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 m². 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 m². Statin therapy in patients with an eGFR of 60–89 mL/min/1.73 m² 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
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 m² compared to those with an eGFR of ≥ 60 mL/min/1.73 m². Furthermore, CKD and ischemic stroke share several vascular risk factors, and dyslipidemia is the one factor which deserves special attention. Dyslipidemia contributes to the worsening of renal function by promoting glomerular and tubulointerstitial injury, and renal dysfunction leads to the deterioration of the lipid profile. This includes elevated low-density lipoprotein (LDL) and triglyceride levels, as well as reduced high-density lipoprotein levels. A high LDL level has been a well-known risk factor for major vascular events. 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. Regarding the influence of statins on stroke risk, statins are beneficial for secondary prevention of ischemic stroke, while the findings are inconsistent for primary prevention of stroke in CKD patients. 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. Furthermore, there was only one study focusing on the association of statins according to renal function in patients with acute ischemic stroke. This study demonstrated that statin use was associated with a lower mortality risk in all eGFR groups, including eGFR <60 mL/min/1.73 m². 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. This study included patients with acute ischemic stroke without loss to follow up, and exclusively enrolled in-hospital mortality, those with missing data (creatinine, sex, or body weight), and age < 18 years.

The retrieved data of this study included risk factors of ischemic stroke, eGFR on admission by CKD-Epidemiological Collaboration (CKD-EPI) equation, 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), 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
to their eGFR levels, which were ≥ 90, 60–89, 30–59, 15–29, and <15 mL/min/1.73 m², and those with an eGFR < 15 mL/min/1.73 m² 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 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 m² at non-dialysis and dialysis stages, respectively; for hypertriglyceridemia: 10.4% and 12.8% in patients with an eGFR < 15 mL/min/1.73 m² 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 non-user 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 m², while no difference was observed between statin users and nonusers in the groups with eGFR of < 15 mL/min/1.73 m². 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 m², 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 m² 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 m²) | ≥ 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) | p-value |
|-----------------------|------------------|-------------------|------------------|------------------|-------------------------|---------------------|---------|
| Age, years            |                  |                   |                  |                  |                         |                     |         |
| Male sex              |                  |                   |                  |                  |                         |                     |         |
| Body mass index (median, IQR, kg/m²) | 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) | 5 (2–10) | 5 (2–12) | 5 (2–11) | 5 (2–10) |                     |         |
| 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 |                |                   |                  |                  |                         |                     |         |
| Large artery atherosclerosis | 2771 (28.1) | 5907 (27.9) | 4178 (28.4) | 699 (30.5) | 233 (28.9) | 288 (23.4) | <0.001  |
| Small vessel occlusion | 4515 (45.7) | 8984 (42.5) | 5384 (36.6) | 767 (33.4) | 316 (39.2) | 436 (35.5) | <0.001  |
| Cardioembolism        | 654 (6.6)        | 2440 (11.5)       | 2257 (15.3)      | 328 (14.3)       | 89 (11.0)              | 163 (13.3)        | <0.001  |
| Other specific etiologies | 383 (3.9) | 253 (1.2) | 138 (0.9) | 21 (0.9) | 8 (1.0) | 17 (1.4) | <0.001 |
| Undetermined etiology | 1554 (15.7) | 3578 (16.9) | 2765 (18.8) | 480 (20.9) | 160 (19.9) | 326 (26.5) | <0.001  |

| 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

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 m², 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 m² was associated with a lower risk of unfavorable outcomes. In patients with an eGFR of <15 mL/min/1.73 m², 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 m², 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
therapy at discharge with a lower mortality risk after stroke was significant only in patients with an eGFR of ≥ 15 mL/min/1.73 m², while using statins at discharge had no significant association with mortality risk for those with eGFR of <15 mL/min/1.73 m². The difference in mortality risk of statin therapy in non-stroke CKD patients has been illustrated to be dependent on the dialysis stage. Statins therapy was significantly associated with lower risks of all-cause mortality and cardiovascular mortality in CKD patients who did not receive dialysis, while statins had no significant correlation with all-cause mortality in dialysis patients. Regardin 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 m² in the Chinese population. 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 m². The discrepancy

