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Renal Function-Dependent Associations of Statins with Outcomes of Ischemic Stroke

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Aim: Chronic kidney disease (CKD) is associated with unfavorable outcomes in patients with ischemic stroke. One major metabolic derangement of CKD is dyslipidemia, which can be managed by statins. This study aimed to investigate whether the association of statins with post-stroke outcomes would be affected by renal function.

Methods: We evaluated the association of statin therapy at discharge with 3-month outcomes according to the estimated glomerular filtration rate (eGFR) of 50,092 patients with acute ischemic stroke from the Taiwan Stroke Registry from August 2006 to May 2016. The outcomes were mortality, functional outcome as modified Rankin Scale (mRS), and recurrent ischemic stroke at 3 months after index stroke.

Results: Statin therapy at discharge was associated with lower risks of mortality (adjusted hazard ratio [aHR], 0.41; 95% confidence interval [CI], 0.34 to 0.50) and unfavorable functional outcomes (mRS 3–5; aHR, 0.80; 95% CI, 0.76 to 0.84) in ischemic stroke patients. After stratification by eGFR, the lower risk of mortality associated with statins was limited to patients with an eGFR above 15 mL/min/1.73 m^2. Using statins at discharge was correlated with a lower risk of unfavorable functional outcomes in patients with an eGFR of 60–89 mL/min/1.73 m^2. Statin therapy in patients with an eGFR of 60–89 mL/min/1.73 m^2 may be associated with a higher risk of recurrent ischemic stroke compared with nonusers (aHR, 1.29; 95% CI, 1.07 to 1.57).

Conclusions: In patients with acute ischemic stroke, the associations of statins with mortality and functional outcomes was dependent on eGFR.

Key words: Brain infarction, Dyslipidemia, Outcome, Renal function, Statins

Introduction

Chronic kidney disease (CKD) and stroke are important global health problems. Over one-third of patients with ischemic stroke concomitantly suffer from CKD[1)], which is independently correlated with

worse outcomes of ischemic stroke. For example, the adjusted odds ratio for 1-year mortality risk after ischemic stroke increased to 3.2 in patients with an estimated glomerular filtration rate (eGFR) of 15–44 mL/min/1.73 m^2 compared to those with an eGFR of ≥ 60 mL/min/1.73 m^2 [2]. Furthermore, CKD and ischemic stroke share several vascular risk factors, and dyslipidemia is the one factor which deserves special attention[3]. Dyslipidemia contributes to the worsening of renal function by promoting glomerular and tubulointerstitial injury[4], and renal dysfunction leads to the deterioration of the lipid profile[5]. This includes elevated low-density lipoprotein (LDL) and triglyceride levels, as well as reduced high-density lipoprotein levels[5, 6]. A high LDL level has been a well-known risk factor for major vascular events[7]. Therefore, control of dyslipidemia is especially important for patients with CKD.

Statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase), the most prevalent therapy for dyslipidemia, have additional benefits such as anti-inflammatory properties and plaque stabilization effects[5]. Regarding the influence of statins on stroke risk, statins are beneficial for secondary prevention of ischemic stroke[8-10], while the findings are inconsistent for primary prevention of stroke in CKD patients[11, 12]. Evidence is lacking about the effect of statins on secondary prevention of stroke in patients with comorbid CKD and ischemic stroke. Regarding the effect of statins on patient outcomes, the dialysis stage strongly influences the efficacy of statins on mortality reduction in CKD patients without stroke[12-14]. Furthermore, there was only one study focusing on the association of statins according to renal function in patients with acute ischemic stroke[15]. This study demonstrated that statin use was associated with a lower mortality risk in all eGFR groups, including eGFR <60 mL/min/1.73 m^2 [15]. It remains unclear whether the effect of statins on mortality risk was homogeneous across the various levels of eGFR in stroke patients with CKD. This study aimed to clarify whether the association of statin therapy with the outcomes of ischemic stroke would be affected by eGFR levels.

Patients and Methods

Patient Population and Data Collection

The data were retrieved from the Taiwan Stroke Registry (TSR), which has prospectively enrolled acute stroke patients in Taiwan from August 2006 to May 2016. The TSR is the first nationwide stroke database in Taiwan, including 60 hospitals (Appendix). The Research Ethics Committee of each hospital approved the TSR individually, and all participants signed informed consent. Details of this registry have been described previously[16]. This study included patients with acute ischemic stroke without loss to follow up (n =72,784), and serially excluded in-hospital mortality (n=3,236), those with missing data (creatinine, sex, or body weight; n=19,370), and age <18 years (n=86).

