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ORIGINAL ARTICLE

Statin use prior to ischemic stroke onset is associated with decreased in-hospital mortality

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ABSTRACT

Statins can reduce the risk of stroke in at-risk populations and improve survival after acute ischemic stroke (AIS) among patients with previous statin use. This study aimed to investigate the impact of statin use before AIS onset on in-hospital mortality and identify the factors related to in-hospital mortality among patients with and without previous statin use. A retrospective cohort study of all patients with AIS attending hospital from June 1, 2008 to December 31, 2008. Data were collected from medical records including demographic information, diagnostic information, risk factors, previous statin use, and vital discharge status. Chi-square, Fisher's exact tests, student's *t*-test, and Mann–Whitney *U* test, whatever appropriate, were used to test the significance between the variables, and multiple logistic regression was used to identify factors associated with in-hospital mortality. Altogether, 386 patients with AIS were studied, of which 113 (29.3%) had a documented previous statin use. A total of 62 (16.1%) patients with AIS died in hospital. In-hospital mortality was significantly lower among previous statin users ($P = 0.013$). The presence of atrial fibrillation (AF) increased in-hospital mortality among patients with or without previous statin use. The independent predictors for in-hospital mortality among AIS patients without previous statin use were the presence of diabetes mellitus ($P = 0.047$), AF ($P = 0.045$), and renal impairment ($P < 0.001$). The prophylactic administration of statins significantly reduces post-AIS in-hospital mortality. Furthermore, the identification of predictors of in-hospital mortality might reduce death rates and enhance the application of specific therapeutic and management strategies to patients at a high risk of dying.

INTRODUCTION

Stroke is one of the most leading causes of significant disability and mortality worldwide [1]. Dyslipidemia is a well-established modifiable risk factor for vascular disease, especially ischemic heart disease (IHD) and acute ischemic stroke (AIS) [2]. Moreover, screening and better lipid control have shown a relative risk reduction for AIS [3,4] and an improvement of AIS outcomes [5,6].

Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] are widely used for the treatment of dyslipidemia. These agents have also been proven to significantly reduce the risk of AIS in at-risk populations [7,8]. Observational studies have also examined the effect of statin use before an AIS event on stroke-related outcomes. These studies show that among patients with AIS, previous use of statins is associated with better functional outcomes [5,6].

There is limited information on the mortality after AIS in hospitalized patients in the region, and none of these studies have taken previous statin use into consideration. In this study, we hypothesized that the prophylactic use of statins before AIS onset might lower the incidence of post-AIS in-hospital mortality. To present this hypothesis, we carried out an observational study to investigate the impact of statin use before AIS onset on in-hospital mortality and to identify the factors related to in-hospital mortality among AIS patients with and without previous statin use.

The results of this study might help reduce morbidity and mortality after AIS by enhancing the application of specific therapeutic and management strategies to patients at a high risk of AIS.

MATERIALS AND METHODS

Settings and study design

This is an observational retrospective cohort study of all patients diagnosed with AIS admitted to a 1200-bed hospital located in northern Malaysia. The hospital provides health care and emergency treatment for all illnesses and accidents. Before the initiation of this study, all aspects of the study protocol, including access to and use of patient clinical information, were authorized by the local health authorities.

Participants and data collection

Data were collected between June 1, 2008 and December 31, 2008. A computer-generated list was obtained from the hospital's record office. We identified our cases according to the International Classification of Diseases 10th revision (ICD-10). Patients with diagnostic codes I63.0–I63.9 (AIS) were included in the study. Patients' records were traced according to their identification card and hospital registration numbers. These cases were identified according to the discharge diagnosis documented in their medical records. The diagnosis of AIS was based on the World Health Organization definition of stroke and computerized tomography (CT) scan or magnetic resonance imaging (MRI) results [9]. By contrast, patients who discharged to another hospital or against medical advice were excluded from the study.

The primary outcomes of interest were the in-hospital mortality rate among patients with or without previous statin use and the factors of in-hospital mortality in the two groups.

