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Discontinuing or continuing statin following intracerebral hemorrhage from the view of a national cohort study

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HIGHLIGHTS

- Continuing statin had less mortality than discontinuing statin after ICH.
- Continuing statin did not increase incidence of recurrent ICH.
- Hydrophilic statin had better outcomes than lipophilic statin in patients after ICH.

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ABSTRACT

Background and aims: Statins improve clinical outcomes in patients with ischemic stroke but there is no evidence of the effect of continuing long-term statin therapy in patients with intracerebral hemorrhage (ICH). The aim of this study was to evaluate the impact of continuing statin after ICH.
Methods: Data on patients with ICH was retrieved from the National Health Insurance Research Database of Taiwan. The final population was separated into two groups according to those who continued and those who discontinued statin treatment. All-cause mortality and cardiovascular outcomes were analyzed after a 3 year follow-up after propensity score matching (PSM).
Results: Of the 114,101 patients with ICH, who were initially enrolled, 2468 patients with dyslipidemia and ICH were included. After PSM, the benefit of statin therapy on mortality appeared from 1 year to the end of the 3-year follow-up period after discharge (statin group *versus* non-statin group: 4.9% *vs.*12.3% at 1 year (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.26–0.57) and 12.9% *vs.* 25.3% at the end of the 3 year follow-up period (HR, 0.45; 95% CI, 0.35–0.58). Compared with the patients using lipophilic statins, those using hydrophilic statins had a significantly lower incidence of all-cause mortality (HR = 0.65, 95% CI = 0.43–0.99). There were no differences between those prescribed moderate-intensity statins and those prescribed high-intensity statins in terms of stroke and all-cause mortality (HR = 0.76; 95% CI = 0.40–1.46).
Conclusions: There was a lower risk of all-cause mortality following ICH in patients who continued statin treatment compared with those without statin treatment, especially in those treated with hydrophilic statins.

1. Introduction

Intracerebral hemorrhage (ICH) accounts for 10%–20% of all strokes worldwide [1], and is associated with a significant risk of mortality, with estimated 1- and 5-year survival rates of 46% and 29%, respectively [2]. Given the high risk of morbidity and mortality associated with ICH, therapies with neuroprotective effects are of clinical importance. In addition, patients with ICH have similar risk factors to those with ischemic stroke, and a relatively higher risk than those without ICH [3]. Statins lower cholesterol through competitive, reversible inhibition of HMG-CoA reductase, and they have also been reported to have a neuroprotective effect [4–6]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study showed a 5-year absolute risk reduction in nonfatal and fatal stroke of 2.2% for

