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Effect of initiating statin therapy on long-term outcomes of patients with dyslipidemia after intracerebral hemorrhage

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HIGHLIGHTS

- Early initiating statin might decrease recurrent intracerebral hemorrhage (ICH)
- Post ICH statin initiation could decrease all-cause mortality for the dyslipidemic population
- Statins with different potency or lipophilicity had similar outcomes after ICH

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ABSTRACT

Background and aims: Intracerebral hemorrhage (ICH) has a higher mortality than ischemic stroke. Statin is beneficial for stroke, but high potency statin treatment has been associated with the risk of hemorrhagic stroke. The aim of this study was to assess the impact of initiating statin therapy after ICH on cardiovascular outcomes.
Methods: Dyslipidemic patients were retrieved from the ICH population from the National Health Insurance Research Database in Taiwan. We retrospectively compared patients prescribed with and without statin treatment after ICH. Outcomes of interest were mortality, myocardial infarction, ischemic stroke, and hemorrhagic stroke during 5 years of follow-up.
Results: Of 17,980 adult patients with ICH and dyslipidemia, 8927 were eligible for analysis over the study period, including 1613 patients receiving statin therapy and 7314 patients not taking statins. After propensity score matching, the mean age was 61.2 ± 12.2 years in the statin group and 61.6 ± 13.0 years in the non-statin group. Hypertension was dominant, followed by diabetes mellitus, and the mean estimated NIHSS score was 12.9. The patients who received statin therapy were associated with lower risks of all-cause mortality (12.7% *vs.* 21.3%; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.45–0.65), cardiovascular death (4.0% *vs.* 7.1%; HR, 0.54; 95% CI, 0.39–0.75) and ICH (5.4% *vs.* 8.5%; HR, 0.62; 95% CI, 0.46–0.83) compared to those who did not receive statins.
Conclusions: Initiating statin therapy after ICH was associated with a decreased risk of recurrent ICH and mortality for dyslipidemia patients.

1. Introduction

Intracerebral hemorrhage (ICH) has been reported to constitute around 10–15% of all strokes, but it is associated with a higher mortality rate than ischemic stroke (40% mortality at 1 year and 70% at 5 years) [1]. A poor functional status after ICH and a high annual recurrence rate (1.3%–7.4%) [2] contribute to a worse prognosis with a low survival rate. Age, inadequate control of hypertension, and dyslipidemia, as similar cardiovascular risk factors to ischemic stroke, affect the recurrence of ICH. In addition, a high incidence rate (3% per year) of ischemic stroke has also been reported after ICH [3]. HMG-CoA reductase inhibitors (statins) are widely used to lower serum cholesterol for primary and secondary prevention of cardiovascular diseases [4], especially in patients at high risk of adverse cardiovascular (CV) events

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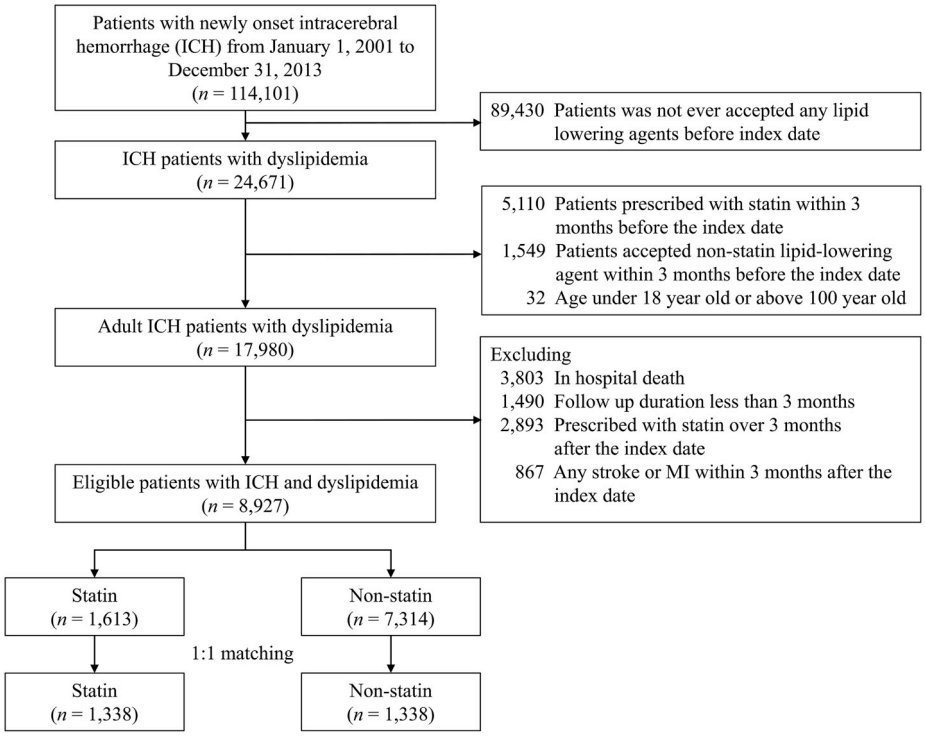


Fig. 1. Inclusion and exclusion of the study cohort design.

and stroke [5].

However, a *post hoc* analysis of SPARCLE trials (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) [7,8] showed that high-dose atorvastatin treatment increased the risk of hemorrhagic stroke and decreased the net benefits due to a high risk of mortality. In addition, statin treatment has also been reported to increase the risk of ICH in those patients already at high risk of adverse CV events [9–11], and a low LDL level has also been associated with a higher incidence of ICH [12,13]. However, an early meta-analysis has not supported a higher risk of ICH due to statin use, but rather that significant reductions in all stroke and all-cause mortality can be achieved with statin therapy [14]. An LDL level < 70 mg/dL did not predict a higher incidence of ICH in populations at high risk in the TET trial [15] and PCSK9 studies [16]. Several studies have shown equivocal safety results for patients receiving statins after an ICH [10,17], and a recent meta-analysis showed that in-hospital statin therapy did not increase the risk of recurrent ICH [18]. Moreover, statin therapy has been reported to potentially provide better functional outcomes after ICH [6,19–21], and several studies have suggested that preexisting statin medications should not be discontinued in the acute phase of ICH [22,23]. However, none of these studies focused on populations not receiving statin therapy before ICH onset. This is an important scenario, because statins should be prescribed for patients with ICH with dyslipidemia and at high risk of adverse CV outcomes. Therefore, we conducted this large nationwide population-based cohort study to evaluate the effect of statin therapy on long-term cerebrovascular outcomes and all-cause mortality after acute ICH events.

