ORIGINAL ARTICLE

Statin Promotes Neurological Improvement in Acute Ischemic Stroke in Resource-limited Settings: A Cross-sectional Study of A Secondary Referral Center in Indonesia

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ABSTRACT

Introduction: In limited resource settings where reperfusion therapy is inaccessible and unaffordable, identifying modifiable factors possibly mitigating neurological deficits is paramount. Statin is an affordable, widely available medication that has numerous pleiotropic effects beyond lipid-reducing, potentially beneficial in acute ischemic stroke. This study aims to evaluate factors associated with neurological improvement in acute ischemic stroke, particularly the role of statin, in a resource-limited setting. **Methods:** This study uses the stroke registry data from a secondary referral center in Indonesia between January 2023 until May 2024 and analyze the socio-demographic factors, onset-to-door time, past medical history, smoking, mean arterial pressure (MAP), body mass index (BMI), laboratory parameters, cardiac rhythm abnormality, chest X-ray results, non-contrast head computed tomography (NCCT) results, and therapy (oxygen supplementation, antihypertensive, antidiabetic medication, statins, dual anti-platelet therapy [DAPT], anticoagulant, and neuroprotector). **Results:** The majority of participants had minor (42.3%) and moderate stroke (42.3%) on admission. Fifty percent of the participants had neurological improvement on discharge. Multivariate analysis revealed a significant association between statin and neurological improvement in acute ischemic stroke, regardless of the lipid profile or duration of hospitalization. This finding highlighted possible mechanisms of statin other than cholesterol-lowering effects in improving neurological deficits. **Conclusion:** Statin use is significantly associated with neurological improvement in acute ischemic stroke, irrespective of cholesterol status. In resource-limited settings where definitive management is not an option, statin is a promising, readily available agent that promotes neurological improvement.
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Keywords: Statin, Pleiotropic Effect, Acute Ischemic Stroke, Outcome, Resource-limited

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INTRODUCTION

Stroke is defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin. Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction (1). The global prevalence of all types of ischemic stroke in 2020 was 89.13 million cases, 76.5% of which were ischemic stroke cases (2). Based on the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, stroke was also the third-leading cause of death and disability combined, as measured by disability-adjusted life-years (DALYs). Ischemic stroke was the largest contributor to total stroke DALYs, accounting for 63.48 million DALYs (3).

The prevalence of stroke in Indonesia, based on Riset Kesehatan Dasar (Riskesdas), increased by 18%, from 7 per 1,000 population in 2013 to 8.3 per 1,000 population in 2023 (4). In developing countries such as Indonesia, several obstacles hinder the optimal management of acute ischemic stroke (AIS), particularly the limited health expenditure and accessibility (5). Due to the

devastating consequences of stroke, the identification of potentially modifiable factors promoting neurological improvement is urgently needed.

Statin is a cholesterol-lowering agent with numerous reported pleiotropic effects, potentially beneficial in AIS (6). The cost-effectiveness of statin use in Indonesia has been established for Acute Coronary Syndrome patients with an incremental cost-effectiveness ratio (ICER) of 31.843.492 IDR (6 months average wage) per quality-adjusted life year (QALY) gained (7). Moreover, in Indonesia statin is an affordable and widely available medication covered by Badan Penyelenggara Jaminan Sosial Kesehatan (BPJS Kesehatan), the national health insurance program that provides access to healthcare services nationwide. This study aims to evaluate factors associated with neurological improvement in AIS, particularly the role of statin.

MATERIALS AND METHODS

This research was a pilot study using a cross-sectional, retrospective, analytical observational method conducted in an academic secondary care center in Jakarta, from January 1st, 2023 to May 31st, 2024. After ethical clearance and informed consent, data were collected using the Stroke Registry. The method of sampling was total sampling. The participants included in this research were adults (≥18 years old) diagnosed with AIS. The exclusion criterion was patients with disability due to neurological conditions other than stroke.