The retrieved data of this study included risk factors of ischemic stroke, eGFR on admission by CKD-Epidemiological Collaboration (CKD-EPI) equation[17], admission score on the National Institutes of Health Stroke Scale (NIHSS), stroke subtypes classified by the criteria of The Trial of Org 10,172 in Acute Stroke Treatment (TOAST)[18], and statin therapy used before admission and at discharge. The risk factors included age, sex, body mass index, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, atrial fibrillation, ischemic heart disease, previous ischemic stroke, previous intracerebral hemorrhage, peripheral artery disease, cancer, smoking, and alcohol consumption. Hypercholesterolemia was defined as serum level of total cholesterol on admission ≥ 200 mg/dL, LDL ≥ 130 mg/dL, or previous diagnosis of hypercholesterolemia under treatment with lipid-lowering agents. The last criterion of hypercholesterolemia was used because treated hypercholesterolemic patients might not have high cholesterol levels upon admission. Hypertriglyceridemia was defined as serum level of triglyceride ≥ 150 mg/dL or previous diagnosis of hypertriglyceridemia under treatment with lipid-lowering agents. One patient could have both diagnoses of hypercholesterolemia and hypertriglyceridemia in this study if he/she met both criteria of hypercholesterolemia and hypertriglyceridemia. Other treatments that may affect stroke outcome were also recorded, including intravenous thrombolysis, antiplatelet, and anticoagulant therapies. The outcomes included mortality, a functional outcome as modified Rankin Scale (mRS), and recurrent stroke within 3 months after the index stroke, which were obtained by telephone follow up and review of medical records. An unfavorable outcome was defined as mRS 3–5.

Statistical Analysis

Patients were divided into five groups according

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to their eGFR levels, which were ≥ 90, 60–89, 30–59, 15–29, and <15 mL/min/1.73 m^2, and those with an eGFR <15 mL/min/1.73 m^2 were further divided into the non-dialysis and dialysis groups. The baseline characteristics of the six groups were compared with the chi-square test for categorical variables or one-way ANOVA for continuous variables. These characteristics in statin users and nonusers were compared with the chi-square test for categorical variables or the Student's *t*-test for continuous variables, showing separately before admission and at discharge. We compared the cumulative incidence of mortality in statin users at discharge with that in nonusers according to their eGFR levels by Kaplan–Meier plots and a log-rank test. We analyzed determinants including statin therapy at discharge for post-stroke mortality or unfavorable functional outcomes (mRS 3–5) by a Cox proportional hazard model with adjustment of the covariates which had significant differences among the eGFR groups, including age, gender, admission NIHSS, hypertension, diabetes, previous cerebral infarction, previous cerebral hemorrhage, ischemic heart disease, ischemic stroke subtype, atrial fibrillation, alcohol consumption, peripheral arterial disease, cancer, statin/antiplatelet/anticoagulant use at discharge, and intravenous thrombolysis. Furthermore, we used a Cox proportional hazard model to evaluate the association of statin therapy at discharge with mortality and unfavorable outcomes stratified with eGFR to clarify whether this association was dependent on eGFR levels. Last, we analyzed the risk of recurrent ischemic stroke within 3 months after the index stroke in statin users and nonusers at discharge according to their eGFR levels by a Cox model. These analyses were performed with the SAS software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics of the 50,092 patients according to their eGFR levels are shown in **Table 1**. The numbers of patients receiving statins at discharge were much larger than those before admission in all eGFR groups. In addition, some patients with poor eGFR levels did not receive statins at discharge even when diagnosed with hypercholesterolemia or hypertriglyceridemia (for hypercholesterolemia: 3.3% and 4.9% in patients with an eGFR <15 mL/min/1.73 m^2 at non-dialysis and dialysis stages, respectively; for hypertriglyceridemia: 10.4% and 12.8% in patients with an eGFR <15 mL/min/1.73 m^2 at non-dialysis and dialysis stages, respectively).

Many baseline characteristics were statistically different between the statin users and nonusers both before admission and at discharge (**Table 2**). Patients using statins at discharge were younger, with higher body mass index, and more likely to have comorbid hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, and peripheral artery disease than nonusers. Patients not using statins had a higher NIHSS, higher percentages of atrial fibrillation, and previous ischemic stroke or intracerebral hemorrhage. The percentages of patients who were classified with large artery atherosclerosis and small vessel disease were higher in statin users than in nonusers, and the percentage of cardioembolism was lower in statin users. Higher percentages of patients received antiplatelet or intravenous thrombolysis in those using statins, while higher percentage of patients in the nonuser group took anticoagulants. Higher percentages in the statin user group had better eGFR levels than in the nonuser group.

Determinants for mortality and unfavorable functional outcomes after ischemic stroke are shown in **Table 3**. Using statins at discharge was associated with a lower risk of mortality (adjusted HR [aHR] = 0.41, 95% confidence interval [CI] = 0.34 to 0.50) and unfavorable functional outcomes (aHR = 0.80, 95% CI = 0.76 to 0.84) after ischemic stroke. A low eGFR level was a strong determinant for post-stroke mortality and unfavorable outcomes with a dose-response relationship. Patients with hypercholesterolemia had a reduced risk of mortality and unfavorable outcomes, while patients with hypertriglyceridemia had an increased risk of unfavorable outcomes.

In each eGFR group, patients using statins at discharge had a lower cumulative mortality rate compared with those without statin treatment (all $p <$ 0.001 by log-rank test; **Fig. 1**). After being stratified by eGFR in **Table 4**, the lower risk of post-stroke mortality in statin users at discharge was only observed in patients with an eGFR of ≥ 15 mL/min/1.73 m^2, while no difference was observed between statin users and nonusers in the groups with eGFR of <15 mL/min/1.73 m^2. Patients using statins at discharge had a lower risk of unfavorable outcomes after stroke only in the patients with an eGFR of 60–89 mL/min/1.73 m^2, while there was no difference between statin users and nonusers in the other eGFR groups.