2. Materials and methods

2.1. Data source

This retrospective longitudinal cohort study was conducted using data from the National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD is derived from claims data of the Taiwan NHI program, a mandatory enrollment, single-payer system that covers more than 99% of Taiwan's 23 million residents. The NHIRD prospectively records all submitted standardized data of healthcare services, including details of demographic characteristics, out-patient medical records, procedures, hospitalizations, drug prescriptions, medical diagnoses of diseases, and vital status. Diseases are registered using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Validation of the NHIRD data is routinely conducted by the NHI Bureau, and all information in the NHIRD is de-identified to protect privacy.

The Research Ethics Committee of Chang-Gung Memorial Hospital approved the study protocol (104–9822B).

2.2. Inclusion criteria and study design

This study was a population-based cohort investigation. Patients with a principal diagnosis of ICH (ICD-9-CM: 431) on admission were selected. The accuracy of the diagnosis of ICH has been validated in a prior NHIRD study [24]. The day of discharge from the index ICH was defined as the index date. A total of 114,101 patients with newly diagnosed ICH between January 1, 2001 and December 31, 2013 were included, of whom 24,671 were diagnosed with dyslipidemia. To ensure that the study patients had not received any statin treatment before the index date, 5110 patients prescribed with statins and 1549 patients prescribed with non-statin lipid-lowering agents within 3 months before the index date were excluded. To assess exposure to statins and the effects of the long-term use of statins on outcomes, other exclusion criteria included patients (1) aged under 18 years and above 100 years, (2) who died during the index ICH admission, (3) with a follow-up duration less than 3 months, and (4) who had any cerebrovascular events within 3 months of the index date. To focus on the early prescriptions of statins after ICH, patients prescribed with statin treatment 3 months after the index ICH were excluded. Finally, the remaining 8927 patients were included for further analysis. After propensity score matching, 1338 patients were enrolled in the statin group and 1338 patients were enrolled in the non-statin group, and their clinical outcomes were analyzed (Fig. 1).

Table 1
Characteristics of the study patients before and after propensity score matching.

Characteristics	Before matching			After matching		
	Statin (n = 1613)	Non-statin (n = 7314)	SMD	Statin (n = 1338)	Non-statin (n = 1338)	SMD
Age (years)	61.3 ± 12.4	66.7 ± 13.1	−0.42	61.2 ± 12.2	61.6 ± 13.0	−0.03
Age group (> 65 yrs)	608 (37.7)	4161 (56.9)	−0.39	496 (37.1)	524 (39.2)	−0.04
Gender						
Male	881 (54.6)	4434 (60.6)	−0.12	750 (56.1)	774 (57.8)	−0.03
Female	732 (45.4)	2880 (39.4)	0.12	588 (43.9)	564 (42.2)	0.03
Comorbidity						
Hypertension	909 (56.4)	4041 (55.3)	0.02	730 (54.6)	740 (55.3)	−0.01
Diabetes mellitus	433 (26.8)	1751 (23.9)	0.07	336 (25.1)	340 (25.4)	−0.01
Atrial fibrillation	47 (2.9)	343 (4.7)	−0.09	30 (2.2)	43 (3.2)	−0.06
Gout	227 (14.1)	960 (13.1)	0.03	198 (14.8)	212 (15.8)	−0.03
Chronic obstructive pulmonary disease	80 (5.0)	640 (8.8)	−0.15	66 (4.9)	77 (5.8)	−0.04
Hepatitis B virus infection	19 (1.2)	141 (1.9)	−0.06	17 (1.3)	18 (1.3)	< 0.01
Hepatitis C virus infection	21 (1.3)	167 (2.3)	−0.08	20 (1.5)	19 (1.4)	0.01
Peptic ulcer	169 (10.5)	1096 (15.0)	−0.14	138 (10.3)	142 (10.6)	−0.01
Peripheral arterial disease	31 (1.9)	209 (2.9)	−0.07	25 (1.9)	22 (1.6)	0.02
Ischemic heart disease	285 (17.7)	1317 (18.0)	−0.01	216 (16.1)	222 (16.6)	−0.01
Immune disease	5 (0.3)	36 (0.5)	−0.03	1 (0.1)	3 (0.2)	−0.03
Liver cirrhosis	12 (0.7)	312 (4.3)	−0.23	11 (0.8)	12 (0.9)	−0.01
Heart failure	71 (4.4)	474 (6.5)	−0.09	50 (3.7)	64 (4.8)	−0.05
Dementia	36 (2.2)	276 (3.8)	−0.09	25 (1.9)	20 (1.5)	0.03
Malignancy	49 (3.0)	412 (5.6)	−0.13	43 (3.2)	45 (3.4)	−0.01
Chronic kidney disease	112 (6.9)	666 (9.1)	−0.08	89 (6.7)	102 (7.6)	−0.03
ESRD on dialysis	38 (2.4)	398 (5.4)	−0.16	34 (2.5)	42 (3.1)	−0.04
History of events						
Major bleeding	114 (7.1)	732 (10.0)	−0.10	56 (4.2)	72 (5.4)	−0.06
Gastrointestinal bleeding	199 (12.3)	1436 (19.6)	−0.20	154 (11.5)	171 (12.8)	−0.04
Old myocardial infarction	36 (2.2)	213 (2.9)	−0.04	15 (1.1)	15 (1.1)	< 0.01
Estimated NIHSS	12.6 ± 6.8	16.4 ± 7.1	−0.55	12.9 ± 6.7	12.9 ± 6.8	< 0.01
Estimated NIHSS group						
≤ 5	288 (17.9)	636 (8.7)	0.27	215 (16.1)	215 (16.1)	< 0.01
6-13	642 (39.8)	1927 (26.3)	0.29	543 (40.6)	537 (40.1)	0.01
> 13	683 (42.3)	4751 (65.0)	−0.47	580 (43.3)	586 (43.8)	−0.01
Medications during the 3 months follow up						
Amiodarone	23 (1.4)	105 (1.4)	< 0.01	19 (1.4)	16 (1.2)	0.02
Anticoagulant agents	25 (1.5)	76 (1.0)	0.05	15 (1.1)	13 (1.0)	0.01
Antiplatelet agents	295 (18.3)	809 (11.1)	0.20	210 (15.7)	221 (16.5)	−0.02
Oral antidiabetic agents	599 (37.1)	1925 (26.3)	0.23	457 (34.2)	452 (33.8)	0.01
Insulin	114 (7.1)	434 (5.9)	0.05	80 (6.0)	81 (6.1)	< 0.01
Hypertension drugs						
ACEI/ARB	1012 (62.7)	3283 (44.9)	0.36	816 (61.0)	821 (61.4)	−0.01
β-blocker	628 (38.9)	2104 (28.8)	0.21	501 (37.4)	509 (38.0)	−0.01
DCCB	1059 (65.7)	4132 (56.5)	0.19	890 (66.5)	864 (64.6)	0.04
Diuretics (Thiazide)	122 (7.6)	392 (5.4)	0.09	98 (7.3)	84 (6.3)	0.04
Other (including α-blocker)	191 (11.8)	826 (11.3)	0.02	154 (11.5)	171 (12.8)	−0.04
Number of anti-HTN drugs						
0	186 (11.5)	1815 (24.8)	−0.35	161 (12.0)	172 (12.9)	−0.03
1	417 (25.9)	2022 (27.6)	−0.04	355 (26.5)	352 (26.3)	< 0.01
2	547 (33.9)	2031 (27.8)	0.13	447 (33.4)	436 (32.6)	0.02
≥ 3	463 (28.7)	1446 (19.8)	0.21	375 (28.0)	378 (28.3)	−0.01
Digoxin	15 (0.9)	145 (2.0)	−0.09	14 (1.0)	14 (1.0)	< 0.01
PPI	68 (4.2)	520 (7.1)	−0.13	59 (4.4)	61 (4.6)	−0.01
NSAID (including COX-2)	372 (23.1)	1413 (19.3)	0.09	311 (23.2)	327 (24.4)	−0.03
Loop diuretics	130 (8.1)	686 (9.4)	−0.05	108 (8.1)	97 (7.2)	0.03
Spironolactone	20 (1.2)	151 (2.1)	−0.07	18 (1.3)	18 (1.3)	< 0.01
Follow up year	4.5 ± 3.2	3.5 ± 2.9	0.33	4.5 ± 3.1	3.9 ± 3.0	0.20

