

# Predictors of Unachieved LDL Levels in Ischemic Stroke Patients Treated with Statins in Yogyakarta Indonesia

Amelia Rumi<sup>1</sup>, Jarir Atthobari<sup>2</sup>, Rizaldy Pinzon<sup>3</sup>, Agung Endro Nugroho<sup>1</sup>

<sup>1</sup>Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, University Gadjah Mada Yogyakarta Indonesia, <sup>2</sup>Department of Pharmacology and Therapy, Faculty of Medicine, University Gadjah Mada Yogyakarta Indonesia, <sup>3</sup>SMF Neurology Department Bethesda Hospital of Yogyakarta Indonesia.

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## ABSTRACT

Ischemic stroke occurs due to barriers in cerebral vascular. The barriers are manifestation of atherosclerosis formation. Statins are widely used in patients with high level of LDL. The aim of the study was to investigate the factors that influence the Unachieved LDL levels in ischemic stroke patients treated with statin. The study was an analytical research performed using a nested case-control study. The subjects were ischemic stroke patients based on inclusion criteria, and treated with statin. The patients were classified into case group if the result of medical record and the stroke register showed the LDL level of the patients was  $>100$  mg/dL. Whereas the ischemic stroke patients with LDL level  $<100$  mg/dL were classified into control group. Clinical characteristics were investigated in the study including gender, age, comorbid conditions, co-medication, initial LDL levels, amount of comorbid and characteristics of statin treatment. The results were then analyzed using bivariate and multivariate analysis. In the study, 236 patients of ischemic stroke met the inclusion criteria. The results showed that patients with highest initial LDL level ( $p=0.003$ ;  $OR=2.618$ ;  $CI95\%=1.398 - 4.904$ ) and patients with more than one comorbid ( $p=0.006$ ;  $OR=3.058$ ;  $CI95\%=1.376 - 6.796$ ) had the most significant contributions on Unachieved LDL level. However, gender, age, comorbid conditions, co-medication, and characteristics of statin treatment did not have specific contribution on Unachieved LDL level. The predictor factors that play significant role in Unachieved LDL level in ischemic stroke patients were patients with a very high initial LDL level ( $\geq 190$  mg/dL) and patients with one more than comorbid.

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## INTRODUCTION

Stroke is a main cause of serious disabilities worldwide. Stroke can immediately be a common cause of death worldwide. At present stroke is the second major cause of death in the West. The stroke incident increases exponentially for 30 years, and the etiology is various pursuant to age (WHO, 2012; Depkes RI, 2006). Based on the data collected by the Indonesian Stroke Foundation, the stroke issues is getting more important and urgent because the amount of stroke patients in Indonesia is the largest and first rank in Asia (Yastroki, 2012). Stroke is a cerebrovascular disease that occurs suddenly and causes neurologic damage. The neurologic damage can be caused by the existence of total or

partial blockage on one or more of cerebral vessels, then hampers the blood stream to brain. The obstacle generally occurred as result of the rupture of blood vessels or blockage of blood vessels by clots (Ikawati, 2011). The brain blood stream is an amount of blood flows to the brain and influenced by several factors such as blood viscosity, ability of vasodilatation, pressure of cerebral perfusion. The increase of blood viscosity is regarding to the lipid metabolism disorders, one of supporting theory of atherosclerosis formation (Gofir, 2012). All human plasma lipids are transported into circulation as protein complexes. Metabolism disorder involving the increase of plasma lipoprotein concentration is called hyperlipoproteinemia or hyperlipidemia. One of main clinical of hyperlipoproteinemia is atherosclerosis (Rang et al, 2003). Atherosclerosis causes serious health diseases such as coroner heart disease, stroke and peripheral vascular disease. Atherosclerosis, particularly the cerebral vascular, is a causative factor in most cases of ischemic stroke (Dipiro et al, 2008).

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### \* Corresponding Author

Prof. Agung Endro Nugroho, Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Sekip Utara Yogyakarta, Indonesia. Tel: (0274)543120, Fax: (0274)543120.  
Email : [agugendronugroho@gmail.com](mailto:agugendronugroho@gmail.com); [nugroho\\_ae@ugm.ac.id](mailto:nugroho_ae@ugm.ac.id)

Atherosclerosis is a systemic disease that can influence entire vascular events. Therefore, the steps to prevent the systemic atherosclerosis will influence the second risk of ischemic stroke and ischemic heart disease. The risk factors of atherosclerosis and ischemic are smoking, hypertension, diabetic and high cholesterol level. There is very interesting evidence on a clinical study that the reduction on LDL and cholesterol levels decreased the risk of first stroke. The LDL can cause the plaque formation in artery. For diabetic patients and patient having a stroke previously or transient ischemic attack, aggressive reduction on the LDL level using statin will reduce the risk of fatal stroke (Marsh and Keyrouz, 2010). Intervention on the patients with ischemic stroke to control the risk factors is using statin drugs. Statin has been proven to reduce the stroke risk about 30% on patient with coroner artery disease and the increase of plasma lipid (Grundy *et al.*, 2004).