The association of statin therapy at discharge with the risk of recurrent ischemic stroke according to various eGFR levels is shown in **Table 5**. Using statins at discharge in the group with an eGFR of 60–89 mL/min/1.73 m^2 seemed to be associated with a higher risk of recurrent ischemic stroke (aHR = 1.29, 95% CI = 1.07 to 1.57). In the groups with other levels of eGFR, using statins at discharge had no significant correlation with the occurrence of recurrent ischemic

Table 1. Baseline Characteristics Classified by Estimated Glomerular Filtration Rate in Patients with Acute Ischemic Stroke

	eGFR (mL/min/1.73 m^2)						*p*-value
	≥ 90 (*n* = 9,877)	60–89 (*n* = 21,162)	30–59 (*n* = 14,722)	15–29 (*n* = 2,295)	< 15 non-dialysis (*n* = 806)	Dialysis (*n* = 1,230)	
Age, years	56.7 ± 11.2	68.7 ± 11.7	74.3 ± 10.6	75.4 ± 12.8	75.5 ± 38.7	68.3 ± 11.7	< 0.001
Male sex	6119 (62.0)	13247 (62.6)	8587 (58.3)	1189 (51.8)	418 (51.9)	667 (54.2)	< 0.001
Body mass index (median, IQR), kg/m^2	24.7 (22.3-27.3)	24.4 (22.1-27.0)	24.3 (21.9-26.9)	24.1 (21.8-26.9)	23.8 (21.6-26.8)	23.3 (21.0-25.8)	0.120
Admission NIHSS (median, IQR)	4 (2-7)	4 (2-6)	5 (2-10)	5 (2-12)	5 (2-11)	5 (2-10)	< 0.001
Hypertension	6721 (68.1)	16379 (77.4)	12426 (84.4)	2034 (88.6)	682 (84.6)	1093 (88.9)	< 0.001
Diabetes mellitus	3895 (39.4)	7810 (36.9)	6382 (43.4)	1325 (57.7)	473 (58.7)	761 (61.9)	< 0.001
Hypercholesterolemia	2427 (24.6)	4611 (21.8)	3511 (23.9)	711 (31.0)	245 (30.4)	359 (29.2)	< 0.001
Hypertriglyceridemia	4178 (42.3)	8416 (39.8)	5846 (39.7)	973 (42.4)	302 (37.5)	456 (37.1)	< 0.001
Ischemic heart disease	669 (6.8)	2376 (11.2)	2316 (15.7)	520 (22.7)	137 (17.0)	326 (26.5)	< 0.001
Atrial fibrillation	407 (4.1)	1504 (7.1)	1307 (8.9)	197 (8.6)	39 (4.8)	134 (10.9)	< 0.001
Smoking	41 (0.4)	110 (0.5)	80 (0.5)	16 (0.7)	3 (0.4)	12 (1.0)	0.400
Alcohol consumption	1803 (18.3)	2916 (13.8)	1507 (10.2)	171 (7.5)	70 (8.7)	85 (6.9)	< 0.001
Previous ischemic stroke	1428 (14.5)	4558 (21.5)	4032 (27.4)	744 (32.4)	245 (30.4)	323 (26.3)	< 0.001
Previous intracerebral hemorrhage	213 (2.2)	515 (2.4)	349 (2.4)	52 (2.3)	19 (2.4)	38 (3.1)	< 0.001
Peripheral artery disease	181 (1.8)	364 (1.7)	330 (2.2)	78 (3.4)	27 (3.4)	63 (5.1)	< 0.001
Cancer	311 (3.2)	631 (3.0)	450 (3.1)	90 (3.9)	27 (3.4)	60 (5.1)	< 0.001
Ischemic stroke subtype							< 0.001
Large artery atherosclerosis	2771 (28.1)	5907 (27.9)	4178 (28.4)	699 (30.5)	233 (28.9)	288 (23.4)	
Small vessel occlusion	4515 (45.7)	8984 (42.5)	5384 (36.6)	767 (33.4)	316 (39.2)	436 (35.5)	
Cardioembolism	654 (6.6)	2440 (11.5)	2257 (15.3)	328 (14.3)	89 (11.0)	163 (13.3)	
Other specific etiologies	383 (3.9)	253 (1.2)	138 (0.9)	21 (0.9)	8 (1.0)	17 (1.4)	
Undetermined etiology	1554 (15.7)	3578 (16.9)	2765 (18.8)	480 (20.9)	160 (19.9)	326 (26.5)	
Medications before admission							
Statins	593 (6.0)	1400 (6.6)	1284 (8.7)	274 (11.9)	85 (10.6)	116 (9.4)	< 0.001
Antiplatelet	1288 (13.0)	3938 (18.6)	3442 (23.4)	618 (26.9)	180 (22.3)	361 (29.4)	< 0.001
Anticoagulant	216 (2.2)	549 (2.6)	421 (2.9)	63 (2.8)	17 (2.1)	21 (1.7)	0.005
Medications at discharge							
Statins	3736 (37.8)	7074 (33.4)	4534 (30.8)	688 (30.0)	218 (27.1)	299 (24.3)	< 0.001
Antiplatelet	8286 (83.9)	17290 (81.7)	11541 (78.4)	1761 (76.7)	623 (77.3)	919 (74.7)	< 0.001
Anticoagulant	810 (8.2)	1893 (8.9)	1405 (9.5)	178 (7.8)	49 (6.1)	78 (6.3)	< 0.001
Intravenous thrombolysis	529 (5.4)	985 (4.7)	635 (4.3)	66 (2.9)	9 (1.1)	28 (2.3)	< 0.001

Values are number (percentage), mean ± standard deviation, median (interquartile range, IQR).
eGFR, estimated glomerular filtration rate; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale

stroke.