SMD, standardized mean difference; ESRD, end-stage renal disease; NIHSS, National Institute of Health Stroke Scale; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCCB, dihydropyrinde calcium channel blocker; HTN, hypertension; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; COX-2, cyclo-oxygenase-2 inhibitor.

2.3. Definition of comorbidities and drug exposure

Comorbidities were diagnosed according to the ICD-9-CM codes recorded in the NHIRD. All comorbidities of interest were confirmed in at least two consecutive out-patient department visits or any hospitalization within 1 year before the index date. A history of critical events (i.e. hemorrhagic and CV events) was verified using inpatient diagnoses before the index date, all of which could be tracked to 1997. Most of the diagnostic codes for these comorbidities have been validated in earlier NHIRD studies [25]. Moreover, some diseases were further confirmed by prescriptions of associated medications (Supplemental Table 1).

Patients with dyslipidemia (ICD-9-CM: 272) were identified according to diagnostic codes and a prescription of hypolipidemic agents. This definition has been reported in previous NHIRD studies. According to the reimbursement policy of the NHI program in Taiwan, statins can be prescribed to patients with a serum low-density lipoprotein (LDL) level of ≥100 mg/dL, patients with CV disease or diabetes, patients with a serum LDL level of ≥130 mg/dL if they have ≥ two risk factors for CV disease, and patients with a serum LDL level of ≥160 mg/dL if they have one risk factor for CV disease. Details of medications were

Table 2
Primary outcomes between the study cohorts.

Outcome#	Statin (n = 1338)	Non-statin (n = 1338)	Statin *vs.* non-statin	
			HR (95% CI)	p-value
1 year follow-up				
Intracerebral hemorrhage	26 (1.9)	40 (3.0)	0.66 (0.40, 1.08)	0.101
Acute ischemic stroke	61 (4.6)	44 (3.3)	1.39 (0.94, 2.04)	0.098
Any stroke	76 (5.7)	75 (5.6)	1.04 (0.75, 1.43)	0.826
Acute myocardial infarction	3 (0.2)	5 (0.4)	0.59 (0.14, 2.48)	0.475
Cardiovascular death	18 (1.3)	30 (2.2)	0.59 (0.33, 1.06)	0.080
Composite ischemic event†	64 (4.8)	49 (3.7)	1.31 (0.90, 1.89)	0.160
All-cause mortality	47 (3.5)	81 (6.1)	0.57 (0.40, 0.81)	0.002
3 year follow-up				
Intracerebral hemorrhage	61 (4.6)	87 (6.5)	0.70 (0.50, 0.96)	0.029
Acute ischemic stroke	113 (8.4)	98 (7.3)	1.14 (0.87, 1.50)	0.336
Any stroke	155 (11.6)	161 (12.0)	0.96 (0.77, 1.20)	0.746
Acute myocardial infarction	12 (0.9)	7 (0.5)	1.68 (0.66, 4.25)	0.276
Cardiovascular death	37 (2.8)	73 (5.5)	0.49 (0.33, 0.73)	< 0.001
Composite ischemic event†	125 (9.3)	104 (7.8)	1.19 (0.92, 1.54)	0.190
All-cause mortality	116 (8.7)	211 (15.8)	0.51 (0.41, 0.65)	< 0.001
5 year follow-up				
Intracerebral hemorrhage	72 (5.4)	114 (8.5)	0.62 (0.46, 0.83)	0.001
Acute ischemic stroke	148 (11.1)	134 (10.0)	1.09 (0.86, 1.37)	0.480
Any stroke	194 (14.5)	209 (15.6)	0.92 (0.76, 1.12)	0.402
Acute myocardial infarction	17 (1.3)	12 (0.9)	1.37 (0.66, 2.87)	0.399
Cardiovascular death	54 (4.0)	95 (7.1)	0.54 (0.39, 0.75)	< 0.001
Composite ischemic event†	164 (12.3)	144 (10.8)	1.12 (0.90, 1.41)	0.307
All-cause mortality	170 (12.7)	285 (21.3)	0.54 (0.45, 0.65)	< 0.001