Stroke severity was quantified using the National Institutes of Health Stroke Scale (NIHSS) score, a widely used scoring system for assessing stroke severity (8). Measurements were done on the day of hospital admission and discharge. The outcome of this research was neurological improvement, defined as a minimum one-point decline in NIHSS score on discharge day compared to the NIHSS score on admission (9).

Factors studied in this research were sociodemographic factors (sex, age, education, and marital status), onset-to-door time, past medical history (hypertension, diabetes mellitus, dyslipidemia, cardiac disease, and transient ischemic attack [TIA]), smoking habit, mean arterial pressure (MAP), body mass index (BMI), laboratory parameters (anemia, leukocytosis, abnormal platelet count, hyperglycemia, renal impairment, hyponatremia, hypokalemia, hypocalcemia, and lipid ratios), cardiac rhythm abnormality based on electrocardiography (ECG), chest X-ray result (pneumonia and cardiomegaly), non-contrast head computed tomography (NCCT) result (acute and old infarction), and therapy (oxygen supplementation, antihypertensive, antidiabetic medication, statins, dual antiplatelet therapy [DAPT], anticoagulant, and neuroprotector).

Age was classified into two categories (<60 and ≥60 years old) (10). Level of education was classified into two categories using the cutoff of 9 years (11). Marital status was classified into married and unmarried (12). Onset-to-door time was classified into two categories using the cutoff of 4.5 hours, a cutoff point with a significant association with better clinical outcomes and lower NIHSS scores (13).

MAP was calculated using the blood pressure measured on admission and classified into two categories using the cutoff of 90 mmHg (14). Based on the World Health Organization's Asian BMI Classification, the participants were classified into overweight (≥23 kg/m2) and not overweight (15).

Laboratory results were categorized based on the normal values of the hospital laboratory. Renal function was classified based on the estimated glomerular filtration rate (eGFR) using 60 mL/minute/1,73 m2 as the cutoff (16). Lipid ratios included in this research were total cholesterol to high-density lipoprotein (TC/HDL) ratio, triglycerides to HDL (TG/HDL) ratio, and low-density lipoprotein to HDL (LDL/HDL) ratio. Cutoffs used for the lipid ratios were >3.47, >0.92, and >1.98, respectively (17). DAPT was defined as receiving any two antiplatelet agents with different mechanisms of action.

Data analysis was conducted using SPSS (Statistical Package for the Social Sciences) version 20.0. Chi-square or Fisher-exact tests were used as the bivariate analyses, as all independent variables were categorical. Step-wise logistic regression was used in the multivariate analysis.

ETHICAL CLEARANCE

This study was approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia No. 02/08/KEP-FKIKUAJ/2024.

RESULTS

A total of 78 AIS cases were included in this study. Demographic characteristics and past medical history are shown in Table I. The respondents were mostly female (53.8%), had a high education (61.5%), were married (78.2%), were non-smokers (82.1%), and had hypertension (80.8%).

Table I: Demographic Characteristics and Past Medical History of Participants

Variable		n (%)	Variable		n (%)
Sex	Male	36 (46.2)	TIA	No	76 (97.4)
	Female	42 (53.8)		Yes	2 (2.6)
Age (years)	<60	39 (50)	Hypertension	No	15 (19.2)
	≥60	39 (50)		Yes	63 (80.8)
Education (years)	<9	26 (33.3)	Dyslipidemia	No	45 (57.7)
	≥9	48 (61.5)		Yes	33 (42.3)
Marital status	Unmarried	16 (20.5)	DM	No	48 (61.5)
	Married	61 (78.2)		Yes	30 (38.5)
Smoking	No	64 (82.1)	Cardiac disease	No	72 (92.3)
	Yes	14 (17.9)		Yes	6 (7.7)
Onset-to-door time (hours)	≤ 4.5	13 (16.7)			
	> 4.5	65 (83.3)			
	Median (h)	20.18			

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack.