Discussion

This study investigated the association of statin therapy at discharge according to eGFR levels on the outcomes of patients at 3 months after ischemic stroke by analyzing the data from a nationwide stroke registry. In patients with an eGFR of ≥ 15 mL/min/1.73 m^2, statin users at discharge was significantly associated with a lower risk of post-stroke mortality compared with nonusers. Using statins at discharge in patients with an eGFR of 60–89 mL/min/1.73 m^2 was associated with a lower risk of unfavorable outcomes. In patients with an eGFR of < 15 mL/min/1.73 m^2, regardless of the dialysis stage, using statins at discharge was not correlated with mortality or functional outcomes. Although using statins at discharge might be associated with a higher risk of recurrent ischemic stroke in patients with an eGFR of 60–89 mL/min/1.73 m^2, using statins at discharge continued to be associated with a lower risk of mortality and unfavorable outcomes in this eGFR group.

This study revealed that the correlation of statin

Table 2. Comparisons of Baseline Characteristics Between Statin Users and Nonusers Separately Before Admission and at Discharge

Variables	Before Admission			At Discharge		
	Statin Use *N*=3,752	No Statin Use *N*=46,340	*p*-value	Statin Use *N*=16,549	No Statin Use *N*=33,543	*p*-value
Age, mean (SD)	68.8 (11.4)	68.3 (14.0)	0.03	66.5 (14.1)	69.3 (13.6)	<0.001
Age, median (IQR)	69.3 (60.5-77.1)	69.6 (59.3-78.0)	0.60	66.9 (57.9-75.3)	70.9 (60.4-79.0)	<0.001
Male	2111 (56.3)	28116 (60.7)	<0.001	9693 (58.6)	20534 (61.2)	<0.001
Body mass index (median, IQR), kg/m^2	25.0 (22.8-27.5)	24.3 (22.0-26.9)	<0.001	25.0 (22.7-27.5)	24.1 (21.7-26.6)	<0.001
Admission NIHSS (median, IQR)	4 (2-8)	4 (2-8)	0.67	4 (2-7)	4 (2-9)	<0.001
Hypertension	3333 (88.8)	36002 (77.7)	<0.001	13410 (81.0)	25925 (77.3)	<0.001
Diabetes mellitus	2307 (61.5)	18339 (39.6)	<0.001	7563 (45.7)	13083 (39.0)	<0.001
Hypercholesterolemia	1324 (35.3)	10540 (22.7)	<0.001	5435 (32.8)	6429 (19.2)	<0.001
Hypertriglyceridemia	2587 (69.0)	17584 (38.0)	<0.001	12186 (73.6)	7985 (23.8)	<0.001
Ischemic heart disease	1022 (27.2)	5322 (11.5)	<0.001	2089 (12.6)	4255 (12.7)	0.84
Atrial fibrillation	381 (10.2)	3207 (6.9)	<0.001	1041 (6.3)	2547 (7.6)	<0.001
Smoking	16 (0.4)	246 (0.5)	0.39	81 (0.5)	181 (0.5)	0.46
Alcohol consumption	337 (9.0)	6215 (13.4)	<0.001	2049 (12.4)	4503 (13.4)	0.001
Previous ischemic stroke	1263 (33.7)	10067 (21.7)	<0.001	3403 (20.6)	7927 (23.6)	<0.001
Previous intracerebral hemorrhage	92 (2.5)	1094 (2.4)	0.72	342 (2.1)	844 (2.5)	0.002
Peripheral artery disease	142 (3.8)	901 (1.9)	<0.001	420 (2.5)	623 (1.9)	<0.001
Cancer	133 (3.6)	1436 (3.1)	0.16	468 (2.8)	1101 (3.3)	0.02
Ischemic stroke subtype			0.001			<0.001
Large artery atherosclerosis	1095 (29.2)	12981 (28.0)		5005 (30.2)	9071 (27.0)	
Small vessel occlusion	1460 (38.9)	18942 (40.9)		7615 (46.0)	12787 (38.1)	
Cardioembolism	34 (0.9)	786 (1.7)		155 (0.9)	665 (2.0)	
Other specific etiologies	489 (13.0)	5442 (11.7)		1411 (8.5)	4520 (13.5)	
Undetermined etiology	674 (18.0)	8189 (17.7)		2363 (14.3)	6500 (19.4)	
eGFR			<0.001			<0.001
≥ 90	593 (15.8)	9284 (20.0)		3736 (22.6)	6141 (18.3)	
60–89	1400 (37.3)	19762 (42.7)		7074 (42.8)	14088 (42.0)	
30–59	1284 (34.2)	13438 (29.0)		4534 (27.4)	10188 (30.4)	
15-29	274 (7.3)	2021 (4.4)		688 (4.2)	1607 (4.8)	
<15 non-dialysis	85 (2.3)	721 (1.6)		218 (1.3)	588 (1.8)	
Dialysis	116 (3.1)	1114 (2.4)		299 (1.8)	931 (2.8)	
Antiplatelet	1874 (50.0)	7953 (17.2)	<0.001	14382 (86.9)	26038 (77.6)	<0.001
Anticoagulant	167 (4.5)	1120 (2.4)	<0.001	1255 (7.6)	3158 (9.4)	<0.001
Intravenous thrombolysis	-	-		830 (5.0)	1422 (4.2)	<0.001