CI, confidence interval.
#Estimated from a Fine and Gray's subdistribution hazard model, which considered overall mortality as a competing risk.
† Any of acute ischemic stroke and acute myocardial infarction.

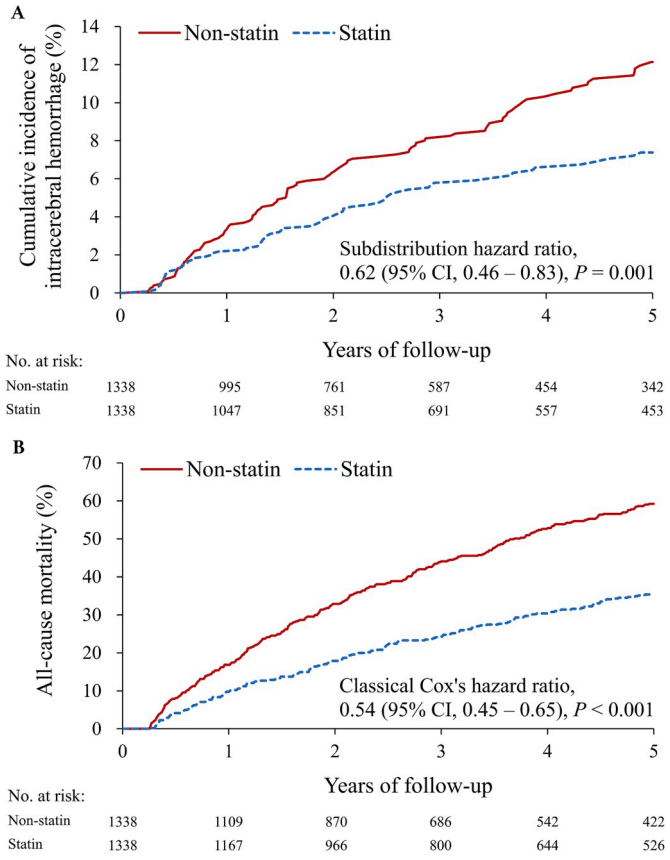


Fig. 2. Cumulative incidence of intracerebral hemorrhage (A) and unadjusted event rate of all-cause mortality (B) during 5 years of follow-up.

obtained from the out-patient pharmacy database, including type, dose, date, and duration of the prescribed drugs. Long-term drug use was defined as a prescription for at least 3 months (Supplemental Table 2). Therefore, the statin use group was defined as patients newly prescribed with statins within 3 months after the ICH index admission. The non-statin group was defined as patients who did not take any statins after the ICH index admission (even after 3 months).

2.4. Definition of outcomes

The primary outcomes included all-cause mortality, CV death and CV outcomes (ICH, acute ischemic stroke, acute myocardial infarction). Mortality was defined by withdrawal from the NHI program. Cardiovascular outcomes were defined as a principle diagnosis for a hospitalization. The high diagnostic accuracy of cerebrovascular outcomes according to ICD-9-CM codes in the NHIRD has been confirmed in previous studies [26]. The secondary outcomes included new-onset diabetes mellitus, newly diagnosed atrial fibrillation, new-onset dementia, newly diagnosed malignancy, acute hepatitis, rhabdomyolysis, and pancreatitis, all of which were identified using ICD-9-CM codes. The patients were followed until the date of an event, death, or the end of the study (December 31, 2013), whichever occurred first.

2.5. Statistical analysis

To reduce treatment selection bias, we performed propensity score matching [27] with a 1:1 ratio where each patient in the statin group was matched with a corresponding patient in the non-statin group. The selected covariates to calculate the propensity score (the predicted probability to be in the statin group derived from multivariate logistic regression analysis) included demographics (age and gender), 17 co-morbidities, history of three events, the estimated National Institute of Health Stroke Scale (NIHSS), 16 kinds of medications, the number of

Table 3
Complications at the 5-year follow-up.

Outcome#	Statin (n = 1354)	Non-statin (n = 1354)	Statin *vs.* non-statin	
			HR (95% CI)	p
New onset diabetes mellitus	246 (18.4)	193 (14.4)	1.28 (1.06, 1.55)	0.010
New onset atrial fibrillation	34 (2.5)	30 (2.2)	1.11 (0.68, 1.82)	0.674
New onset dementia	46 (3.4)	42 (3.1)	1.07 (0.70, 1.62)	0.764
New onset malignancy	50 (3.7)	65 (4.9)	0.74 (0.51, 1.06)	0.103
Acute hepatitis	11 (0.8)	5 (0.4)	2.15 (0.75, 6.16)	0.157
Rhabdomyolysis	6 (0.4)	2 (0.1)	2.94 (0.60, 14.50)	0.186
Acute pancreatitis	13 (1.0)	7 (0.5)	1.80 (0.72, 4.51)	0.208
Chronic pancreatitis	2 (0.1)	3 (0.2)	0.64 (0.11, 3.80)	0.624

HR, hazard ratio; CI, confidence interval.
#Estimated from Fine and Gray's subdistribution hazard model which considered overall mortality as a competing risk.

anti-hypertensive drugs used, and the index date. The matching was processed using a greedy nearest neighbor algorithm without replacement and with a random order [28]. The caliper was set as 0.2 times the logit of the propensity score. The quality of matching was checked using the standardized mean difference, and a value less than 0.1 was considered to have a negligible difference between groups.