Table II showed that the majority of respondents were overweight (70.5%), had high MAP on admission (85.9%), leukocytosis (53.8%), hyperglycemia (65.4%), high TC/HDL ratio (70.5%), TG/HDL ratio (80.8%), and LDL/HDL ratio (73.1%). As seen in Table III, the medications given to the majority of participants were DAPT (61.5%), antihypertensives (67.9%), statins (92.3%), and neuroprotector (62.8%). Table IV showed that half of the respondents had neurological improvement upon discharge, with a median of 1-point improvement from their baseline NIHSS.

Table II: Baseline Clinical Characteristics of the Participants

Variable		n (%)	Variable		n (%)
MAP (mmHg)	≤ 90	11 (14.1)	**Renal impairment**	No	56 (71.8)
	> 90	67 (85.9)		Yes	18 (23.1)
Overweight	No	19 (24.4)	**TC/HDL ratio**	≤3.47	13 (16.7)
	Yes	55 (70.5)		>3.47	55 (70.5)
Anemia	No	60 (76.9)	**TG/HDL ratio**	≤0.92	3 (3.8)
	Yes	18 (23.1)		>0.92	63 (80.8)
Leukocytosis	No	36 (46.2)	**LDL/HDL ratio**	≤1.98	11 (14.1)
	Yes	42 (53.8)		>1.98	57 (73.1)
Platelet count	Normal	66 (84.6)	**Cardiac rhythm abnormality**	No	55 (70.5)
	Abnormal	12 (15.4)		Yes	8 (10.3)
Hyperglycemia	No	25 (32.1)	**Pneumonia**	No	67 (85.9)
	Yes	51 (65.4)		Yes	5 (6.4)
Hyponatremia	No	64 (82.1)	**Cardiomegaly**	No	44 (56.4)
	Yes	11 (14.1)		Yes	28 (35.9)
Hypokalemia	No	65 (83.3)	**Acute infarct**	No	36 (46.2)
	Yes	11 (14.1)		Yes	32 (41.0)
Hypocalcemia	No	52 (66.7)	**Old infarct**	No	17 (21.8)
	Yes	17 (21.8)		Yes	51 (65.4)

Abbreviation: HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; TC, total cholesterol; TG, triglycerides.

Table III: Therapy administered to Participants

Variable		n (%)	Variable		n (%)
Oxygen	Yes	23 (29.5)	**Antidiabetics**	Yes	26 (33.3)
	No	55 (70.5)		No	52 (66.7)
DAPT	Yes	48 (61.5)	**Statin**	Yes	72 (92.3)
	No	30 (38.5)		No	6 (7.7)
Anticoagulant	Yes	9 (11.5)	**Neuroprotector**	Yes	49 (62.8)
	No	69 (88.5)		No	29 (37.2)
Antihypertensive	Yes	53 (67.9)			
	No	25 (32.1)			

Abbreviation: DAPT: dual antiplatelet therapy

Bivariate analyses are presented in Table V, while Table VI depicts the adjusted association between neurological improvement and the significant factors found in bivariate analyses, namely no history of hypertension, no history of dyslipidemia, newly diagnosed anemia, oxygen supplementation, and statin therapy. In the present study, multivariate analysis demonstrated significant independent associations between neurological improvement and no history of dyslipidemia (adjusted odd ratio [AOR] 3.018, 95% CI 1.040 – 8.838), statin use (AOR 21.134, 95% CI 1.46 – 305.94), and oxygen supplementation (AOR 4.313, 95% CI 1.225 – 15.185).

Table IV: Acute Ischemic Stroke Severity based on National Institutes of Health Stroke Scale (NIHSS)

NIHSS Categories	n (%)	
	Admission	Neurological Improvement
No stroke symptoms (0)	6 (7.7)	0
Minor stroke (1-4)	33 (42.3)	12 (15.4)
Moderate stroke (5-15)	33 (42.3)	22 (28.2)
Moderate to severe stroke (16-20)	2 (2.6)	2 (2.6)
Severe stroke (21-42)	4 (5.1)	3 (3.8)
Total	78 (100)	39 (50)

Table V: Bivariate Analysis of Factors Associated with Neurological Improvement in the Participants