Values are number (percentage), mean ± standard deviation, median (interquartile range, IQR).
eGFR, estimated glomerular filtration rate; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale

therapy at discharge with a lower mortality risk after stroke was significant only in patients with an eGFR of ≥ 15 mL/min/1.73 m^2, while using statins at discharge had no significant association with mortality risk for those with eGFR of <15 mL/min/1.73 m^2. The difference in mortality risk of statin therapy in non-stroke CKD patients has been illustrated to be dependent on the dialysis stage[12-14, 19]. Statins therapy was significantly associated with lower risks of all-cause mortality and cardiovascular mortality in CKD patients who did not receive dialysis[14], while statins had no significant correlation with all-cause mortality in dialysis patients[12, 13]. Regarding statin therapy in ischemic stroke patients with CKD, the only one previous report demonstrated that statins were significantly associated with a lower risk of mortality after ischemic stroke even in patients with an eGFR of < 60 mL/min/1.73 m^2 in the Chinese population[15]. The present study similarly focused on ischemic stroke patients and revealed that statins had no significant correlation with mortality risk in patients with an eGFR of <15 mL/min/1.73 m^2. The discrepancy

Table 3. Determinants for Mortality and Unfavorable Functional Outcome at 3 Months After Ischemic Stroke

	Mortality		Unfavorable outcome	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
eGFR (mL/min/1.73 m^2)				
≥ 90	1.00	1.00	1.00	1.00
60–89	1.60 (1.29, 1.98)	1.33 (1.06, 1.67)	1.48 (1.40, 1.58)	1.03 (0.97, 1.11)
30–59	2.71 (2.19, 3.35)	1.81 (1.43, 2.28)	2.01 (1.89, 2.15)	1.13 (1.05, 1.21)
15–29	5.51 (4.26, 7.13)	3.44 (2.59, 4.57)	2.49 (2.25, 2.75)	1.25 (1.12, 1.40)
<15 non-dialysis	5.68 (4.01, 8.03)	3.25 (2.19, 4.83)	1.99 (1.69, 2.34)	1.06 (0.89, 1.27)
Dialysis	6.49 (4.84, 8.69)	4.09 (2.96, 5.65)	2.08 (1.82, 2.38)	1.32 (1.14, 1.52)
Hypercholesterolemia	0.48 (0.41, 0.57)	0.66 (0.55, 0.80)	0.81 (0.77, 0.85)	0.87 (0.82, 0.92)
Hypertriglyceridemia	0.54 (0.47, 0.61)	0.98 (0.84, 1.13)	1.02 (0.98, 1.06)	1.27 (1.21, 1.34)
Statin use at discharge	0.27 (0.23, 0.33)	0.41 (0.34, 0.50)	0.77 (0.73, 0.80)	0.80 (0.76, 0.84)
Age	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.04 (1.03, 1.04)	1.03 (1.03, 1.03)
Admission NIHSS	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)
Hypertension	0.80 (0.70, 0.91)	0.77 (0.66, 0.89)	1.26 (1.19, 1.32)	1.07 (1.01, 1.13)
Diabetes	0.97 (0.86, 1.09)	1.05 (0.93, 1.20)	1.24 (1.19, 1.29)	1.26 (1.20, 1.32)
Ischemic stroke subtype				
Large artery atherosclerosis	0.50 (0.43, 0.59)	0.63 (0.54, 0.74)	0.92 (0.87, 0.98)	1.01 (0.95, 1.07)
Small vessel occlusion	0.16 (0.13, 0.19)	0.25 (0.22, 0.31)	0.48 (0.46, 0.51)	0.62 (0.58, 0.66)
Cardioembolism	2.06 (1.60, 2.67)	2.00 (1.48, 2.69)	0.54 (0.45, 0.65)	0.92 (0.76, 1.13)
Other specific etiologies	1.06 (0.90, 1.23)	0.77 (0.65, 0.92)	1.01 (0.94, 1.09)	0.89 (0.83, 0.96)
Undetermined etiology	1.00	1.00	1.00	1.00
Alcohol consumption	0.65 (0.53, 0.79)	0.96 (0.78, 1.20)	0.69 (0.65, 0.74)	0.90 (0.84, 0.97)
Cancer	3.39 (2.74, 4.19)	1.89 (1.50, 2.38)	0.94 (0.83, 1.06)	0.74 (0.65, 0.84)
Recurrent ischemic stroke	2.38 (1.87, 3.04)	2.52 (1.93, 3.27)	0.58 (0.22, 1.52)	1.44 (1.28, 1.62)