We compared the risk of all-cause mortality between the two groups using a Cox proportional hazard model. The risk of other event outcomes (e.g., recurrent ICH, new-onset diabetes) between the two groups was compared using the Fine and Gray's subdistribution hazard model, which considered all-cause mortality during the follow-up as a competing risk. The study group (statin *vs.* non-statin) was the only predictor in both Cox and Fine and Gray's models. We further performed two subgroup analyses. First, we analyzed ICH and all-cause mortality during the 5-year follow-up period stratified by 15 pre-specified baseline variables to investigate whether the beneficial effect of statins was inconsistent across different levels of some subgroups. Second, we studied the beneficial effect according to potency and lipophilicity of statins on all primary outcomes during the 5-year follow-up period. We generated plots of cumulative incidence rates using the subdistribution hazard function for non-fatal outcomes. For all-cause mortality, we plotted unadjusted cumulative event rates. We also compared the risks of mortality and recurrent ICH among individual statins.

We performed a sensitivity analysis to assess the robustness of the primary analysis for mortality and recurrent ICH. We calculated the dose of statin measured by medication possession rate (MPR) during the follow up, which was the day of event occurrence, death or December 31, 2013, whichever occurred first. The MPR quantifies medication adherence by summing up the days of supply for statin and by dividing the number of days within the observation period. Statin users were classified into three groups: MPR less than 30%, 30–49% and ≥50%. This sensitivity analysis restricted on statin users who initiated statin therapy within 90 days after the discharge of the index ICH admission. A two-sided p value < 0.05 was considered to be statistically significant. No adjustments of multiple testing (multiplicity) were made in this study. All statistical analyses were performed using commercial software (SAS 9.4, SAS Institute, Cary, NC), including '*psmatch*' for propensity score matching, '*phreg*' for survival analysis, and the macro '*%cif*' for cumulative incidence function.

3. Results

3.1. Baseline characteristics

After applying the exclusion criteria, a total of 8297 dyslipidemia patients with a first ICH were included in the analysis (Fig. 1). After propensity score matching, 1338 patients who received statins after ICH were compared with 1338 patients who did not receive statins (Table 1) (all absolute standardized mean difference values < 0.1). The mean age was 61.2 ± 12.2 years in the statin group and 61.6 ± 13.0 years in the non-statin group. Nearly 40% of the patients were aged > 65 years in both groups, with male predominance (56–58%). Hypertension was the most common comorbidity, followed by diabetes mellitus. Previous hospitalizations for major bleeding and gastrointestinal bleeding were recorded in 4–5% and 12% of the patients, respectively. The mean estimated NIHSS score was 12.9, and 43–44% of the patients had severe stroke (NIHSS score > 13). Anticoagulants and antiplatelet agents were prescribed to 1% and 16% of the patients, respectively. Angiotensin converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs) and dihydropyridine calcium-channel blockers (DCCBs) were the most frequently prescribed anti-HTN drugs, and the combination of three (or more) was prescribed to 28% of the patients.

3.2. Primary outcomes between the study cohorts

Statin therapy was associated with a reduced risk of all-cause mortality during the 1-year, 3-year and 5-year follow-up periods (Table 2). Over a follow-up period of more than 1 year, the protective effects of statins on ICH and CV death were observed. The risk of ICH was lower in the statin group than in the non-statin group in the third year (4.6% *vs.* 6.5%; hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.50–0.96) and fifth year (5.4% *vs.* 8.5%; HR 0.62; 95% CI 0.46–0.83). There was a higher incidence of ICH and mortality in the statin group than in the non-statin group (Fig. 2A and B).

3.3. Complications at 5 years of follow-up

During 5 years of follow up, there was a higher incidence of new-onset diabetes mellitus in the statin group compared with the non-statin group (18.4% *vs.* 14.4%; HR 1.28; 95% CI 1.06–1.55). There were no significant differences in other complications including new-onset atrial fibrillation, new-onset dementia, new-onset malignancy, acute hepatitis, rhabdomyolysis, acute pancreatitis, and chronic pancreatitis between the two groups (Table 3).

3.4. Subgroup analysis

We performed two subgroup analyses. We first analyzed ICH and mortality stratified by the 15 pre-specified baseline characteristics. The results showed that the observed protective effect on ICH was more apparent in the female subjects (p interaction = 0.028) and in those without chronic kidney disease (CKD) (p interaction = 0.033) (Fig. 3A). Likewise, the observed protective effect on mortality was more apparent in the female subjects (p interaction = 0.021), those without CKD (p interaction = 0.043), and in those with mild or moderate stroke (p interaction = 0.014) (Fig. 3B). We then analyzed the beneficial effect according to potency and lipophilicity of statins. The incidence rates of ICH and other associated outcomes were not significantly different among the high or moderately potent statin users. Hydrophilic statins provided similar protective effects on all outcomes of interest compared