Specially designed data collection forms were used to collect data from the medical records including demographic information, diagnostic information, risk factors, previous statin use, anticoagulant medication (oral, intravenous, or subcutaneous) used on admission, and vital status at discharge (alive or dead). Previous statin use was ascertained by identifying patients on any of the following statin drugs on admission: hydrophobic statins (such as lovastatin, atorvastatin, simvastatin, fluvastatin) and hydrophilic statin (such as pravastatin and rosuvastatin) [10]. The main risk factors considered in this study were hypertension, IHD, diabetes mellitus (DM), previous stroke attack, dyslipidemia, atrial fibrillation (AF), heart failure, and renal impairment. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, a physician diagnosis of hypertension or a patient's self-report of a history of hypertension or antihypertensive use. IHD was defined as a history of angina or myocardial infarction. DM was diagnosed based on a history of fasting blood glucose levels >7 mM from medical records of either diet-controlled, oral hypoglycaemic-treated or insulin-treated disease. Recurrent stroke was defined as a previous history of stroke attacks. Dyslipidemia was defined by the presence of one or more abnormal serum lipid concentrations. A previous history of AF was noted in addition to a screen for AF by the hospital physician from an electrocardiogram (ECG) performed either during the patient's hospital stay or from previous history for community-treated patients [11,12]. Heart failure was defined based on medical and family histories, a physical exam, or the results of tests that indicate any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood [13]. A serum creatinine concentration of ≥150 μM or at least 50% higher than baseline was selected as indicator of renal impairment because it is used in routine clinical practice to indicate the need for further evaluation [14].

Statistical analysis

Data were entered and analyzed using the Statistical Package for Social Sciences program version 15 (SPSS Inc., Chicago, IL, USA). Data were expressed as frequency (%) for categorical variables and mean ± SD for continuous variables. Variables that were not normally distributed were expressed as median (lower–upper quartiles). The chi-square or Fischer's exact tests, as appropriate, were used to test significance between categorical variables. An independent student's *t*-test was used to compare the means of continuous variables. If assumptions of the equality of variance and normality (assumed for the *t*-test) were not met, the Mann–

Whitney *U*-test was performed as appropriate. A *P*-value <0.05 was considered significant. Multiple logistic regression analysis was used to identify factors associated with in-hospital mortality. Variables included in the regression were those with significant *P* values (<0.05) in the univariate analysis.

RESULTS

During the study period, 410 patients with a diagnosis of AIS were admitted to the hospital. Of these, 24 patients were excluded. Thirteen patients were discharged against medical advice, and 11 were discharged to another hospital; therefore, the study population consisted of 386 patients.

The average age of those patients was 64.4 ± 12.4 years (range: 23.9–93.9). The majority (n = 240, 62.2%) were males; giving a male: female ratio of 1.64: 1. Chinese patients represented 54.1% (n = 209) of the study population, followed by Malays (n = 110, 28.5%) and Indians (n = 61, 15.8%). Other ethnic groups consisted of foreigners from neighboring Asian countries.

A total of 113 (29.3%) patients were on statin therapy before admission. Of them, 101 (89.4%) were on lovastatin, 10 (8.8%) were on simvastatin, one (0.9%) on atorvastatin, and only one (0.9%) on pravastatin; a hydrophobic statin.

Table I compares the clinical and demographic characteristics of patients with and without previous statin use. Patients on statins were more likely to have suffered a previous stroke attack ($P < 0.001$), hypertension ($P = 0.002$), dyslipidemia ($P < 0.001$), or IHD ($P < 0.001$) than patients without previous statin use. Therefore, those patients on statins before admission had a significantly higher median of the total number of chronic diseases than patients without statin use [3 (2–4) vs. 2 (1–3), $P < 0.001$].

Sixty-two (16.1%) of the patients with AIS died in hospital. In-hospital mortality was significantly lower among previous statin users ($P = 0.013$). Ten (8.8%) of the 113 patients on statins before admission died in hospital, compared with 52 (19%) of the 273 patients not on statins before (*Table I*). Moreover, there was no significant difference in the survival rate based on the type of statin as a hydrophobic or a hydrophilic statin type ($P = 0.754$).

The results of clinical characteristics analysis of AIS patients with previous statin use based on vital discharge status indicated that only AF ($P = 0.003$) was signifi-

Table I Baseline demographic and clinical characteristics of previous statin users and nonusers among patients with acute ischemic stroke.