HR, hazard ratio; CI, confidence intervals; eGFR, estimated glomerular filtration rate; NIHSS, National Institute of Health Stroke Scale.
The adjusted variables included age, gender, admission NIHSS, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, previous cerebral infarction, previous cerebral hemorrhage, ischemic heart disease, ischemic stroke subtype, atrial fibrillation, peripheral arterial disease, alcohol consumption, cancer, statin use at discharge, antiplatelet/anticoagulant use at discharge, intravenous thrombolysis, and recurrent ischemic stroke within 3 months after the index stroke.

between these two studies might arise from different methods for patient grouping by eGFR, and that gathering a wide-range of eGFR patients as one group might mask the findings within a narrow-range of eGFR. Besides, patients with an eGFR of <15 mL/min/1.73 m^2 were not necessarily receiving dialysis, thus this study presented a numeral cutoff point of eGFR in addition to dialysis stage as a determinant for the association of statins on stroke outcomes. Since the mortality of CKD patients is largely attributable to cardiovascular death[20], the renal function-dependent association of statins on mortality risk might indicate that the cumulative influence of severe CKD on cardiovascular atherosclerosis may not be reversible by statins added at this late stage.

In non-stroke patients with CKD stages 1 to 3, a meta-analysis study found that the correlation of statins with primary prevention of stroke was non-significant[21]. However, using statins was associated with an increased risk of stroke occurrence in non-stroke dialysis patients[12, 13], and the risk of stroke was higher with LDL cholesterol lowering, resulting in a U-shape relationship[22]. Evidence is lacking regarding the effect of statins on secondary prevention of stroke in CKD patients with ischemic stroke. The present study revealed that using statins at discharge in stroke patients with an eGFR of 60–89 mL/min/1.73 m^2 seemed to be associated with an increased risk of stroke recurrence. As many baseline characteristics were different between statin users and nonusers, the results may be affected by the significant selection bias despite the multivariate regression analysis. Further well-designed studies on this topic are needed to verify this finding.

This study showed the association of statin therapy at discharge with mortality and functional out-

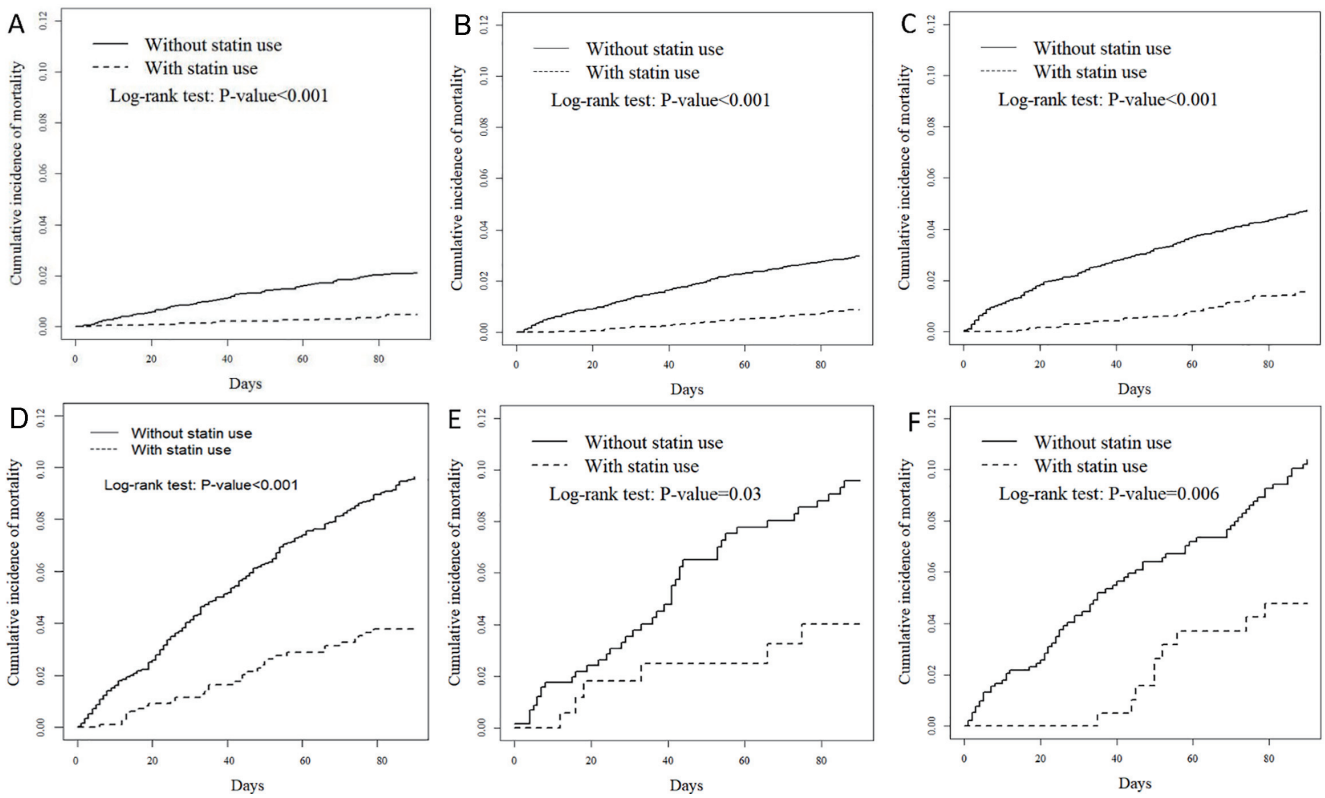

Fig. 1. Cumulative mortality rates at 3 months after ischemic stroke according to statin use, classified by estimated glomerular filtration rate (eGFR) levels

