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Efficacy of Statin therapy in post-stroke seizure prophylaxis: Clues from an observational study of routine secondary prevention treatment

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ABSTRACT

Purpose: To confirm that statin use can reduce the risk of post-stroke seizures (PSS), and to further investigate the association between the details of specific statin therapy, including the initial time, types, doses, courses, and the risk of PSS.

Methods: Patients with newly-onset ischemic stroke and no history of epilepsy before stroke were enrolled. After an average of 2 years follow-up, with the aim of establishing a PSS diagnosis, logistic regression was utilized to assess the association between specific statin therapy and the risk of PSS.

Results: Of 1051 enrolled patients, 24 (2.3%) developed early-onset seizures (ES) and 38 (3.6%) had late-onset seizures (LS), 28 of whom had LS twice or more, and thus fell in the category of post-stroke epilepsy (PSE) patients. Statin therapy was associated with a lower risk of ES ($P = 0.009$), LS ($P = 0.007$), and PSE ($P = 0.009$), and this reduction was even more pronounced in patients using intensive-dose statins (ES [$P = 0.003$], LS [$P = 0.004$], PSE [$P = 0.006$]). In addition, the risk of PSE was significantly reduced in long-course statin therapy compared with short-course statin therapy ($P = 0.015$). However, no significant association was found between the initial time of treatment and PSS risk (ES [$P = 0.321$], LS [$P = 0.050$], PSE [$P = 0.108$]).

Conclusions: Statin treatment, especially with intensive-dose statins, can reduce the risk of PSS. In addition, the risk of developing PSE appears to be significantly lower for prolonged statin treatment. However, due to the observational nature of this study, more investigations are warranted to confirm its findings.

1. Introduction

Stroke is a common cause of epilepsy in the elderly population. The abnormal neuronal discharges of post-stroke seizures (PSS) can cause damage to neurons and worsen the outcome of stroke. Numerous studies have focused on the clinical epidemiology of PSS; and the reported incidence varies from 2% to 20%, depending on the study population, stroke subtype, and the seizure onset time after the stroke [1–4]. Patients with early-onset seizures (ES) have a high risk of disability and mortality [1,5], whereas those with late-onset seizures (LS) and post-stroke epilepsy (PSE) tend to end up with poorer outcomes [6]. PSS and stroke form a vicious circle [5], and are heavy healthcare and social burdens. Thus, an effective PSS prophylaxis is of the utmost importance. Various anti-epileptic drugs (AEDs) are effective for treating PSS; however, disappointingly, they are not recommended for PSS prevention [7], even in patients with a high risk of developing PSE [8], because of their interaction profiles and the potential severe adverse effects [9]. Moreover, prophylactic AED therapy may be associated with poor outcomes in patients with stroke [10,11].

Statins were already widely used in the secondary prevention of cerebrovascular diseases long before their anticonvulsant effects were recognized. In recent years, statins have been shown to protect the cortical neuronal cells from excitotoxicity, and to modify epileptogenesis, making them promising candidates for epilepsy prophylaxis [12,13]. According to several fundamental studies and clinical trials, statin treatment is associated with a lower likelihood of epilepsy [14,20,21] and a lower mortality in patients with epilepsy [22]. Etminan et al. have demonstrated that statins can reduce the risk of hospitalization of patients with epilepsy in a dose-dependent manner; every 1 g increase in the dose of atorvastatin reduced the risk by 5% [15]. Regarding PSS, Guo et al. were the first to show that the use of statins can reduce the risk of ES [19]. In this connection, it has also been reported that statins have a risk-lowering effect in patients with high cumulative defined daily dose [13].

The efficacy of statin treatment for PSS prophylaxis has been elaborated in the previously mentioned studies. However, specific

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questions regarding the statin therapy have not been answered yet, including the statin types to be used, timing of treatment initiation, doses of statin drugs to be used, and the optimum duration of treatment. This study aimed to further investigate the association between specific statin therapy, including the initial time, types, doses, courses, and the risk of PSS, on the basis of confirming that the use of statins can reduce the risk for PSS.