Variables	Total (n = 386)	With previous statins (n = 113)	Without previous statins (n = 273)	P-value
Age (years), mean ± SD	64.4 ± 12.4	63.5 ± 11.2	64.8 ± 12.8	0.255[$]
Number of chronic diseases				
Mean ± SD	2.2 ± 1.2	2.8 ± 1.2	2.0 ± 1.1	<0.001[#]
Median	2	3	2	
[Q1–Q3]	[1–3]	[2–4]	[1–3]	
Gender				
Male	240 (62.2%)	78 (69%)	162 (59.3)	0.074
Female	146 (37.8%)	35 (31%)	111 (40.7%)	
Race				
Malay	110 (28.5%)	31 (27.4%)	79 (28.9%)	0.720
Chinese	209 (54.1%)	60 (53.1%)	149 (54.6%)	
Indian	61 (15.8%)	21 (18.6%)	40 (14.7%)	
Others	6 (1.6%)	1 (0.9%)	5 (1.8%)	
Stroke event				
First ever	268 (69.4%)	54 (47.8%)	214 (78.4%)	<0.001
Recurrent	118 (30.6%)	59 (52.2%)	59 (21.6%)	
Hypertension				
Present	328 (85%)	106 (93.8%)	222 (81.3%)	0.002*
Absent	58 (15%)	7 (6.2%)	51 (18.7%)	
Diabetes mellitus				
Present	187 (48.4%)	62 (54.9%)	125 (45.8%)	0.104
Absent	199 (51.6%)	51 (45.1%)	148 (54.2%)	
Dyslipidemia				
Present	162 (42%)	72 (63.7%)	90 (33%)	<0.001
Absent	224 (58%)	41 (36.3%)	183 (67%)	
Atrial fibrillation				
Present	26 (6.7%)	8 (7.1%)	18 (6.6%)	0.862*
Absent	360 (93.3%)	105 (92.9%)	255 (93.4%)	
Ischemic heart disease				
Present	72 (18.7%)	36 (31.9%)	36 (13.2%)	<0.001
Absent	314 (81.3%)	77 (68.1%)	237 (86.8%)	
Renal impairment				
Present	49 (12.7%)	20 (17.7%)	29 (10.6%)	0.057
Absent	337 (87.3%)	93 (82.3%)	244 (89.4%)	
Heart failure				
Present	8 (2.1%)	3 (2.7%)	5 (1.8%)	0.605*
Absent	378 (97.9%)	110 (97.3%)	268 (98.2%)	
Vital status at discharge				
Alive	324 (83.9%)	103 (91.2%)	221 (81%)	0.013
Dead	62 (16.1%)	10 (8.8%)	52 (19%)	

Q1–Q3, lower quartile to upper quartile; SD, standard deviation.
Categorical variables are expressed as frequency (%), whereas continuous variables are expressed as mean ± SD or median (lower quartile to upper quartile).
[$]Significance of differences estimated with the student's *t*-test.
[#]Significance of differences estimated with the Mann–Whitney *U* test.
*Significance of differences estimated with Fischer's exact test.

cantly associated with in-hospital mortality. However, among AIS patients without previous statin use, results showed that DM ($P = 0.011$), AF ($P = 0.027$), IHD ($P = 0.019$), renal impairment ($P < 0.001$), and heart failure ($P = 0.019$) were significantly associated with in-hospital mortality (*Table II*).

Table II Clinical characteristics of acute ischemic stroke (AIS) patients with and without previous statin use based on status at discharge.