Variables	Category	Neurological improvement n (%)		P value	UOR (95% CI)
		Yes	No		
Demographics and Onset-to-door time					
Sex	Female	21 (50)	21 (50)	1.000	1.00 (0.411 – 2.436)
	Male	18 (50	18 (50)		
Age (years)	<60	20 (51.3)	19 (48.7)	0.821	1.108 (0.456 – 2.693)
	≥60	19 (48.7)	20 (51.3)		
Education (years)	≥ 9	25 (52.1)	23 (47.9)	0.864	1.087 (0.418 – 2.824)
	< 9	13 (50)	13 (50)		
Marital status	Married	29 (47.5)	32 (52.5)	0.535	0.705 (0.233 – 2.135)
	Unmarried	9 (56.3)	7 (43.8)		
Onset-to-door time (hours)	≤4.5	5 (38.5)	8 (61.5)	0.362	0.57 (0.168 – 1.928)
	>4.5	34 (52.3)	31 (47.7)		
Medical History and Smoking Habit					
Stroke	No	23 (48.9)	24 (51.1)	0.817	0.898 (0.363 – 2.226)
	Yes	16 (51.6)	15 (48.4)		
Hypertension	No	10 (66.7)	5 (33.3)	0.151	2.345 (0.719 – 7.649)
	Yes	29 (46)	34 (54)		
Dyslipidemia	No	27 (60)	18 (40)	0.039	2.625 (1.039 – 6.631)
	Yes	12 (36.4)	21 (63.6)		
DM	No	25 (52.1)	23 (47.9)	0.642	1.242 (0.498 – 3.098)
	Yes	14 (46.7)	16 (53.3)		
Cardiac disease*	No	35 (48.6)	37 (51.4)	0.675	0.473 (0.081 – 2.747)
	Yes	4 (66.7)	2 (33.3)		
TIA*	No	39 (51.3)	37 (48.7)	0.494	0.487 (0.386 – 0.613)
	Yes	0	2 (100)		
Smoking	No	31 (48.4)	33 (51.6)	0.555	0.705 (0.219 – 2.262)
	Yes	8 (57.1)	6 (42.9)		
Physical Examination					
MAP	Not high	6 (54.5)	5 (45.5)	0.745	1.236 (0.344 – 4.446)
	High	33 (49.3)	34 (50.7)		
Overweight	No	11 (57.9)	8 (42.1)	0.35	1.65 (0.575 – 4.734)
	Yes	25 (45.5)	30 (54.5)		
Ancillary tests					
Anemia	No	33 (55)	27 (45)	0.107	2.444 (0.810 – 7.374)
	Yes	6 (33.3)	12 (66.7)		
Leukocytosis	No	18 (50)	18 (50)	1.000	1.000 (0.411 – 2.436)
	Yes	21 (50)	21 (50)		
Platelet count	Normal	33 (50)	33 (50)	1.000	1.000 (0.292 – 3.422)
	Abnormal	6 (50)	6 (50)		
Hyperglycemia	No	11 (44)	14 (56)	0.372	0.645 (0.246 – 1.691)
	Yes	28 (54.9)	23 (45.1)		
Hyponatremia	No	31 (48.4)	33 (51.6)	0.708	0.783 (0.217 – 2.827)
	Yes	6 (54.5)	5 (45.5)		
Hypokalemia	No	32 (49.2)	33 (50.8)	0.817	1.164 (0.323 – 4.196)
	Yes	5 (45.5)	6 (54.5)		
Hypocalcemia	No	24 (46.2)	28 (53.8)	0.948	0.964 (0.322 – 2.889)
	Yes	8 (47.1)	9 (52.9)		
Renal impairment	No	20 (48.8)	21 (51.2)	0.98	1.012 (0.404 – 2.532)
	Yes	16 (48.5)	17 (51.5)		
TC/HDL ratio	≤3.47	8 (61.5)	5 (38.5)	0.297	1.920 (0.557 – 6.615)
	>3.47	25 (45.5)	30 (54.5)		
TG/HDL ratio*	≤0.92	1 (33.3)	2 (66.7)	1.000	0.516 (0.045 – 5.986)
	>0.92	31 (49.2)	32 (50.8)		
LDL/HDL ratio	≤1.98	7 (63.6)	4 (36.4)	0.274	2.087 (0.549 – 7.925)
	>1.98	26 (45.6)	31 (54.4)		
Cardiac rhythm abnormality*	No	29 (52.7)	26 (47.3)	1.000	1.115 (0.253 – 4.917)
	Yes	4 (50)	4 (50)		
Pneumonia*	No	33 949.3)	34 (50.7)	1.000	0.647 (0.102 – 4.124)
	Yes	3 (60)	2 (40)		
Cardiomegaly	No	21 (47.7)	23 (52.3)	0.629	0.791 (0.306 – 2.045)
	Yes	15 (53.6)	13 (46.4)		
Acute infarction	No	18 (50)	18 (50)	0.606	0.778 (0.299 – 2.024)
	Yes	18 (56.3)	14 (43.8)		
Old infarction	No	10 (58.8)	7 (41.2)	0.575	1.374 (0.452 – 4.172)
	Yes	26 (51)	25 (49)		
Therapy					
Oxygen therapy	Yes	15 (65.2)	8 (34.8)	0.082	2.422 (0.882 – 6.65)
	No	24 (43.6)	31 (56.4)		
DAPT	Yes	26 (54.2)	22 (45.8)	0.352	1.545 (0.617 – 3.873)
	No	13 (43.3)	17 (56.7)		
Anticoagulant*	Yes	6 (66.7)	3 (33.3)	0.481	2.182 (0.505 – 9.434)
	No	33 (47.8)	36 (52.2)		
Antihypertensive	Yes	28 (52.8)	25 (47.2)	0.467	1.425 (0.548 – 3.709)
	No	11 (44)	14 (56)		
Antidiabetic	Yes	14 (53.8)	12 (46.2)	0.631	1.26 (0.49 – 3.237)
	No	25 (48.1)	27 (51.9)		
Statin*	Yes	38 (52.8)	34 (47.2)	0.200	5.588 (0.621 – 50.249)
	No	1 (16.7)	5 (83.3)		
Neuroprotector	Yes	25 (51)	24 (49)	0.815	1.116 (0.445 – 2.797)
	No	14 (48.3)	15 (51.7)		