2. Methods

2.1. Study population

Patients admitted to the Neurology Department of Chengdu Second People's Hospital between January 2015 and June 2017 were enrolled. Those with a newly-onset ischemic cerebral infarction, diagnosed clinically and confirmed by computed tomography or magnetic resonance imaging, and no previous history of epilepsy were included in this study. The exclusion criteria were as follows: (1) other types of cerebral vascular disease, such as a transient ischemic attack, intracranial hemorrhage, or subarachnoid hemorrhage; (2) presence of other craniocerebral diseases, such as craniocerebral tumors, brain trauma, or central nervous system infections; and (3) patients with other conditions that may cause seizures, such as metabolic diseases, neurodegenerative diseases, use of drugs, poisoning, and cortical dysplasia. Approval for this study was obtained from the hospital's Ethics Committee.

2.2. Data collection

We searched the medical database in our hospital using "ischemic cerebral infarction" as a keyword contained in the discharge diagnosis. The following data were collected by a doctor who was unaware of the study: (1) patients' baseline characteristics: sex, age, address, and telephone number; (2) stroke characteristics, including, the trial of ORG 10,172 in acute stroke treatment (TOAST) classification: large artery atherosclerosis, cardioembolism, small vessel disease, other determined or undetermined etiology; subgroup of stroke patient according to the National Institutes of Health Stroke Scale (NIHSS) score on admission—mild (NIHSS < 5), moderate (NIHSS 5–15), moderate to severe (NIHSS 16–20), or severe (NIHSS > 20); and stroke location (cortical involvement or subcortical stroke); (3) risk factors for cerebral infarction: hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking, and excessive drinking; (4) statin therapy during hospitalization: (a) whether statins were used or not, statins use here referred that the patients had regular use of statins for at least three days; (b) types of statins—three types of statins were commonly used in our hospital: atorvastatin, rosuvastatin, and simvastatin. For patients who had changed the types of statins, the ones used for a longer time were recorded; (c) the doses of statins— based on the clinical practice in China, the intensive doses of atorvastatin, rosuvastatin, and simvastatin were 40 mg, 20 mg, and 20 mg per day, respectively, whereas the standard doses were 20 mg, 10 mg, and 10 mg per day, respectively. The patients who initially took intensive doses of statins for two or more weeks, and then changed to standard doses, were considered to have used intensive-dose statins; (d) initial time—the statin therapy was divided into three phases: before stroke, in the acute phase (within the first three days after stroke onset), and after the acute phase (three days later); (e) course of statin therapy—the total course of the statin therapy included the time using statins during the hospitalization and after discharge. The patients were divided in two groups according to the therapy course: short-course statin therapy (those who took statins for a period shorter than two weeks), and long-course statin therapy; (5) PSS—it was recorded whether the seizures occurred during hospitalization, and if so, the time and frequency of their occurrence, as well as the type of seizures were noted. Since the International League Against Epilepsy has redefined epilepsy in 2014, the concept of PSS in this study was consistent with the new definition: seizures occurring within 7 days of stroke onset were classified as ES, whereas those occurring after 7 days from stroke onset were classified as LS [16–18].

2.3. Follow-up

An experienced doctor blinded to the study was in charge of the patients' follow-up. The patients were followed up for an average of 2 years (1 to 3.5 years) via telephone interview or a face-to-face assessment. First, the patients were asked over the phone whether they had experienced any seizure-like events or been diagnosed with epilepsy after the discharge. The patients suspected to have PSS were then further evaluated with a detailed inquiry, and underwent physical examinations and an electroencephalogram examination in the outpatient clinic. Furthermore, information was obtained from all patients regarding the use of statin therapy after discharge, including whether they had started or continued taking statins, and if so, the types, initial time, doses, and the total course of statin therapy were noted. The criteria for PSS diagnosis in this study were in line with the new definition and classification of epilepsy put forward by the International League Against Epilepsy in 2017.

2.4. Statistical analysis

SPSS 22.0 was used for statistical analysis. Continuous variables were presented as mean values and standard deviations, and were compared using the Student t-test. Categorical variables were presented as percentages. Logistic regression was utilized to test the association between statin therapy and the risk of PSS. The clinically significant variables that may influence the results of this study, namely the confounding factors, including sex, hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking and excessive drinking, TOAST types, NIHSS scores, and stroke location, were entered into the regression as covariates. The results were presented as odds ratios (ORs) with 95% confidence intervals (95% CI) and a P value. All tests were bidirectional, and P values of less than 0.05 were considered statistically significant.