	AIS patient with previous statin use *n* = 113			AIS patient without previous statin use *n* = 273		
Variables	Alive *n* = 103 (%)	Dead *n* = 10 (%)	*P*-value	Alive *n* = 221 (%)	Dead *n* = 52 (%)	*P*-value
Age (years), mean ± SD	62.6 ± 10.9	73.4 ± 9.7	0.369[$]	63.2 ± 12.8	71.3 ± 10.9	0.166[$]
Number of chronic diseases						
Mean ± SD	2.7 ± 1.16	3.3 ± 1.76	0.500[#]	1.9 ± 1.1	2.3 ± 1.3	0.024[#]
Median	3	3		2	2	
[Q1–Q3]	[2–4]	[2–4.25]		[1–3]	[1.25–3]	
Gender						
Male	73 (70.9)	5 (50)	0.173*	133 (60.2)	29 (55.8)	0.560
Female	30 (29.1)	5 (50)		88 (39.8)	23 (44.2)	
Race						
Malay	29 (28.2)	2 (20)	0.934	65 (29.4)	14 (26.9)	0.620
Chinese	54 (52.4)	6 (60)		117 (52.9)	32 (61.5)	
Indian	19 (18.4)	2 (20)		35 (15.8)	5 (9.6)	
Others	1 (1)	0 (0)		4 (1.8)	1 (1.9)	
Stroke event						
First ever	50 (48.5)	4 (40)	0.606*	175 (79.2)	39 (75)	0.509
Recurrent	53 (51.5)	6 (60)		46 (20.8)	13 (25)	
Hypertension						
Present	96 (93.2)	10 (100)	0.395*	182 (82.4)	40 (76.9)	0.366
Absent	7 (6.8)	0 (0)		39 (17.6)	12 (23.1)	
Diabetes mellitus						
Present	56 (54.4)	6 (60)	0.733*	93 (42.1)	32 (61.5)	0.011
Absent	47 (45.6)	4 (40)		128 (57.9)	20 (38.5)	
Dyslipidemia						
Present	66 (64.1)	6 (60)	0.798	79 (35.7)	11 (21.2)	0.051
Absent	37 (35.9)	4 (40)		142 (64.3)	41 (78.8)	
Atrial fibrillation						
Present	5 (4.9)	3 (30)	0.003*	11 (5)	7 (13.5)	0.027*
Absent	98 (95.1)	7 (70)		210 (95)	45 (86.5)	
Ischemic heart disease						
Present	34 (33)	2 (20)	0.399*	24 (10.9)	12 (23.1)	0.019
Absent	69 (67)	8 (80)		197 (89.1)	40 (76.9)	
Renal impairment						
Present	16 (15.5)	4 (40)	0.053*	15 (6.8)	14 (26.9)	<0.001
Absent	87 (84.5)	6 (60)		206 (93.2)	38 (73.1)	
Heart failure						
Present	2 (1.9)	1 (10)	0.130*	2 (0.9)	3 (5.8)	0.019*
Absent	101 (98.1)	9 (90)		219 (99.1)	49 (94.2)	
Anticoagulant						
Yes	5 (4.9)	0 (0)	0.476*	9 (4.1)	2 (3.8)	0.940*
No	98 (95.1)	10 (100)		212 (95.9)	50 (96.2)	

Q1–Q3, lower quartile to upper quartile; SD, standard deviation.

Categorical variables are expressed as frequency (%), whereas continuous variables are expressed as mean ± SD or median (lower quartile to upper quartile).

[$]Significance of differences estimated with the student's *t*-test.

[#]Significance of differences estimated with the Mann–Whitney *U* test.

*Significance of differences estimated with Fischer's exact test.

Table III shows the multivariate logistic regression analysis of factors related to in-hospital mortality among AIS patients without previous statin use. All the included variables had a significant *P* value in the univariate analysis based on status at discharge. Multiple logistic regression showed that the independent predictors for in-hospital mortality among AIS patients without previous statin use were the presence of DM ($P = 0.047$), AF ($P = 0.045$) and renal impairment ($P < 0.001$). The model was significant with a chi-squared of 31.87 (DF = 5, $P < 0.001$).

DISCUSSION

In this retrospective cohort study, there was a strong association between previous statin use and lower in-hospital mortality after AIS. A reduction in in-hospital mortality among patients taking statins was present even though statin users were more likely to have a higher number of major comorbid diseases, such as hypertension, IHD, prior stroke attack, and dyslipidemia, which are considered conditions that increase the risk of mortality after AIS and counteract the beneficial effects of statins on reducing the incidence of in-hospital mortality [15]. Moreover, the higher proportion of patients with a previous transient ischemic attack in the statins group could have triggered an ischemic tolerance [5].

In this study, the overall in-hospital mortality was 16.1%, which is within the range of mortalities reported from the surrounding regions. The in-hospital mortality was higher than previous studies carried out in Malaysia [16], Thailand [17], Singapore [18], or Japan [19], in which the mortality rate was 11.7, 10, 8.8, and 6%, respectively. But lower than the mortality rate observed in Pakistan 30.6% [20] and India 29.8% [21].

Table III Independent factors associated with in-hospital mortality among nonprevious statin users using multiple logistic regression analysis (enter method).