(A) ≥ 90 mL/min/1.73 m^2, (B) 60–89 mL/min/1.73 m^2, (C) 30–59 mL/min/1.73 m^2, (D) 15–29 mL/min/1.73 m^2, (E) <15 mL/min/1.73 m^2 non-dialysis, (F) Dialysis

Table 4. Association of Statin Therapy at Discharge Stratified by eGFR with Mortality and Unfavorable Outcome at 3 Months After Ischemic Stroke

	Mortality		Unfavorable outcome	
eGFR (mL/min/1.73 m^2)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥ 90	0.21 (0.12, 0.39)	0.46 (0.24, 0.89)	0.88 (0.79, 0.97)	0.91 (0.81, 1.02)
60–89	0.27 (0.20, 0.37)	0.45 (0.32, 0.64)	0.85 (0.80, 0.91)	0.92 (0.86, 0.99)
30–59	0.29 (0.22, 0.39)	0.49 (0.36, 0.68)	0.89 (0.83, 0.95)	0.98 (0.91, 1.06)
15–29	0.34 (0.21, 0.57)	0.53 (0.31, 0.91)	0.94 (0.81, 1.10)	0.97 (0.82, 1.15)
<15 non-dialysis	0.40 (0.17, 0.94)	0.74 (0.29, 1.89)	0.78 (0.57, 1.06)	0.77 (0.54, 1.08)
Dialysis	0.39 (0.20, 0.79)	0.67 (0.32, 1.39)	0.97 (0.76, 1.24)	1.05 (0.80, 1.37)

HR, hazard ratio; CI, confidence intervals; eGFR, estimated glomerular filtration rate.
The adjusted variables included age, gender, admission NIHSS, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, previous cerebral infarction, previous cerebral hemorrhage, ischemic heart disease, ischemic stroke subtype, atrial fibrillation, peripheral arterial disease, alcohol consumption, cancer, antiplatelet/anticoagulant use after admission, and intravenous thrombolysis.

come at 3 months in patients with acute ischemic stroke, and over 12,000 patients received statins only after the index stroke events. This short-term association of statins with stroke outcomes was consistent with other reports. A study from Fukuoka Stroke Registry demonstrated that post-stroke statin therapy instead of pre-stroke use was significantly associated with favorable functional outcomes at discharge[23]. Another cohort study revealed that statin therapy during hospitalization of acute ischemic stroke was associ-

Table 5. Association of Statin Therapy at Discharge According to eGFR with Recurrence of Ischemic Stroke Within 3 Months After Ischemic Stroke

eGFR (mL/min/1.73 m^2)	Crude HR (95% CI)	Adjusted HR (95% CI)
≥ 90	1.00 (0.77, 1.31)	0.86 (0.63, 1.17)
60–89	1.21 (1.02, 1.43)	1.29 (1.07, 1.57)
30–59	1.21 (1.00, 1.47)	1.15 (0.92, 1.44)
15–29	1.48 (0.94, 2.34)	1.10 (0.66, 1.83)
<15 non-dialysis	2.06 (1.01, 4.18)	1.37 (0.60, 3.14)
Dialysis	1.88 (1.02, 3.46)	1.98 (0.95, 4.13)

HR, hazard ratio; CI, confidence intervals; eGFR, estimated glomerular filtration rate.
The adjusted variables included age, gender, admission NIHSS, hypertension, diabetes, hypercholesterolemia, hypertriglyceridemia, previous cerebral infarction, previous cerebral hemorrhage, ischemic heart disease, ischemic stroke subtype, peripheral arterial disease, atrial fibrillation, antiplatelet/anticoagulant use at discharge, and intravenous thrombolysis treatment.

ated with lower risks of mortality and poor functional outcomes at 3 months in patients with NIHSS higher than 4 [24]. In addition to the potential contribution of pleotropic effects of statins to these findings[5], the influence of selection bias cannot be completely excluded even after regression analysis in this study.

The strength of this study was the systematic analysis of the eGFR-dependent association of statins at discharge with stroke outcomes in a large population. It revealed a cutoff level of the eGFR in addition to dialysis stage about the association of statins at discharge with post-stroke outcomes. This study had several limitations. First, the types of statin therapy varied among the patients, but a meta-analysis demonstrated that the differences among the statins were modest in the effect of secondary prevention of stroke in ischemic stroke patients[25]. Second, proteinuria is another marker for CKD, but urine protein levels were not recorded in this registry. Third, there was no data about the cause of mortality in the registry, thus we cannot analyze what kind of death was lower in statin users. Fourth, several variables were different between statins users and nonusers, leading to potential selection bias even after regression analysis. Furthermore, it is difficult to clarify causality issues in observational studies; therefore, the findings in this study should be interpreted carefully regarding causality. Fifth, the Asian population with CKD have a particularly higher risk of stroke[26], thus our results may not be directly applicable to other races.