In Indonesia, the number of stroke patients is very high and the cost for patient treatment is also very high. The investigation of predictor factors for the Unachieved LDL levels in patients with ischemic stroke treated with statin is very important indicator in assessing the therapeutic efficacy and the quality of ischemic stroke patient treatment.

## METHODS

### Subject

The subject of the study was ischemic stroke patients who receive treatment in Stroke Unit in a private hospital of Yogyakarta. We included all patients with following criteria: ischemic stroke patients with statin, age more than 18 years, disease history related to risk factor on the increase in LDL.

### Methods and analysis

The study was an analytical research performed using a nested case-control study. This study compared between the case group i.e. ischemic stroke patients who treated with statin that the LDL level did not reach <100 mg/dL, and control group which reach LDL level <100 mg/dL. The study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine University Gadjah Mada, Ministry of Education and Culture Indonesia (Reference number : KE/FK/271/EC 2013.).

The analysis of predictor factors on Unachieved LDL levels was using a descriptive analysis method of ischemic stroke patients in a private hospital of Yogyakarta. The data consist of total of patients, gender, age, payment status, primary diagnosis (ischemic stroke), and secondary and main predictor factors of Unachieved LDL levels. The analysis of patient characteristic was using descriptive method to observe the data characteristic of each group. Then, we conducted analysis using chi square from the bivariate analysis, and the logistic regression of multivariate analysis.

## RESULT

### *Predictor Factors of Unachieved LDL Levels*

Ischemic stroke patients were divided into two groups, i.e. case group and control group. The clinical characteristics

observed in the study were gender, age and patients comorbid (hypertension, dyslipidemia, renal disorders, cardiovascular diseases and diabetes mellitus). The data were then analyzed using bivariate chi square. The analysis of this study was showed in Table 1. In Table 1, the number of male and female patients who did not reach target were 45.5% and 55.9% ( $P>0.05$ ), respectively. Evidence of Unachieved LDL levels in age above 55 years old on case group were 48.8%. The high number of female patient with age above 55 years old in the study was showed in Table 2. Table 1 showed that the number of more and less than 55 years old ischemic stroke patients were 170 and 66, respectively. In the study, a main comorbid accompanied in the ischemic stroke was hypertension (53.8%). High hypertension case was related to Unachieved LDL levels (<100 mg/dL). The patient with hypertension who did not reach the targeted-LDL levels was 50.4% in comparison to who reach the targeted-LDL levels (49.6%). The other comorbid conditions accompanied in ischemic stroke were diabetes mellitus (32.6%), dyslipidemia (28.8%), renal disorders (19.1%) and cardiovascular diseases (8.1%). The significance of these bivariate chi square analysis were showed in Table 1.

In this study, we investigated the significance of the effect of each co-medication given to the patient on LDL levels. Results of factor analysis of the influence of co-medication predictors given to patients were presented in Table 3.

In Table 3, the treatment of anticoagulants in patients with ischemic stroke influenced the Unachieved LDL levels. However, the anticoagulants provided a protective effect on ischemic stroke to achieve the LDL level <100 mg/dL. The significance value was 0.037, and OR was 0.558 (CI 95% 0.321 – 0.969). It means that the ischemic stroke patients using anticoagulant and simultaneously using statins had a lower probability in Unachieved LDL level (<100mg/dL) than who did not use the anticoagulant.

Table 4 showed the analysis of the effect of initial LDL level on Unachieved LDL level (<100mg/dL) with statin. Patients with very high initial LDL level condition ( $\geq 190$  mg/dL) had 64.9% higher risk to not achieve the targeted-LDL ( $P<0.05$ ). It means that the use of statins in ischemic stroke patients has a high probability in Unachieved LDL level if the patients have very high initial LDL level condition ( $\geq 190$  mg/dL). The use of statin will be useful if it used in patients with mild and moderate initial LDL level condition.

The ischemic stroke patients who came to the hospital had various levels of severity. The severity level was closely related to the number of comorbid in ischemic stroke. In the study, we evaluated the influence of the number of comorbid on Unachieved LDL level (<100mg/dL) with statin. Results of factor analysis of the influence of the number of comorbid were presented in Table 5. This table showed that the number of comorbid influenced the Unachieved LDL level (<100mg/dL) with statin. The number of patients with more than one comorbid

(59,9%) who did not achieve the targeted-LDL level (<100mg/dL) was much higher than this with one comorbid (35,3%).