*Fisher exact test

Abbreviation: CI, confidence interval; DAPT, dual antiplatelet therapy; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MAP, mean arterial pressure; TC, total cholesterol; TIA, transient ischemic attack; UOR, unadjusted odd ratio.

DISCUSSION

Consistent with various studies across Indonesia, the majority of AIS patients were non-smokers, had hypertension, and had no history of dyslipidemia or diabetes (18–20). Most of the respondents had onset-to-door time of >4.5 h, with a median of 20.18 h, which was longer than another similar study conducted in Surabaya (10.58 h) (21).

History of dyslipidemia has been proven to be a significant independent risk factor for ischemic stroke, with associations particularly strongest for the atherosclerotic subtype (22,23). However, there are still limited studies exploring its association with neurological outcomes, both deterioration and improvement. The present study shows that the absence of a history of dyslipidemia is a significant predictor of neurological improvement after adjusting for history of hypertension, anemia, oxygen, and statin therapy. Without dyslipidemia, the endothelium is not predisposed to cholesterol deposition and chronic inflammation – the two main processes of

atherosclerosis – hence a healthier blood vessel and lower risk of ASCVD (Atherosclerosis Cardiovascular Disease) (24).

The relationship between traditional lipid parameters and the incidence of ischemic stroke has been well-established (23). Additionally, traditional lipid parameters have been reported to be predictive of neurological outcomes (25–27). In an attempt to optimize the predictive capacity of the lipid profile, there is a growing body of literature investigating lipid ratio parameters as predictors for ischemic stroke and neurological outcomes. Most evidence supports the lipid ratios as a predictor of AIS (17,28).