Conclusion

In conclusion, this study revealed that the association of statin therapy at discharge with lower risks of mortality and unfavorable functional outcomes was dependent on eGFR levels. Statin therapy at discharge was significantly associated with a lower mortality risk in patients with an eGFR ≥ 15 mL/min/1.73 m^2, and significantly associated with a lower risk of unfavorable functional outcomes in patients with an eGFR of 60–89 mL/min/1.73 m^2. Of note, statin therapy at discharge was not associated with risk of mortality or functional outcomes in patients with the other eGFR levels.

Appendix

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References

1) Ovbiagele B, Schwamm LH, Smith EE, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, and Fonarow GC: Patterns of care quality and prognosis among hospitalized ischemic stroke patients with chronic kidney disease. J Am Heart Assoc, 2014; 3: e000905
2) Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, Sela BA, and Tanne D: Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke, 2009; 40: 1296-1303
3) Toyoda K, and Ninomiya T: Stroke and cerebrovascular diseases in patients with chronic kidney disease. Lancet Neurol, 2014; 13: 823-833
4) Cases A, and Coll E: Dyslipidemia and the progression of renal disease in chronic renal failure patients. Kidney Int Suppl, 2005; 99: S87-93
5) Lewis D, Haynes R, and Landray MJ: Lipids in chronic kidney disease. J Ren Care, 2010; 36 Suppl 1: 27-33
6) Yan YL, Qiu B, Wang J, Deng SB, Wu L, Jing XD, Du JL, Liu YJ, and She Q: High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. BMJ Open, 2015; 5: e006886
7) Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, and Sabatine MS: Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. JAMA, 2016; 316: 1289-1297
8) Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, and Zivin JA; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med, 2006; 355: 549-559
9) Amarenco P, Callahan A 3rd, Campese VM, Goldstein LB, Hennerici MG, Messig M, Sillesen H, Welch KM, Wilson DJ, and Zivin JA: Effect of high-dose atorvastatin on renal function in subjects with stroke or transient ischemic attack in the SPARCL trial. Stroke, 2014; 45: 2974-2982
10) Collins R, Armitage J, Parish S, Sleight P, and Peto R; Heart Protection Study Collaborative Group: Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet, 2004; 363: 757-767
11) Obialo CI, Ofili EO, and Norris KC: Statins and Cardiovascular Disease Outcomes in Chronic Kidney Disease: Reaffirmation vs. Repudiation. Int J Environ Res Public Health, 2018; 15: E2733
12) Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, and Ritz E; German Diabetes and Dialysis Study Investigators: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med, 2005; 353: 238-248
13) Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V,

Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, and Zannad F; AURORA Study Group: Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med, 2009; 360: 1395-1407
14) Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, Craig JC, and Strippoli GF: HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev, 2009; 2: CD007784
15) Zhang X, Jing J, Zhao X, Liu L, Wang C, Pan Y, Meng X, Wang Y, and Wang Y: Statin use during hospitalization and short-term mortality in acute ischaemic stroke with chronic kidney disease. Eur Neurol, 2018; 79: 296-302
16) Hsieh FI, Lien LM, Chen ST, Bai CH, Sun MC, Tseng HP, Chen YW, Chen CH, Jeng JS, Tsai SY, Lin HJ, Liu CH, Lo YK, Chen HJ, Chiu HC, Lai ML, Lin RT, Sun MH, Yip BS, Chiou HY, and Hsu CY; Taiwan Stroke Registry Investigators: Get With the Guidelines-Stroke performance indicators: surveillance of stroke care in the Taiwan Stroke Registry: Get With the Guidelines-Stroke in Taiwan. Circulation, 2010; 122: 1116-1123
17) Levey AS, and Stevens LA: Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis, 2010; 55: 622-627
18) Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, and Marsh EE 3rd: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Stroke, 1993; 24: 35-41
19) Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, and Collins R; SHARP Investigators: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet, 2011; 377: 2181-2192
20) Webster AC, Nagler EV, Morton RL, and Masson P: Chronic Kidney Disease. Lancet, 2017; 389: 1238-1252
21) Major RW, Cheung CK, Gray LJ, and Brunskill NJ: Statins and Cardiovascular Primary Prevention in CKD: A Meta-Analysis. Clin J Am Soc Nephrol, 2015; 10: 732-739
22) Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellström B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R, and Baigent C: Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol, 2016; 4: 829-839
23) Ishikawa H, Wakisaka Y, Matsuo R, Makihara N, Hata J, Kuroda J, Ago T, Kitayama J, Nakane H, Kamouchi M, and Kitazono T; Fukuoka Stroke Registry Investigators: Influence of Statin Pretreatment on Initial Neurological Severity and Short-Term Functional Outcome in Acute Ischemic Stroke Patients: The Fukuoka Stroke Registry. Cerebrovasc Dis, 2016; 42: 395-403
24) Song B, Wang Y, Zhao X, Liu L, Wang C, Wang A, Du W, and Wang Y: Association between statin use and short-term outcome based on severity of ischemic stroke: a cohort study. PLoS One, 2014; 9: e84389
25) Tramacere I, Boncoraglio GB, Banzi R, Del Giovane C, Kwag KH, Squizzato A, and Moja L: Comparison of statins for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. BMC Med, 2019; 17: 67
26) Gutiérrez OM, Judd SE, Muntner P, Rizk DV, McClellan WM, Safford MM, Cushman M, Kissela BM, Howard VJ, and Warnock DG: Racial differences in albuminuria, kidney function, and risk of stroke. Neurology, 2012; 79: 1686-1692