3. Results

A total of 1243 patients who met the inclusion criteria and none of the exclusion criteria were initially enrolled in this study. Of those, 192 (15.4%) patients were lost to follow-up due to death (n = 100), change of phone number (n = 68), or unwillingness to participate (n = 24). There was no difference in the baseline data between the respondents and the untraced patients ($P > 0.05$). Among the 1051 respondents, 601 (57.2%) were males. The mean age was 70.17 years. The baseline characteristics of the patients with and without PSS were shown in Table 1. Notably, 19 of the 24 patients with ES were males, and the difference in the sex ratio was statistically significant ($P = 0.028$). In the patients with ES, the incidence of atrial fibrillation ($P = 0.002$), hyperlipidemia ($P = 0.004$), and excessive drinking ($P = 0.047$) was significantly higher than in those without ES.

Table 2 presented the stroke characteristics, including the TOAST types, grades according to the NIHSS scores on admission and stroke location. Consistent with previous studies, the large artery atherosclerosis type, high NIHSS scores, and cortical involvement were found to be risk factors for PSS ($P < 0.001$).

Of the 1051 respondents, 933 had used statins. Among them, 904 (96.9%) used atorvastatin, 10 (1.1%) used rosuvastatin, and 19 (2.0%) used simvastatin. Intensive-dose statins were used by 334 (35.8%) patients, and the rest used a standard dose. Twenty-five (2.7%) patients started the statin therapy before stroke onset, 760 (81.5%) within three days after stroke onset, and 148 patients (15.8%) started it three days later. The majority of patients (875 or 93.8%) had continued to use statins for longer than two weeks, whereas 58 (6.2%) used them for a

Table 1
Baseline characteristics of patients with and patients without PSS.

	ES Yes No *P*	LS Yes No *P*	PSE Yes No *P*
Age (Mean ± SD)	71.17 ± 17.00 0.15 ± 12.04 0.685	68.68 ± 12.50 70.23 ± 12.15 0.727	67.36 ± 11.38 70.25 ± 12.18 0.215
Sex (males)	19(79.2%) 582(56.7%) 0.028	19(50.0%) 582(57.5%) 0.286	14(50.0%) 587(57.4%) 0.437
Hypertension	17(70.8%) 678(64.7%) 0.261	25(65.8%) 670(64.8%) 0.695	17(60.7%) 678(64.9%) 0.306
Diabetes mellitus	9(37.5%) 351(33.5%) 0.546	18(47.3%) 342(34.1%) 0.053	13(46.4%) 347(33.2%) 0.089
Atrial fibrillation	7(29.2%) 155(14.8%) 0.002	8(21.1%) 154(14.9%) 0.052	5 (17.9%) 157(15.0%) 0.484
Hyperlipidemia	3(12.5%) 286(27.3%) 0.004	11(28.9%) 278(26.9%) 0.561	9 (32.1%) 280(26.8%) 0.319
Smoking	6(25%) 293(28.0%) 0.415	10(26.3%) 289(27.9%) 0.217	7 (25.0%) 292(28.0%) 0.377
Excessive drinking	3(12.5%) 71(6.8%) 0.047	2 (5.3%) 72(7.0%) 0.421	2 (7.1%) 72(6.9%) 0.966

Abbreviations: SDStandard Deviation; ESearly-onset seizures; LSlate-onset seizures; PSEpost-stroke epilepsy; PSSpost-stroke seizures.

shorter period. The details of the statin therapy were summarized in Table 3.

As shown in Table 4, in patients with ischemic stroke, the statin treatment was associated with a lower risk of PSS, including ES (OR 0.240, 95% CI 0.100–0.573, $P = 0.001$), LS (OR 0.332, 95% CI 0.152–0.683, $P = 0.003$), and PSE (OR 0.301, 95% CI 0.130–0.700, $P = 0.005$); After adjusting for the confounding factors mentioned above, the difference was still significant (ES [OR 0.198, 95% CI 0.059–0.662, $P = 0.009$], LS [OR 0.273, 95% CI 0.106–0.699, $P = 0.007$], and PSE [OR 0.245, 95% CI 0.085–0.706, $P = 0.009$]).