The capacity of lipid ratios to predict neurological outcomes in AIS is still an underexplored area of research. A nonlinear relationship between TG/HDL ratio and the risk of unfavorable 3-month outcomes (modified Rankin Scale ≥3) in AIS patients has been established with an inflection point of 3.515. Each 1-unit decrease in TG/HDL ratio was associated with a 22.6% lower risk of unfavorable outcomes (OR 0.774, 95% CI 0.656 – 0.914), whereas each 1-unit increase propels the risk of unfavorable outcomes by 19.5% (OR 1.195, 95% CI 1.004 – 1.423) (29). Among AIS patients receiving mechanical thrombectomy, a low TG/HDL ratio was a significant independent predictor of parenchymal hemorrhage after mechanical thrombectomy with an AUC (area under the curve) of 0.704 (95% CI 0.612 – 0.796) (30). From the opposite viewpoint, evaluating associations between lipid ratios and neurological improvement, the present study did not find any (TC/HDL, TG/HDL, and LDL/HDL ratios). This might be due to the cutoffs used, which were meant to predict the incidence of ischemic stroke. To date, there is no available research discussing the cutoffs of the lipid ratios for predicting neurological improvement, prompting studies exploring the appropriate cutoffs for the outcome of interest.

Our result shows a significant independent association between statin administration and neurological improvement regardless of current cholesterol status. Additionally, the statin administration in the present study was relatively short (4.73 ± 3.09 days). These findings further emphasize other mechanisms of statin (other than lipid-reducing effect), which play a role in improving neurological deficits. No large randomized trial has been conducted to evaluate the effect of statin on neurological improvement in AIS patients not receiving reperfusion therapy. It was associated with good functional outcomes (modified Rankin scale of 0 – 2 at 3 months) in the aforementioned subpopulation (OR 3.68, 95% CI 1.13 – 12.01) (31). This knowledge gap is yet to be elucidated and thus becomes a potential area for research. Meanwhile, in AIS patients receiving intravenous thrombolysis, statin use was significantly related to NIHSS improvement, both low-intensity (OR 4.697) (32) and high-intensity (OR 9.47, 95% CI 1.98 – 45.37) (33).

Through multiple large-scale studies, the effect of statin on neurological outcomes has been attributed to their pleiotropic effect beyond lipid-lowering (6,22). Possible cholesterol-independent mechanisms can generally be divided into five, which are anti-inflammatory, immunomodulation, reduction of oxidative stress, enhancement of endothelial function, and plaque stabilization (34).

Insults to the brain, such as ischemic stroke induce reactive oxidative stress (ROS) production, which mediates blood-brain barrier (BBB) disruption. Statin anti-inflammatory effect was the downregulation of nuclear factor-κB (NF-κB), activator protein-1, and hypoxia-inducible factor-1α in endothelial and arterial smooth muscle cells, which have roles in the downstream activity of pro-inflammatory molecules. Statin also has direct antioxidant properties by scavenging free radicals and decreasing macrophage activity to oxidize lipoproteins (34). By attenuating the inflammation, statin potentially ameliorates BBB dysfunction in ischemic stroke (35).

When the endothelium is injured and becomes dysfunctional, it releases endothelium-derived nitric oxide (NO), leading to vasodilation, inhibition of leukocyte adhesion and platelet aggregation, and reduced vascular smooth muscle proliferation. Statin upregulates endothelial NO synthase (eNOS) and thus increases the protective NO bioavailability. Long-term high-intensity statin therapy has been shown to promote plaque stabilization and induce atheroma regression (36).

Several unfavorable side effects have been associated with statin therapy, which are also attributed to its pleiotropy. The most common adverse effect is statin-associated muscle symptoms (SAMS), which occur in around 5 – 20% of statin users. Other rare complications of statin include clinically relevant hepatotoxicity (±0.001%), rhabdomyolysis (<0.1%), and statin-induced newly diagnosed diabetes mellitus (±0.2%) (37). Nevertheless, statin use is generally safe, and the benefits greatly outweigh the risks.