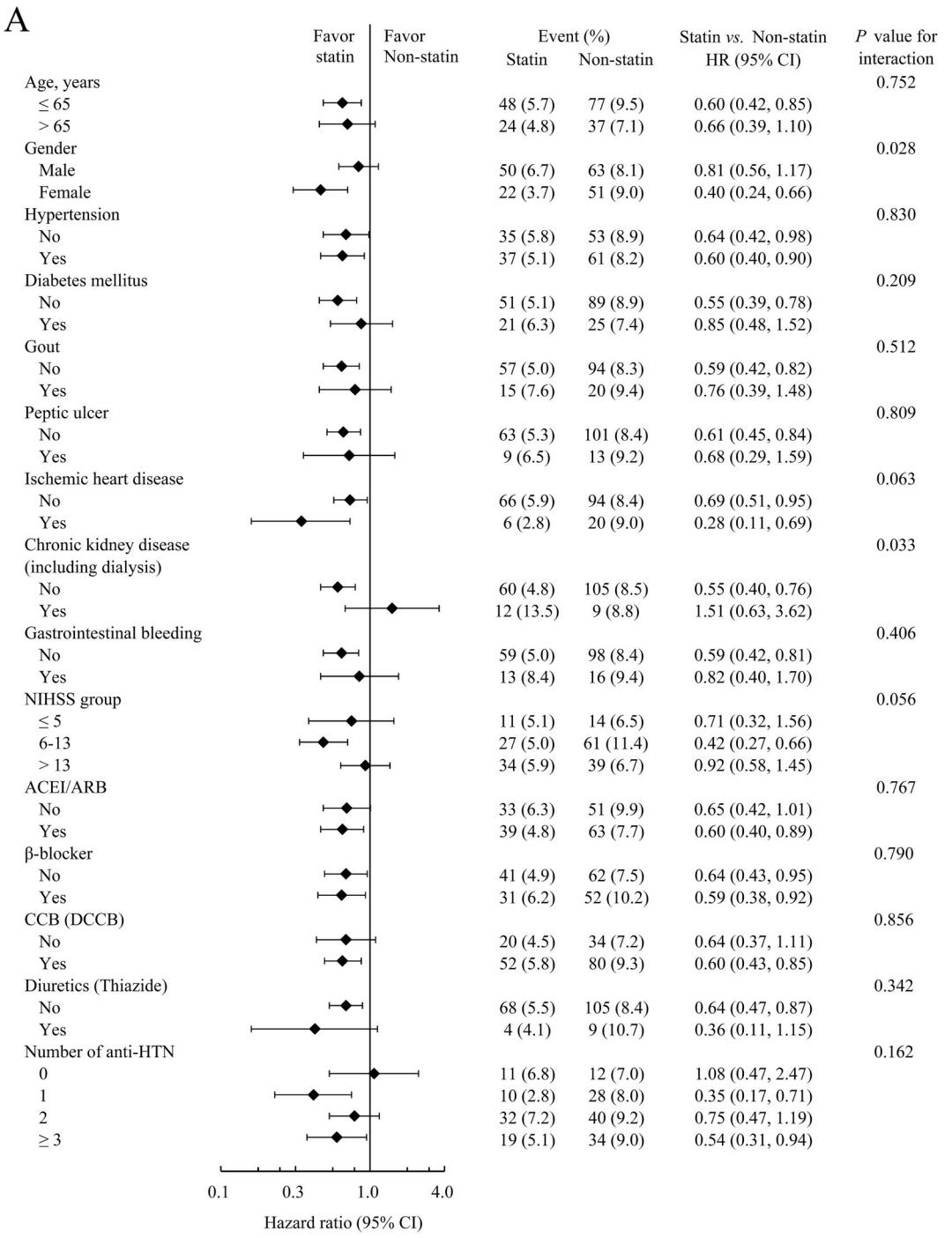


Fig. 3. Pre-specified subgroup analysis of intracerebral hemorrhage (A) and all-cause mortality (B) during 5 years of follow-up.

with lipophilic statins (Table 4). In addition, different statins had similar effects on associated outcomes; however, rosuvastatin and simvastatin had a slightly factorable effect for CV death (Supplemental Table 3).

3.5. Sensitivity analysis

The result of the association between dose of statin measured by MPR during the exposure time window and risks of recurrent ICH and all-cause mortality is listed in Supplemental Table 4 and Supplemental Figs. 2A and B. We found that a higher dose of statin was associated with an increased reduction of ICH and all-cause mortality occurrence.

4. Discussion

In this large-scale cohort study, we found that early use of statins after ICH wass safe. We also demonstrated that use of statins after ICH provided significant protective benefits, including a 38% reduction in the risk of recurrent ICH, 46% reduction in CV death, and 46% reduction in all-cause mortality at 5 years. These findings indicate the benefits of statin therapy in patients with acute ICH with dyslipidemia, and at high risk of adverse CV outcomes.

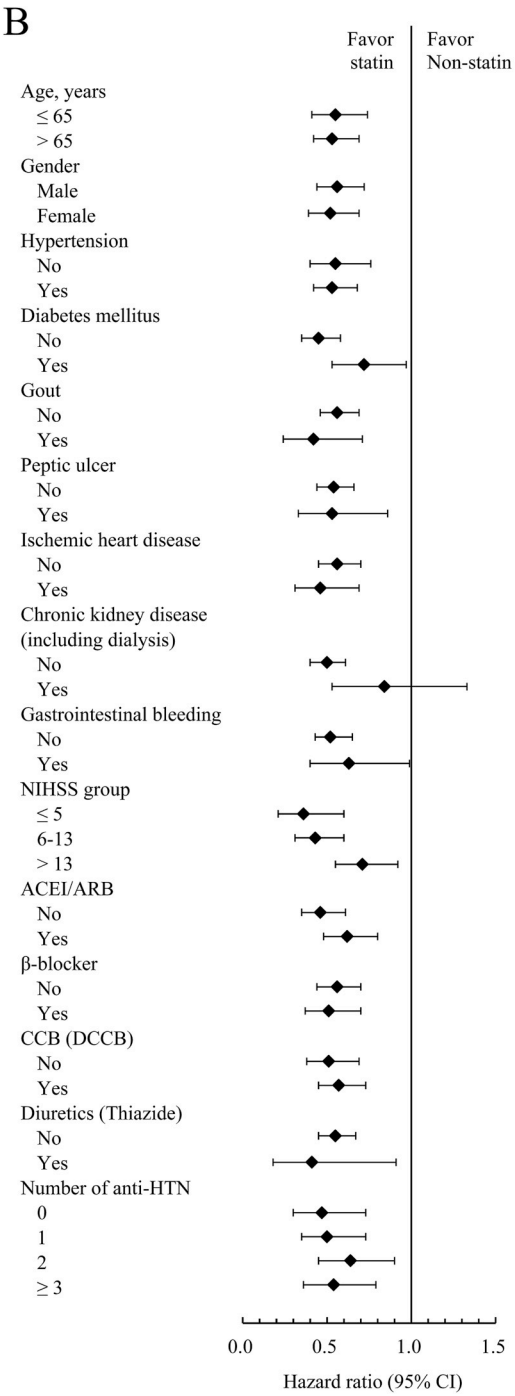
4.1. Early initiation of statin therapy against recurrent ICH

