0.263
Hemorrhagic stroke	2/2897	0.09 (0.00–2.00)	3/2850	0.10 (0.01–1.60)	0.885

Primary outcome: composite of stroke, myocardial infarction, and all-cause death.
*Based on the cumulative incidence function for competing risk data (death).
†P value by Gray's test (before inverse probability of treatment weighting) and the Fine–Gray subdistribution hazard model (after inverse probability of treatment weighting).

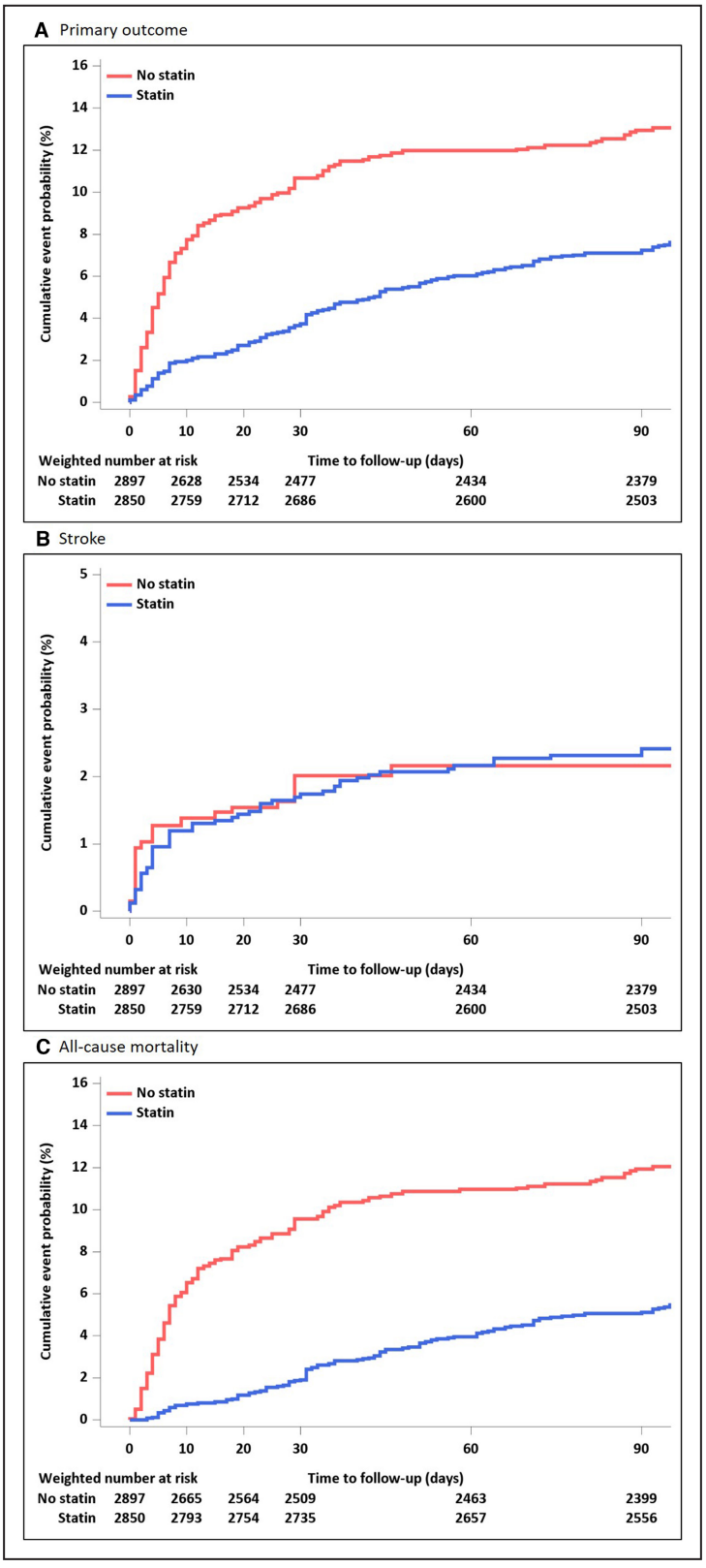

Figure 1. Kaplan–Meier curves for 3-month vascular outcomes.
(**A**) Primary outcome. (**B**) Stroke. (**C**) All-cause death.