| Variables                                | Before Admission | Statin Use  | No Statin Use | p-value | At Discharge | Statin Use  | No Statin Use | p-value |
|------------------------------------------|------------------|-------------|---------------|----------|--------------|-------------|---------------|---------|
| Age, mean (SD)                           |                  | N = 3,752   | N = 46,340    | 0.03     |              | N = 16,549  | N = 33,543    | <0.001  |
| Age, median (IQR)                        |                  | 68.8 (11.4) | 68.3 (14.0)   | 0.03     |              | 66.5 (14.1) | 69.3 (13.6)   | <0.001  |
| Male                                     |                  | 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  |
| Body mass index (median, IQR), kg/m²     |                  | 2111 (56.3) | 28116 (60.7)  | <0.001   |              | 9693 (58.6) | 20534 (61.2)  | <0.001  |
| Hypertension                             |                  | 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  |
| Diabetes mellitus                        |                  | 3.85 (88.8) | 36002 (77.7)  | <0.001   |              | 13410 (81.0) | 25925 (77.3)  | <0.001  |
| Hypercholesterolemia                     |                  | 2307 (61.5) | 18339 (39.6)  | <0.001   |              | 7563 (45.7) | 13083 (39.0)  | <0.001  |
| Previous ischemic stroke                 |                  | 1324 (35.3) | 10540 (22.7)  | <0.001   |              | 5435 (32.8) | 6429 (19.2)   | <0.001  |
| Previous intracerebral hemorrhage        |                  | 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  |
| Peripheral artery disease                |                  | 92 (2.5)    | 1094 (2.4)    | 0.72     |              | 342 (2.1)   | 844 (2.5)     | 0.002   |
| Cancer                                   |                  | 142 (3.8)   | 901 (1.9)     | <0.001   |              | 420 (2.5)   | 623 (1.9)     | <0.001  |
| Ischemic stroke subtype                  |                  |             |               | 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 ≥ 90                                |                  |              |               | <0.001   |              |              |               | <0.001  |
| 60–89                                    |                  |              |               |          |              |              |               |         |
| 30–59                                    |                  |              |               |          |              |              |               |         |
| 15–29                                    |                  |              |               |          |              |              |               |         |
| <15 non-dialysis                         |                  |              |               | <0.001   |              |              |               |         |
| Dialysis                                 |                  |              |               |          |              |              |               |         |
| Antiplatelet                             |                  |              |               | <0.001   |              |              |               | <0.001  |
| Anticoagulant                            |                  |              |               | <0.001   |              |              |               |         |
| Intravenous thrombolysis                 |                  |              |               | <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.

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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 m². The discrepancy...
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 outcomes. 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.

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

| eGFR (mL/min/1.73 m\(^2\)) | Mortality |  |  | Unfavorable outcome |  |  |
|-----------------------------|-----------|---|---|---------------------|---|---|
|                             | Crude HR (95\% CI) | Adjusted HR (95\% CI) | Crude HR (95\% CI) | Adjusted HR (95\% CI) |
| ≥ 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.
istry demonstrated that post-stroke statin therapy instead of pre-stroke use was significantly associated with favorable functional outcomes at discharge\(^2\))

Another cohort study revealed that statin therapy during hospitalization of acute ischemic stroke was associated with improved outcomes 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\(^2\)). Another cohort study revealed that statin therapy during hospitalization of acute ischemic stroke was associ-

Fig. 1. Cumulative mortality rates at 3 months after ischemic stroke according to statin use, classified by estimated glomerular filtration rate (eGFR) levels
(A) \(\geq 90\) 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

| eGFR (mL/min/1.73 m\(^2\)) | Mortality | Unfavorable outcome |
|-----------------------------|-----------|---------------------|
|                             | Crude HR (95% CI) | Adjusted HR (95% CI) | Crude HR (95% CI) | Adjusted HR (95% CI) |
| \(\geq 90\)                  | 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.
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 m²) | 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.

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 m², and significantly associated with a lower risk of unfavorable functional outcomes in patients with an eGFR of 60–89 mL/min/1.73 m². 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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- E-Da Hospital / I-Shou University: Shih-Pin Hsu (Principal Investigator), Han-Jung Chen, Cheng-Sen Chang, Hung-Chang Kuo, Lian-Hui Lee, Huan-Wen Tsui, Jung-Chi Tsou, Yan-Tang Wang, Yi-Cheng Tai, Kun-Chang Tsai, Yen-Wen Chen, Kan Lu, Pochao Liliang, Yu-Tun Tsai, Cheng-Loong Liang, Kuo-Wei Wang, Hao-Kuang Wang, Jui-Sheng Chen, Po-Yuan Chen, Cien-Leong Chye, Wei-Jie Tzeng, Pei-Hua Wu
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Kuang Tien General Hospital: Ming-Hui Sun (Principal Investigator), Li-Ying Ke

Tai-chung Veterans General Hospital: Po-Lin Chen (Principal Investigator), Yu-Shan Lee

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