Our study demonstrated that the in-hospital initiation of statins was

safe and did not increase the risk of hemorrhagic events within the first year after ICH. A prior study reported that statin therapy did not affect peri-hematoma and ipsilateral hemispheric cerebral blood flow [28]. In addition, Chen et al. reported a neutral effect on recurrent ICH with statin therapy initiated during hospitalization or within 3 months after discharge [19]. FitzMaurice and colleagues also reported that use of statins post ICH was not associated with an increased risk of ICH recurrence at 90 days of follow-up [29]. However, there were some limitations. The observational period was short, the timing of the initiation of statin therapy varied, and it was unclear whether or not the enrolled subjects had prior dyslipidemia. By balancing the severity in both cohorts according to the estimated NIHSS score and the number of anti-HTN agents used, our study shows that early statin therapy may reduce the incidence of ICH during a long observation period of more than 5 years.

Our study also demonstrates that female patients seem to benefit more than male patients, who had inadequate HTN control and a high percentage of smoking and alcoholism and were on more anti-HTN medications. These findings are compatible with the SPARCL study, which showed that old age, male sex and hypertension were strong risk factors for ICH [7,8]. An association between the rate of mean arterial pressure decline and mortality was found in male patients, but not in female patients ($p = 0.08$). Patients with diabetes with a high NIHSS score are another high-risk population [30], and the early use of statins may be able to protect them against recurrent hemorrhagic stroke.

B



	Event (%)		Statin *vs.* Non-statin	*P* value for
	Statin	Non-statin	HR (95% CI)	interaction
Age, years				0.870
≤ 65	75 (8.9)	122 (15.0)	0.55 (0.41, 0.74)	
> 65	95 (19.2)	163 (31.1)	0.53 (0.42, 0.69)	
Gender				0.702
Male	99 (13.2)	165 (21.3)	0.56 (0.44, 0.72)	
Female	71 (12.1)	120 (21.3)	0.52 (0.39, 0.69)	
Hypertension				0.888
No	61 (10.0)	101 (16.9)	0.55 (0.40, 0.76)	
Yes	109 (14.9)	184 (24.9)	0.53 (0.42, 0.68)	
Diabetes mellitus				0.021
No	95 (9.5)	190 (19.0)	0.45 (0.35, 0.58)	
Yes	75 (22.3)	95 (27.9)	0.72 (0.53, 0.97)	
Gout				0.305
No	151 (13.2)	242 (21.5)	0.56 (0.46, 0.69)	
Yes	19 (9.6)	43 (20.3)	0.42 (0.24, 0.71)	
Peptic ulcer				0.971
No	143 (11.9)	242 (20.2)	0.54 (0.44, 0.66)	
Yes	27 (19.6)	43 (30.3)	0.53 (0.33, 0.86)	
Ischemic heart disease				0.391
No	135 (12.0)	219 (19.6)	0.56 (0.45, 0.70)	
Yes	35 (16.2)	66 (29.7)	0.46 (0.31, 0.69)	
Chronic kidney disease (including dialysis)				0.043
No	136 (10.9)	246 (19.9)	0.50 (0.40, 0.61)	
Yes	34 (38.2)	39 (38.2)	0.84 (0.53, 1.33)	
Gastrointestinal bleeding				0.464
No	139 (11.7)	239 (20.5)	0.52 (0.43, 0.65)	
Yes	31 (20.1)	46 (26.9)	0.63 (0.40, 0.99)	
NIHSS group				0.014
≤ 5	20 (9.3)	48 (22.3)	0.36 (0.21, 0.60)	
6-13	51 (9.4)	104 (19.4)	0.43 (0.31, 0.60)	
> 13	99 (17.1)	133 (22.7)	0.71 (0.55, 0.92)	
ACEI/ARB				0.122
No	74 (14.2)	143 (27.7)	0.46 (0.35, 0.61)	
Yes	96 (11.8)	142 (17.3)	0.62 (0.48, 0.80)	
β-blocker				0.663
No	112 (13.4)	178 (21.5)	0.56 (0.44, 0.70)	
Yes	58 (11.6)	107 (21.0)	0.51 (0.37, 0.70)	
CCB (DCCB)				0.583
No	67 (15.0)	127 (26.8)	0.51 (0.38, 0.69)	
Yes	103 (11.6)	158 (18.3)	0.57 (0.45, 0.73)	
Diuretics (Thiazide)				0.472
No	161 (13.0)	268 (21.4)	0.55 (0.45, 0.67)	
Yes	9 (9.2)	17 (20.2)	0.41 (0.18, 0.91)	
Number of anti-HTN				0.684
0	29 (18.0)	59 (34.3)	0.47 (0.30, 0.73)	
1	44 (12.4)	78 (22.2)	0.50 (0.35, 0.73)	
2	57 (12.8)	80 (18.3)	0.64 (0.45, 0.90)	
≥ 3	40 (10.7)	68 (18.0)	0.54 (0.36, 0.79)	

Fig. 3. (*continued*)

Table 4
Primary outcomes at the 5-year follow-up by potency and lipophilicity.