Table 3. Associations of Vascular Outcomes at 3 Months

		Crude sHR (95% CI)	*P* value	Adjusted* sHR (95% CI)	*P* value	Weighted sHR† (95% CI)	*P* value
Primary outcome			<0.001		<0.001		<0.001
	No statin	1 (Ref)		1 (Ref)		1 (Ref)	
	Statin	0.27 (0.22–0.35)		0.43 (0.33–0.55)		0.55 (0.42–0.71)	
Secondary outcome							
Stroke			0.736		0.961		0.692
	No statin	1 (Ref)		1 (Ref)		1 (Ref)	
	Statin	0.91 (0.53–1.57)		1.01 (0.58–1.76)		1.14 (0.60–2.15)	
All-cause death			<0.001		<0.001		<0.001
	No statin	1 (Ref)		1 (Ref)		1 (Ref)	
	Statin	0.19 (0.15–0.25)		0.33 (0.25–0.44)		0.42 (0.32–0.56)	
Myocardial infarction			0.055				0.263
	No statin	1 (Ref)				1 (Ref)	
	Statin	0.28 (0.07–1.03)		Not Estimated		0.47 (0.12–1.77)	
Hemorrhagic stroke			0.753				0.885
	No statin	1 (Ref)				1 (Ref)	
	Statin	0.68 (0.06–7.48)		Not Estimated		1.19 (0.11–13.24)	

sHR and *P* value by the Fine–Gray subdistribution hazard model for competing risk data (death). sHR indicates subdistribution hazard ratio.
*Adjusted for variables in Table 1.
†Weighted Cox proportional hazards model or Poisson regression model with robust standard error.

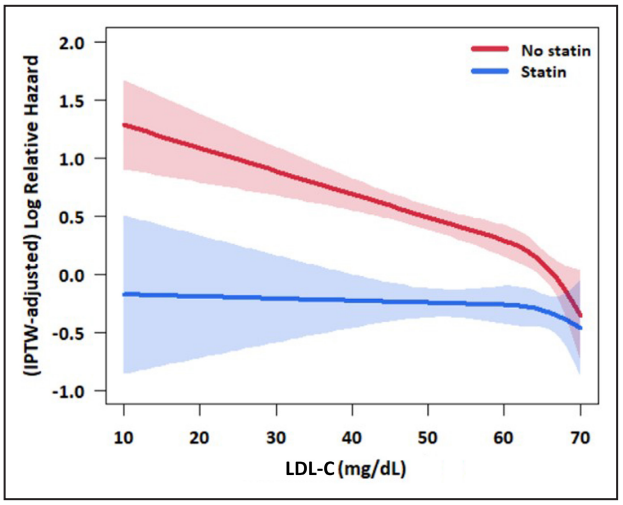

Figure 2. Associations of primary outcome at 3 months with LDL-C levels.
IPTW indicates inverse probability of treatment weighting; and LDL-C, low-density lipoprotein cholesterol.

LDL-C–lowering therapy added to statin therapy. In the TST (Treat Stroke to Target) trial, the overall mortality rate for patients treated with an LDL-C target level of <100 mg/dL versus <70 mg/dL was not significantly different.[8] However, it should be considered that this study population was different from ours. Our results are noteworthy for treating patients with acute ischemic stroke with low LDL-C levels <70 mg/dL with statin therapy.

In our study, the event rates of the primary outcome within 3 months were high because of the real-world data from academic hospitals or tertiary stroke centers, with 21.5% in the no-statin treatment group versus 6.7% in the statin group, but the weighted 3-month risk difference for the primary outcome of 5.5% (13.1% in the no-statin group versus 7.6% in the statin group) might be comparable to the ≈10% to 15% risk differences (for a duration of ≥1 year) observed in previous studies.[16,17] Statin therapy appears to mainly reduce the risk of early death. In particular, significant interactions among stroke subtypes were observed, with a substantial association for the cardioembolism subtype and an intermediate association for the large-artery atherosclerosis subtype but the smallest association for the small-vessel occlusion subtype. Statins seemed to have considerable effectiveness in reducing the risk of early vascular outcomes, mainly death, which might be related to the pleiotropic effect of statins. These might include neuroprotection, improved collateral flows, and anti-inflammatory effects,[18–21] but their effect in reducing the risk of recurrent stroke by reducing atherothrombosis is less substantial in the early periods after acute ischemic stroke. Based on our study, early statin treatment would be more beneficial for early outcomes of patients with cardioembolism and large-artery atherosclerosis but less beneficial for those with small-vessel occlusion. The results support previous studies of patients with cardioembolic stroke, for whom statin therapy was shown to reduce the risk of major vascular events or death.[16,17] Also, a prior Taiwan nationwide cohort study suggested that statin therapy was associated with a reduced risk of death but not associated with a reduced risk of recurrent stroke in patients with stroke and atrial fibrillation.[22] In the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) and TST trials, there were only few patients having atrial fibrillation and therefore statin therapy to reduce recurrent stroke and major cardiovascular events in patients with atrial fibrillation and stroke were not established in randomized controlled trials. There is an ongoing randomized controlled trial investigating the effects of statin in patients with cardioembolism stroke (https://cris.nih.go.kr; KCT0006806). Our findings therefore partly support the current American Heart Association/American Stroke Association stroke performance measure that encourages statin treatment for all patients with ischemic stroke.[23]