Lack of public awareness regarding the emergency nature and warning signs of stroke, which warrant prompt evaluation and treatment, contributes to pre-hospital delay in AIS (21), deterring patients from obtaining reperfusion therapy. Furthermore, the main challenge that hinders the implementation of definitive stroke management is the paucity of healthcare resources, for example, the uneven distribution of neurologists and trained medical professionals, as well as the unavailability and inaccessibility of neuroimaging and the costly hyperacute stroke therapy which is only limited in tertiary care center (38). In the limited

resource setting where the only possible treatment is a conservative approach, the identification of therapy that possibly mitigates neurological deficits is of the utmost importance. Statin is a promising, readily available modality that likely promotes neurological improvement in AIS, irrespective of cholesterol status. Statin administration possibly yields even further neurological improvement since it is associated with favorable functional outcomes when administered longer (39).

Statin use in AIS is recommended based on the discussion above, and fortunately, the medication is covered by the Indonesian National Health Insurance for ASCVD (40). A dilemma persists around the safety of statin administration in hemorrhagic stroke, as concern arises regarding the potential elevated risk of recurrent intracerebral hemorrhage, further emphasizing the importance of determining the type of stroke. Unfortunately, only 372 out of 3,200 hospitals have CT scan facilities nationwide (5), which further complicates determining the type of stroke. Favorably, recent statin trials failed to show an association between statin administration and increased hemorrhagic stroke risk in patients with a prior history of hemorrhagic or ischemic stroke (41,42). Hence, statin prescription is generally safe in both types of stroke in settings where the type of stroke is impossible to determine.

To address stated issues, collaboration between academic institutions, medical associations, and government agencies is mandatory. Research focus should be shifted toward identifying measures promoting neurological improvements whose implementation is feasible in low-resource settings, alongside regulatory actions in overcoming disparities in healthcare expenditure and accessibility nationwide. Early education and large-scale campaigns emphasizing stroke symptoms recognition and immediate activation of emergency medical services utilizing digital media are reasonable in hopes of raising community awareness, thereby shortening the pre-hospital delay and subsequently increasing the number of cases eligible for definitive therapy.

The current study has several limitations, the most important of which are the limitations inherent to cross-sectional design, the sample size, and the varying time of neurological improvement assessment. As this is a retrospective, cross-sectional study, causation cannot be inferred, and temporal bias is a concern. Nevertheless, to answer the limitations posed by the cross-sectional design, we included all clinical factors listed in our National Stroke Registry that may affect outcome in the study analysis.

Regarding sample size, we acknowledge that our limited sample size may contribute to the wide confidence interval of the adjusted odds ratio shown on the association between neurological improvement and statin use, reflecting high variability and possibly limited power of the association. Thus, while a statistical relationship is reported, the clinical significance of this study may not be generalizable to other resource-limited settings.

The varying time of neurological improvement assessment may introduce bias and affect comparability across subjects. However, it should be noted that each patient came with varied levels of stroke severity and consequently needed varied durations of hospitalization. The NIHSS data obtained during discharge reflects a certain level of uniformity, i.e, the time when each patient was deemed stable enough for discharge. Moreover, this variability reflects the real-world clinical setting in which data were collected, where follow-up intervals often depend on patient condition, access to care, and institutional workflow. While we recognize this as a potential source of bias, we believe that the overall trends observed remain robust and provide valuable insight, especially given the limited existing data on this topic.

This study contributes to the field of research and epidemiology by providing the incidence and characteristics of AIS cases in a secondary referral center in Indonesia. To the best of our knowledge, the present study is the pioneer to explore the associations between statin administration and neurological improvement in AIS with conservative therapy. Further research with a multicentre cohort design investigating the effect of longer administration of statin on neurological improvement is needed, in addition to identifying factors that can be executed in limited-resourced settings.

CONCLUSIONS

Statin use is a significant independent factor of neurological improvement in AIS in a secondary care center in Indonesia, which may be attributed to its pleiotropic mechanisms beyond anti-dyslipidemic effects. Statin administration is feasible in a limited-resource setting where reperfusion therapy is unavailable.

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