Variable	β	SE	Wald test	*P* value	Exp(β) [95% CI for Exp(β)]
Diabetes mellitus	0.677	0.341	3.941	0.047	2 [1–3.8]
Atrial fibrillation	1.143	0.571	4.002	0.045	3.1 [1–9.6]
Ischemic heart disease	0.777	0.431	3.253	0.071	2.2 [0.9–5.1]
Renal impairment	1.814	0.432	17.629	<0.001	6.1 [2.6–14.3]
Heart failure	1.503	0.987	2.320	0.128	4.5 [0.7–8.3]

β, Coefficient of the predictor variables; CI, confidence interval; SE, standard error.

The result of this study together with the results of a previous observational study supports the hypothesis that statin use before the onset of AIS reduces post-AIS in-hospital mortality [22]. However, in another study lower mortality among patients with previous statin use was also seen, but not significant [6]. The exact mechanisms by which statins benefit patients with AIS remain uncertain. Studies indicate that statins have multiple effects beyond lowering the cholesterol level [23,24]. Some of these effects could be neuroprotective [24]. In addition, statins might interfere with platelet aggregation or have anti-inflammatory, antioxidative, and antiapoptotic properties [24–27] and improve blood flow to the ischemic brain [27]. In our study, the appearance of previous statin use effect on mortality could suggest a greater cardioprotective effect [22].

By contrast, the valuable effects of statin treatment on AIS are weighed against the potential risks. Low cholesterol might be associated with hemorrhagic stroke [28]; however, in trials of patients with coronary artery disease, no increased risk of hemorrhagic stroke was noted among statin-treated patients [7]. Moreover, statin therapy might interfere with the neuroprotective effect of cholesterol [29,30].

The statin mainly used in our study was lovastatin. This is a hydrophobic statin [10]. Hydrophilic statins, such as pravastatin, have the most evidence for the secondary prevention of cardiac events [31]. However, in the present study, there was no significant difference in the survival rate based on the type of statin as a hydrophobic or a hydrophilic statin type ($P = 0.754$), and only 0.9% of our patients were taking a hydrophilic pravastatin drug.

Atrial fibrillation was significantly associated with in-hospital mortality among patients with and without previous statin use. This result might be because AF accounts for over one-third of all strokes over the age of 60 [32] and is associated with significant morbidity and increased mortality after AIS attack [33]. However, statin therapy has been associated with a reduction in the incidence and recurrence of AF in previous clinical trials [34,35] and might reduce the number of cardioembolic strokes [36].

Previous studies have shown that the presence of DM is a predictor of mortality after stroke attack [16,37]. However, in our study, a history of DM was only an

independent predictor of in-hospital mortality among patients without previous statin use. This result is consistent with previously reported results showing that pretreatment with statins among patients with diabetes is associated with a reduction in the risk of first stroke, improvement of stroke outcome, and reduction in poststroke mortality [38]. Therefore, guidelines have recognized the increase in cardiovascular and cerebrovascular risk in patients with diabetes and endorsed the use of statins for patients with diabetes, especially those at risk of cardiovascular disease [39].

In our study, renal insufficiency was also an independent predictor for in-hospital mortality among patients without previous use of statins. In previous studies, renal impairment has been shown to be a predictor of mortality after ischemic attack regardless of statin use [40,41]. An association between dyslipidemia and renal impairment has been described, and atherogenic mechanisms have been implicated in the progression of renal disease [42]. Moreover, a previous study showed that statin therapy was associated with a significant reduction in the deterioration of renal function [43].

Although this study is the first of its type in Malaysia, it had some limitations including its retrospective nature, so we cannot be sure of the lengths of statin treatments, which might affect the beneficial effect of statins [44]. Moreover, mortality was only assessed during the inpatient period and thereby mortality after discharge was excluded from the analysis. Finally, the beneficial effects of the adjunctive cardiac drug were not assessed in this study.

CONCLUSION

We believe that our study is an important step toward understanding the impact of statins on the improvement of post-AIS survival. It provides exploratory evidence that the prophylactic administration of statins reduces post-AIS in-hospital mortality, and it is a potential life-saving strategy. Furthermore, the identification of predictors for mortality during hospitalization might contribute to reducing death rates after AIS by enhancing the application of specific therapeutic and management strategies to patients at a high risk of dying.

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CONFLICT OF INTERESTS

We would like to declare that there is no conflict of interests in conducting this research.

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