Although high-intensity statins and target LDL-C levels <70 mg/dL are strongly recommended among patients with established atherosclerotic cardiovascular diseases,[24] only 39% of patients achieved the goal of LDL-C levels <70 mg/dL in previous studies.[25] One of the potential reasons for this finding, especially for patients with acute ischemic stroke, might be the concerns of hemorrhagic stroke. A previous study found that low LDL-C levels (<70 mg/dL) were associated with a higher risk of intracerebral hemorrhage than LDL-C levels of 70 to 99 m/dL.[9] However, our study found that approximately three-quarters of the patients received statin treatment after index stroke, despite having low LDL-C levels (<70 mg/dL) at baseline, and early statin initiation did not increase the risk of hemorrhagic stroke. Consistent results were also observed in the recent FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study in which further lowering of LDL-C levels to <50 mg/dL by a proprotein convertase subtilisin/kexin type 9 inhibitor did not increase the risk of intracerebral hemorrhage,[15] although further study for longer-term risk would be warranted.

Our study is also noteworthy for analyzing patients with no statin pretreatment and first-ever acute ischemic stroke without a history of atherothrombotic diseases. These results could exclude unexpected influences of prestroke statin therapy on early outcomes in patients with stroke with low LDL-C levels at admission. In previous studies, prestroke statin treatment was linked to a lower initial stroke severity and early favorable outcomes.[26] We unexpectedly found that the lower LDL-C levels at baseline were, the higher the risk of 3-month primary outcomes among patients with no