Notably, intensive-dose statins may be more efficient in lowering the risk of PSS compared with standard-dose statins, both before (ES [OR 0.339, 95% CI 0.176–0.655, $P = 0.001$], LS [OR 0.437, 95% CI 0.258–0.741, $P = 0.002$], PSE [OR 0.402, 95% CI 0.220–0.736, $P = 0.003$] and after adjusting for confounding factors (ES [OR 0.261, 95% CI 0.108–0.630, P 0.003]; LS [OR 0.396, 95% CI 0.211–0.744, $P = 0.004$]; PSE [OR 0.356, 95% CI 0.171–0.740, $P = 0.006$]).

In addition, compared with the short-time use of statins, the long-course statin therapy could significantly lower the risk of PSE ($P < 0.05$) after an average follow-up of 2 years, as shown by the results before (OR 0.566, 95% CI 0.367–0.872, $P = 0.010$) and after adjusting for confounding factors (OR 0.516, 95% CI 0.303–0.879, $P = 0.015$).

Unexpectedly, no significant association between the time of therapy start and the risk of PSS was found in ES (unadjusted [OR 0.718, 95% CI 0.457–1.128, $P = 0.151$] and adjusted [OR 0.750, 95% CI 0.425–1.324, $P = 0.321$]), as well as PSE (unadjusted [OR 0.696, 95% CI 0.459–1.053, $P = 0.086$] and adjusted [OR 0.668, 95% CI 0.409–1.093, P 0.108]). As for LS, the association was statistically significant (OR 675, 95% CI 0.471–0.967, $P = 0.032$); however, after adjusting for confounding factors, the difference was no longer significant (OR 0.648, 95% CI 0.420–1.001, $P = 0.050$). Thus, the time of treatment start was not found to be related to the reduction in the risk of PSS.

Table 3
Statin therapy in patients with and patients without PSS.

Variables	Value	ES Yes	ES No	LS Yes	LS No	PSE Yes	PSE No
Statin use	yes	16	917	28	906	20	913
	no	8	110	10	108	8	110
Types	atorvastatin	15	889	27	877	20	884
	rosuvastatin	1	9	1	9	1	9
	simvastatin	1	18	0	19	0	19
Dose	intensive dose	3	331	6	328	4	330
	standard dose	13	586	21	577	16	582
Initial time	before stroke onset	1	24	2	23	1	24
	during the acute phase of stroke	8	752	19	741	12	748
	after the acute phase of stroke	8	140	7	141	7	141
Course	within 2 weeks	–	–	–	–	1	57
	longer than 2 weeks	–	–	–	–	19	

Abbreviations: ES = early-onset seizures; LS = late-onset seizures; PSE = post-stroke epilepsy; PSS = post-stroke seizures.

4. Discussion

Statins have been shown to have anticonvulsant effects in various fundamental experiments and clinical trials [12,14,15]. However, to the best of our knowledge, there are only two clinical studies on statins use in the prevention of PSS [13,19]. This study aimed to delineate the association between the details of specific statin therapy, including the types of statins, initial time, doses, and courses of treatment, and the risk of PSS on the basis of confirming that post-stroke statin exposure can reduce the risk of PSS. The main findings of the present study are that an intensive-dose statin treatment may exert better preventive effects for PSS, and that a prolonged statin therapy can significantly lower the risk of developing PSE, compared with the

short-course therapy. Our findings reveal for the first time the concrete association between statin therapy and the reduction of PSS

Table 2
Stroke characteristics of patients with and patients without PSS.