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

Characteristics	Before matching			After matching		
	Continued statin (n = 1655)	Discontinued statin (n = 813)	p	Continued statin (n = 708)	Discontinued statin (n = 708)	p
Age (years)	65.0 ± 11.5	67.0 ± 11.6	< 0.001	66.2 ± 11.0	66.5 ± 11.7	0.572
Age group (> 65 years)	852 (51.5)	469 (57.7)	0.004	391 (55.2)	396 (55.9)	0.789
Gender			0.048			0.790
Male	848 (51.2)	451 (55.5)		388 (54.8)	383 (54.1)	
Female	807 (48.8)	362 (44.5)		320 (45.2)	325 (45.9)	
Comorbidity						
Hypertension	1391 (84.0)	620 (76.3)	< 0.001	561 (79.2)	553 (78.1)	0.604
Diabetes mellitus	885 (53.5)	402 (49.4)	0.060	349 (49.3)	353 (49.9)	0.832
Atrial fibrillation	87 (5.3)	38 (4.7)	0.535	31 (4.4)	30 (4.2)	0.896
Gout	253 (15.3)	90 (11.1)	0.004	90 (12.7)	85 (12.0)	0.686
Chronic obstructive pulmonary disease	121 (7.3)	57 (7.0)	0.786	43 (6.1)	49 (6.9)	0.518
Hepatitis B virus infection	38 (2.3)	18 (2.2)	0.898	15 (2.1)	14 (2.0)	0.851
Hepatitis C virus infection	22 (1.3)	8 (1.0)	0.462	10 (1.4)	8 (1.1)	0.635
Peptic ulcer	222 (13.4)	129 (15.9)	0.101	102 (14.4)	109 (15.4)	0.601
Peripheral arterial disease	66 (4.0)	29 (3.6)	0.609	24 (3.4)	28 (4.0)	0.572
Ischemic heart disease	588 (35.5)	209 (25.7)	< 0.001	200 (28.2)	189 (26.7)	0.513
Immune disease	18 (1.1)	5 (0.6)	0.251	7 (1.0)	5 (0.7)	0.562
Liver cirrhosis	30 (1.8)	16 (2.0)	0.789	14 (2.0)	15 (2.1)	0.851
Heart failure	138 (8.3)	56 (6.9)	0.208	44 (6.2)	46 (6.5)	0.828
Dementia	61 (3.7)	28 (3.4)	0.762	26 (3.7)	27 (3.8)	0.889
Malignancy	89 (5.4)	36 (4.4)	0.312	33 (4.7)	34 (4.8)	0.900
Chronic kidney disease	183 (11.1)	86 (10.6)	0.720	73 (10.3)	76 (10.7)	0.795
ESRD on dialysis	81 (4.9)	27 (3.3)	0.073	24 (3.4)	25 (3.5)	0.884
History of events						
Major bleeding	112 (6.8)	62 (7.6)	0.433	43 (6.1)	42 (5.9)	0.911
Gastrointestinal bleeding	271 (16.4)	132 (16.2)	0.930	111 (15.7)	115 (16.2)	0.772
Prior ischemic stroke	125 (7.6)	66 (8.1)	0.621	48 (6.8)	48 (6.8)	1.000
Old myocardial infarction	123 (7.4)	30 (3.7)	< 0.001	24 (3.4)	24 (3.4)	1.000
Medications						
Amiodarone	35 (2.1)	12 (1.5)	0.275	6 (0.8)	11 (1.6)	0.222
Anticoagulant agents	51 (3.1)	14 (1.7)	0.047	13 (1.8)	14 (2.0)	0.846
Antiplatelet agents	458 (27.7)	77 (9.5)	< 0.001	80 (11.3)	76 (10.7)	0.734
Oral antidiabetic agents	902 (54.5)	328 (40.3)	< 0.001	325 (45.9)	324 (45.8)	0.957
Insulin	248 (15.0)	88 (10.8)	0.005	92 (13.0)	88 (12.4)	0.750
Hypertension drugs						
ACEI/ARB	1109 (67.0)	367 (45.1)	< 0.001	371 (52.4)	360 (50.8)	0.559
β-blockers	767 (46.3)	267 (32.8)	< 0.001	283 (40.0)	262 (37.0)	0.251
DCCB	1003 (60.6)	462 (56.8)	0.073	436 (61.6)	438 (61.9)	0.913
Diuretics (thiazide)	102 (6.2)	44 (5.4)	0.457	47 (6.6)	42 (5.9)	0.584
Other (including α-blockers)	223 (13.5)	97 (11.9)	0.283	92 (13.0)	93 (13.1)	0.937
Number of anti-HTN drugs			< 0.001			0.795
0	166 (10.0)	204 (25.1)		123 (17.4)	128 (18.1)	
1	392 (23.7)	217 (26.7)		185 (26.1)	196 (27.7)	
2	601 (36.3)	209 (25.7)		207 (29.2)	206 (29.1)	
≥ 3	496 (30.0)	183 (22.5)		193 (27.3)	178 (25.1)	
Digoxin	53 (3.2)	11 (1.4)	0.007	13 (1.8)	11 (1.6)	0.681
PPI	108 (6.5)	66 (8.1)	0.146	63 (8.9)	60 (8.5)	0.777
NSAID (including COX-2)	370 (22.4)	127 (15.6)	< 0.001	139 (19.6)	122 (17.2)	0.244
Loop diuretics	247 (14.9)	87 (10.7)	0.004	91 (12.9)	86 (12.1)	0.688
Spironolactone	38 (2.3)	11 (1.4)	0.114	7 (1.0)	11 (1.6)	0.343
Follow up year	4.0 ± 2.9	3.0 ± 2.7	< 0.001	4.0 ± 3.0	3.1 ± 2.6	< 0.001

ESRD, end-stage renal disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCCB, dihydropyridine calcium channel blocker; HTN, hypertension; PPI, proton pump inhibitor; NSAID, non-steroidal anti-inflammatory drug; COX-2, cyclo-oxygenase-2 inhibitor.

patients taking high doses of atorvastatin [4]. In addition, the use of statins during hospitalization for ischemic stroke has been strongly associated with improved outcomes [5,6]. However, a *post hoc* analysis of the SPARCL study revealed a significant increase in hemorrhagic stroke in the high-dose atorvastatin group [4] and highlighted concerns about the potential risk of recurrent ICH [7–9]. Similar results were observed in a subgroup of patients in the Heart Protection Study (HPS), who had a history of cerebrovascular disease, in whom simvastatin increased the occurrence of hemorrhagic stroke without an effect on the overall incidence of stroke [10] Therefore, the use of statins in patients after ICH may be a serious concern, particularly in Asian patients, as they are a population reported to be at potential risk of ICH [11,12]. However, discontinuing statin therapy following ICH has been significantly associated with an increased risk of 30-day mortality and decreased favorable discharge in several short-term studies [13,14]. Differences in the types and regimens of statins used and their associations with outcomes in patients with ICH are unclear. In addition, the mean follow-up duration of previous statin and ICH trials was short, usually lasting 24 months or less. Therefore, we conducted this large nationwide population-based cohort study to evaluate the effect of continuing or discontinuing statin therapy on long-term cerebrovascular outcomes and all-cause mortality in patients after ICH.