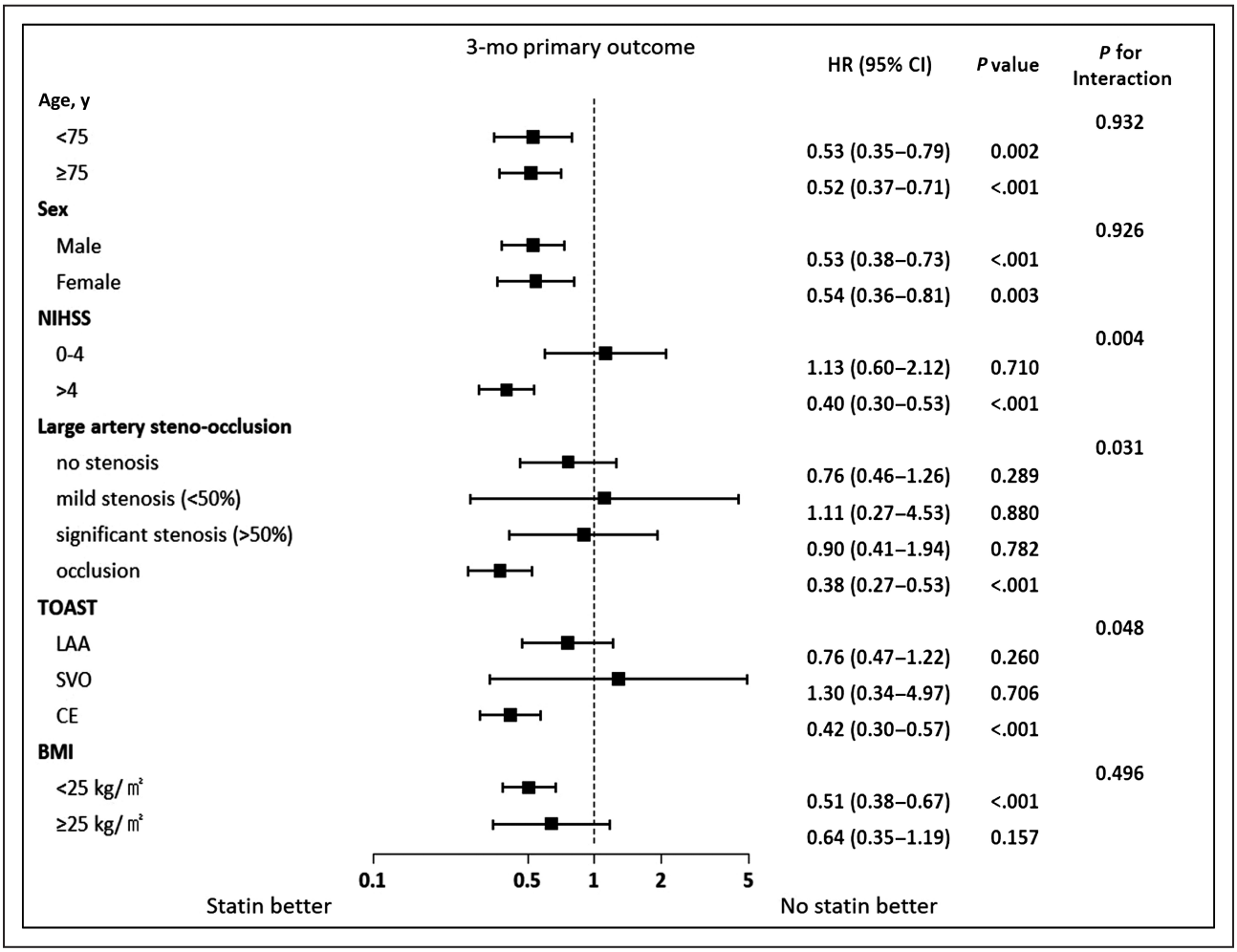

Figure 3. Subgroup analysis.
BMI indicates body mass index; CE, cardioembolism; HR, hazard ratio; LAA, large-artery atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; SVO, small-vessel occlusion; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

statin treatment but not among those with statin treatment. Although the underlying mechanism of the lipid paradox phenomenon is still unclear, statin treatment might offset this negative phenomenon.[27] Thus, further study is warranted.

There were several limitations of the study. First, because of the lack of randomization, there is a potential for bias in that patients treated versus not treated with statins after hospitalization may be systematically different. Several clinical characteristics were present among the no-statin group, indicating a higher baseline risk of death, including lower body mass index, higher NIHSS scores, the cardioembolism stroke subtype, and the presence of atrial fibrillation. This might lead to a higher mortality rate in a potentially more at-risk or frail arm of the study, which is unrelated to the fact that statins were not initiated following stroke. Second, conditioning the study cohort on a population with low LDL-C levels might introduce a specific form of selection bias called collider stratification bias or index event bias.[28] Collider bias refers to the bias that occurs when only patients with a relationship between the cause and outcome variables are included, resulting in biased results. On the other hand, index event bias is a form of selection bias that arises when only patients with specific conditions are included in a study. In our study, we included only stroke patients with admission LDL-C levels <70 mg/dL from a stroke registry. This might distort the relationship between baseline risk factors and the outcome of interest. Third, because of incomplete information on follow-up LDL-C levels and statin intensity, the optimal LDL-C target for these patients could not be investigated. However, as the maximum percentage change occurs 4 to 12 weeks after statin treatment is initiated, LDL-C levels could presumably be <55 mg/dL in these patients treated with statins. These findings might support the endorsement by the European Society of Cardiology for patients with high-risk atherosclerotic cardiovascular disease to continue lowering their cholesterol even after their level

is <70 mg/dL.[24] Additionally, previous studies reported that statin therapy reduced the risk of vascular events regardless of baseline LDL-C levels.[1,2] Fourth, longer-term effects of statin treatment were not investigated. As the study focused on early statin initiation and early vascular outcomes in acute ischemic stroke, the long-term effects of statin treatment should be further investigated in the study population. Instead, we found that early initiation of statins seemed to improve early survival, and more interest in the early effect of statins in acute ischemic stroke is needed. Fifth, the extended duration of this study, spanning from 2011 to 2021, raises the possibility that changes in the standard of stroke care over time may have influenced the prescribing patterns of statins, potentially impacting the results in a significant manner. Sixth, this was a large, prospective, nationwide study, but the patient cohort was restricted to an Asian population; studies involving other racial and ethnic groups are needed to confirm generalizability. This may be important because intracranial atherosclerosis is common in Korean patients, and historical trials emphasize vascular risk factor control for patients with intracranial atherosclerosis.[29,30] Finally, there are inherent limitations of registry-based retrospective studies. Unmeasured confounding could not be excluded despite the rigorous adjustment to mitigate baseline imbalances. A prospective randomized study is warranted to confirm our results.

CONCLUSIONS

In this study, early statin treatment reduced the risk of 3-month composite stroke, MI, and all-cause death but did not alter the risk of stroke recurrence in patients with first-ever ischemic stroke with baseline LDL-C levels <70 mg/dL. Further study to confirm the results would be warranted for patients with acute ischemic stroke.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S2
Figure S1

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