Outcome[a]	Potency[a]			Lipophilicity[b]		
	High (n = 106)	Moderate (n = 1001)	p-value	Hydrophilic (n = 287)	Lipophilic (n = 941)	p-value
Intracerebral hemorrhage						
Event number, n (%)	7 (6.60)	52 (5.19)		10 (3.48)	55 (5.84)	
Hazard ratio (95% CI)	1.25 (0.57, 2.75)	Reference	0.572	0.68 (0.35, 1.34)	Reference	0.270
Acute ischemic stroke						
Event number, n (%)	10 (9.43)	115 (11.49)		26 (9.06)	116 (12.33)	
Hazard ratio (95% CI)	0.80 (0.42, 1.52)	Reference	0.499	0.82 (0.53, 1.25)	Reference	0.353
Any stroke						
Event number, n (%)	15 (14.15)	152 (15.18)		33 (11.50)	154 (16.37)	
Hazard ratio (95% CI)	0.89 (0.53, 1.50)	Reference	0.661	0.78 (0.54, 1.13)	Reference	0.187
Acute myocardial infarction						
Event number, n (%)	2 (1.89)	12 (1.20)		3 (1.05)	13 (1.38)	
Hazard ratio (95% CI)	1.59 (0.35, 7.10)	Reference	0.547	0.91 (0.26, 3.18)	Reference	0.883
Cardiovascular death						
Event number, n (%)	4 (3.8)	40 (4.0)		7 (2.4)	44 (4.7)	
Hazard ratio (95% CI)	0.96 (0.35, 2.68)	Reference	0.941	0.63 (0.28, 1.39)	Reference	0.253
Composite ischemic event†						
Event number, n (%)	12 (11.3)	126 (12.6)		29 (10.1)	128 (13.6)	
Hazard ratio (95% CI)	0.88 (0.49, 1.57)	Reference	0.658	0.83 (0.56, 1.25)	Reference	0.372
All-cause mortality						
Event number, n (%)	16 (15.09)	120 (11.99)		25 (8.71)	134 (14.24)	
Hazard ratio (95% CI)	1.34 (0.79, 2.26)	Reference	0.274	0.72 (0.47, 1.11)	Reference	0.136

HR, hazard ratio; CI, confidence interval.
[#]Estimated from Fine and Gray's subdistribution hazard model which considered overall mortality as a competing risk.
†Any of acute ischemic stroke and acute myocardial infarction.
[a] 18 patients were excluded due to switch between moderate potency statin and high potency statin.
[b] 40 patients were excluded due to switch between hydrophilic and lipophilic statin.

4.2. Reduction in mortality and associated net benefits

Most previous studies have shown that early use of statins has a strong protective effect against all-cause mortality [31], which may be due to a large reduction in recurrent ICH. Beyond ICH, the benefits of a reduction in mortality rate began from the first year in this study, which is comparable with a previous meta-analysis [18] and other major studies [19–23]. Tapia-Perez et al. reported that ICH patients receiving early statin therapy had a significantly lower risk of intubation, admission to an intensive care unit, and disruption into the subarachnoid space [32]. In-hospital statin therapy has also been shown to potentially increase survival through improved functional rehabilitation [21], and discontinuation of statin therapy has been suggested to increase the risk of mortality for ICH patients [33]. However, there are limitations to these investigations, including a short observational period (2 years), no matching of baseline characteristics, and variable combinations of lipid lowering agents in Pan et al. analysis [20].

In addition to a direct reduction in cholesterol, statins also exert many pleiotropic effects [34], including anti-inflammatory, antithrombotic, antioxidative, improved endothelial function, myocardial perfusion, immunity and neuroprotection. Beyond CV death, our findings support that early use of statins can reduce long-term mortality associated with malignancy or infections in ICH patients (Supplemental Fig. 1), who tended to have septic deterioration due to severe disability. Moreover, emergency statin use had a lesser protective effect on recurrent hemorrhagic stroke in patients with CKD, which may have been due to hemostatic dysfunction or platelet depletion due to renal impairment. Patients with CKD may thus potentially be at higher risk of hemorrhagic stroke beyond traditional risk factors. However, the benefits of the reduction in all-cause mortality in patients with CKD were compatible with our prior study in patients with advance CKD [35]. Statins may provide more protective effects on preserving renal function, proteinuria, and systemic inflammation, which tend to reduce atherosclerotic events and renal-associated complications.

4.3. Impact of statins on the outcomes of interest and adverse effects

Previous studies have reported that different potencies and lipophilicity of statins [36] are correlated with the risk of ICH. Tai et al. proposed that hydrophilic statin therapy may be associated with a reduced risk of recurrent ICH in post-ICH patients [17]. In our subgroup analysis, high intensity and lipophilic statins did not increase the risk of recurrent hemorrhagic stroke, which is in contrast with the *post hoc* analysis of the SPARCLE trials [7,8].

Although the use of statins has been reported to increase the incidence of new-onset diabetes, the results of a recent meta-analysis were equivocal [37]. Major factors associated with the use of statins resulting in new-onset diabetes including obesity, metabolic syndrome, very high intensity and long-term prescriptions. However, we could not stop statin therapy in our population, especially in those at high risk of adverse CV events.

4.4. Limitation

There are several inherent limitations within the retrospective study, including misclassification bias, residual confounding or detecting bias. Therefore, we need future large scale randomized controlled trials. First, the location and volume of hematomas, consciousness level, hemodynamic status and premorbid modified Rankin Scale are not available in the NHIRD, however, we surveyed modified NIHSS scores to assess ICH severity. We tried to balance the risk of confounding by indication bias. Second, the physical condition, renal function, platelet count, coagulation function, and lipid profiles are not available in the NHIRD. In this study, we evaluated the approximate stage of CKD by ICD-9-CM codes and any drugs related to renal function or affecting platelet function. In addition, recent PCKSK9 inhibitor investigations have demonstrated no increased incidence of ICH in patients with a much lower LDL level than that presented in previous statin studies [16]. Therefore, the level of LDL does not seem to influence the incidence of LDL.

4.5. Conclusion

Our long-term cohort study demonstrated that statins use post ICH might improve the survival rate and reduce ICH recurrence in patients with dyslipidemia at high risk of adverse CV events. Further large-scale randomized controlled trials are needed to confirm our findings.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

All authors contributed to the statistical analysis and writing of the study. M.S.L and C.M.C participated in the study design, acquisition of data, critical review and writing of the manuscript; Y.S.L, S.T.C and C.M.C participated in the acquisition of data and designed the research; M.S.L, and P.C.W participated in the analysis and interpretation of data; V.C.C.W and W.Y.L collected data and contributed to study direction.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.07.009.

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