	ES Yes No *P*	LS Yes No *P*	PSE Yes No *P*
NIHSS scores < 0.001 < 0.001 < 0.001			
< 5	3(12.5%) 581 (46.6%)	4(10.5%) 546 (53.9%)	2 (7.1%) 548 (53.6%)
5-15	6(25.0%) 357 (34.8%)	8(21.0%) 375 (37.0%)	7 (25.0%) 376 (36.8%)
16-20	6(25.0%) 65 (6.3%)	10 (26.3%) 71 (7.0%)	7 (25.0%) 74 (7.2%)
> 20	9(37.5%) 24 (2.3%)	16 (42.2%) 21 (2.1%)	12 (42.9%) 25 (2.4%)
TOAST subtypes < 0.001 < 0.001 < 0.001			
Large artery atherosclerosis	13 (54.1%) 632 (61.5%)	23 (60.5%) 598 (59.0%)	18 (64.3%) 603 (59.0%)
Cardioembolism	8 (33.3%) 287 (28.0%)	10 (26.3%) 276 (27.2%)	7 (25.0%) 279 (27.3%)
Small vessel disease	1 (4.2%) 56 (5.5%)	2 (5.3%) 48 (4.7%)	0 (0.0%) 50 (4.8%)
Other determined etiology	1 (4.2%) 23 (2.2%)	1 (2.6%) 42 (4.2%)	1 (3.6%) 42 (4.1%)
Undetermined etiology	1 (4.2%) 29 (2.8%)	2 (5.3%) 49 (4.9%)	2 (7.1%) 49 (4.8%)
Stroke location < 0.001 < 0.001 < 0.001			
Cortical involvement	16 (66.7%) 340 (33.1%)	27 (71.1%) 356 (35.1%)	21 (75.0%) 362 (35.4%)
Subcortical stroke	8 (33.3%) 687 (66.9%)	11 (28.9%) 657 (64.9%)	7 (25.0%) 661 (64.6%)

Abbreviations: ES = early-onset seizures; LS = late-onset seizures; PSE = post-stroke epilepsy; PSS = post-stroke seizures.

Table 4
Association between statin therapy and PSS.

Variables	ES				LS				PSE			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
Statin use	0.240(0.100-0.573)	0.001	0.198(0.059-0.662)	0.009	0.332(0.152-0.683)	0.003	0.273(0.106-0.699)	0.007	0.301(0.130-0.700)	0.005	0.245(0.085-0.706)	0.009
Statin dose	0.339(0.176-0.655)	0.001	0.261(0.108-0.630)	0.003	0.437(0.258-0.741)	0.002	0.396(0.211-0.744)	0.004	0.402(0.220-0.736)	0.003	0.356(0.171-0.740)	0.006
Prescribing time	0.718(0.457-1.128)	0.151	0.750(0.425-1.324)	0.321	0.675(0.471-0.967)	0.032	0.648(0.420-1.001)	0.050	0.696(0.459-1.053)	0.086	0.668(0.409-1.093)	0.108
Course	–	–	–	–	–	–	–	–	0.566(0.367-0.872)	0.010	0.516(0.303-0.879)	0.015

Abbreviations: OR = Odds Ratio; 95% CI = 95% Confidence Interval; ES = early-onset seizures; LS = late-onset seizures; PSE = post-stroke epilepsy; PSS = post-stroke seizures.
Note"Adjusted" refers to the results after adjusting for confounding factors; "Unadjusted" refers to the results before adjusting for confounding factors.

risk, providing a preliminary reference for clinical practice.Statins are proven to reduce the risk of ES. Since ES are well known to be induced by metabolic and biochemical dysfunction. There are three possible mechanisms for the risk-lowering effect of statins. First, acute ischemia leads

to a significant increase in the glutamate level, which in turn may cause epileptiform discharges [6]. Statins are found to inhibit the excitotoxicity of glutamate by reducing its uptake [23,24], regulating the activity of the NMDA receptors [25,26], and adjusting the intracellular level of calcium [27]. Second, since inflammation could enhance the neuronal excitability and increase the blood brain barrier (BBB) permeability, resulting in an abnormal neuronal discharge and aggravating cerebral hypoxia, statins are speculated to produce anticonvulsant effects through

their anti-inflammatory actions, and by reducing the permeability of the BBB [27], upregulating the synthesis of endothelial nitric oxide [28–30], downregulating the expression of proinflammatory genes, attenuating the release of proinflammatory cytokines [21,26,31], increasing the synthesis of IL-10 [42], and inhibiting free radical formation and lipid peroxidation [26,32]. Third, a previous study has clearly stated that excitotoxic cell death in stroke may share some common pathogenesis with epilepsy [33]. Statins can promote neuronal survival by modulating the apoptosis pathways involved in Bax and Bcl, regulating the expression of pro-apoptotic and anti-apoptotic proteins, and increasing Akt phosphorylation [24,32,34].

Another important finding of the present study is that statin treatment can reduce the risk of LS and PSE. The pathophysiologic processes of LS and PSE, in which gliosis is a key factor, are quite different from those of ES. Statins can exert preventive effects on LS and PSE through suppressing reactive astrogliosis, which is in accordance with the results of previous studies [35,36].

Intensive-dose statins may exert more potent effects on PSS prophylaxis. Moreover, compared with the short-course therapy, statin therapy with a long course can significantly lower the risk of LS and PSE. Statins have pleiotropic neuroprotective effects, and they have been found to exert different effects at varying doses [38,39]. The dose of statins that can exert an anticonvulsant effect was found to be much higher than the necessary dose for inhibiting the cholesterol synthesis [25,37]. Another study conducted in rat models stated that high-dose atorvastatin can decrease the risk of epilepsy [21]. Fang et al. have reported that statins reduce the risk of PSE in a dose-dependent manner, that is, the higher the cumulative defined daily dose is, the lower the risk is [13]. These studies can help explain why, in this study, intensive-dose statins and a long-course therapy had better effects on PSS prevention. According to a a pioneering study conducted in animal models, low-dose statins also have an anticonvulsive effect [40]. This does not contradict to our finding that standard-dose statins do have an anticonvulsant effect; nonetheless, intensive-dose statins exert this effect more evidently.

According to their lipophilicity, statins can be divided into lipophilic agents (simvastatin, atorvastatin and lovastatin), which are capable of crossing the BBB, and lipophobic agents (pravastatin and rosuvastatin) [31,37]. Because of their different abilities to cross the BBB, statins are present at varying concentrations in the brain, which may influence their neuroprotective effects. However, because the number of patients who accepted the treatment with rosuvastatin or simvastatin in the study was quite small, we could not perform an effective subgroup analysis of the relation between statin type and PSS risk.

Disappointingly, no significant association between the moment of prescription and the risk of PSS was found in this study, which is inconsistent with the findings of a clinical observational study performed by Guo et al [19]. There are two possible explanations for this result. First, most of the patients in our study began using statins in the acute phase, immediately after stroke onset, due to the positive attitude towards the secondary prevention of stroke. Second, since the incidence of PSS is relatively low, the positive results were diluted by the large non-PSS population.

Moreover, there was a significant difference in the sex ratio among the patients with ES, that is, men with an ischemic stroke were more likely to develop ES than their female counterparts, which is in accordance with the findings of previous studies [8]; however, the reasons remain unclear.

The abnormal discharges of PSS can damage the neurons and thus worsen the prognosis of stroke, resulting in a high susceptibility to a second stroke, which in turn leads to the occurrence of a subsequent PSS [6]. Stroke and seizures seem to form a vicious cycle; therefore, PSS prophylaxis is as important as the secondary prevention of stroke. Various AEDs are effective for treating PSS; however, disappointingly, they are not recommended for PSS prophylaxis by the contemporary professional guidelines, because of their interaction profiles and potential side effects [43]. In addition, as stroke is the main cause of seizures in elderly people [15], the best PSS prophylaxis would be to prevent the initial stroke [11]. Statins, as classical neuroprotective agents, can improve the prognosis of stroke and prevent the occurrence of seizures. Compared with traditional AEDs, statins are more tolerable in the elderly population, have fewer interactions with other drugs, and have fewer side effects. Therefore, statins may be the best candidates for PSS prophylaxis.

This study has two main limitations. The first of them, related to the fact that this study was retrospective, is the range of the follow-up period, which should be similar in all the patients to reach a more reliable result. Moreover, both the range of the admission dates of patients and the range of the follow-up periods were relatively large

(about 2.5 and 3.5 years respectively), which may have affected the results to some extent, particularly regarding the prevalence of PSE. Second, the sample size in this study was relatively small (1051), and the patients considered to have taken intensive doses of statins, had done so during different periods longer than two weeks after the stroke onset. The result that intensive-dose statins may be more efficient in lowering the risk of PSS should be further investigated.

5. Conclusions

In this cohort study, we found that statins are effective for PSS prophylaxis, which is in accordance with the findings of previous clinical trials. This study has provided evidence for the first time that intensive-dose statins may be more efficient in lowering the risk of PSS. In addition, long-course statin therapy can help reduce the risk of developing PSE. Good patient care and reduction in the burden of PSS could be achieved if statin therapy becomes widely used for PSS prophylaxis as well as for routine secondary prevention of stroke. Nevertheless, because of the observational nature of this investigation, prospective studies or clinical trials with larger sample sizes are warranted to validate these findings.

Declaration of Competing Interest

None.

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