The characteristics of statin treatment on ischemic stroke patients also can influence the Unachieved LDL levels (<100 mg/dL). These characteristics are type of statins, dosage, patient compliance, combination with other drug and duration of statin treatment. Results of factor analysis of the influence of characteristics of statin treatment were presented in Table 6.

#### *Relationship of Predictor Factor and Unachieved LDL Levels*

The predictor factors had significance value  $p < 0.05$  on analysis of bivariate chi square, then continued with analysis of multivariate using logistic regression to evaluate the most influencing factor on Unachieved LDL level (<100 mg/dL) on ischemic stroke patients with statin. In the study, these predictor factors included for next analysis (multivariate logistic regression) based on analysis of bivariate chi square were treatment of anticoagulant ( $p = 0.037$ ), the very high initial LDL ( $p = 0.003$ ), and patients with more than one comorbid ( $p = 0.032$ ).

In Table 7, the analysis of logistic regression showed that predictor factors having most influence on Unachieved LDL levels were the very high initial LDL ( $\geq 190$  mg/dL) ( $p = 0.003$ ), and patients with more than one comorbid ( $p = 0.006$ ). Beside these factors, the patients compliance factor in consumption of the drugs and statin medication schedule might influence Unachieved LDL level (<100 mg/dL).

## **DISCUSSION**

Male patients have a higher risk in stroke than female patients especially at post menopause age. In pre-menopause female and in menstruation condition, ferritin, a substance promoting a risk for coroner heart, can be controlled. In addition, the presence of estrogen contributes a protection effect on high level of blood cholesterol. Estrogen has antioxidative effect so that it can prevent the oxidation processes of LDL and vasodilate the blood vessels (Pamela, 2008; Aaronson et al, 2012).

Comorbid is a disease diagnosed in ischemic stroke patients that can influence the clinical response. Hypertension is a disease that influences about 65 million people in US and a major risk factor of infark in brain. There is a closely relationship between blood pressure and cardiovascular risk (Sacco et al, 2006). Hypertension patients after the stroke attack, the body produces excessive catecholamines thus can cause the peripheral resistance. The catecholamine is a substance having catecol structure. One of them is adrenaline, thus the catecholamines effect on heart mediated by the receptor  $\beta_1$  including increasing of heartbeat, increasing of heart contractility, and increasing of endothelial dysfunction that form atherosclerosis plaque.

In this study, the diabetes mellitus (DM) is a second largest comorbid after hypertension. DM is related to systemic plasma metabolism disorders that can cause atherosclerosis plaque on blood vessel walls.

The atherosclerosis plaque is a cause of ischemic stroke. The diabetes mellitus accelerates the formation of atherosclerosis in small blood vessel (microangiopathy) and large blood vessels (macroangiopathy) including the blood vessel around the brain blood vessels. The DM is related to endothelial damage, oxidized LDL, and blood coagulation due to elevations on inhibition of plasminogen activator and on thrombocyte aggregation capabilities. Diabetic patient with endothelial damage can be observed on high level of blood LDL and glucose.

Patients with dyslipidemia condition is related to lipid metabolism disorder characterized by an alteration in the fraction of fat in the blood, such as increase in total cholesterol, LDL cholesterol and triglyceride levels, and decrease in HDL level. Statins function as an inhibitor of HMG coenzyme-A reductase to inhibit cholesterol synthesis in the liver, however can cause an increase the number of LDL receptors. The statin also causes plaque stabilization.

To obtain optimal results in the treatment of ischemic stroke patients, combination therapy should be performed between some classes of drugs, among others, such as thrombolytic agents used to lysis thrombus. The lysis can help to restore restore blood flow to the brain. In addition therapy to treat the risk factor and comorbid are also very important as drugs to treat hypertension, dyslipidemia, cardiovascular disease and diabetes mellitus.

Long term of simultaneous oxidation of LDL can be vascular damage and thrombus formation through atherosclerosis process (Braunwald et al, 2012). In this process, anticoagulant acts to inhibit the clotting cascade, and then prevents thrombin formation (Aaronson et al, 2012; Bassand, 2008). In addition, the statin functions to stabilize the plaque, reduce the formation of thrombus, as an anti-inflammatory agent, and reduce lipid oxidation (pleiotropic effect) by increasing the LDL receptor. Combination between anticoagulant and statin is subjected to prevent the formation of new thrombus.

The fat and cholesterol are particles that do not dissolve in the blood, so in the body require transporter namely lipoprotein. LDL is one of the most important lipoprotein because LDL contains the most cholesterol so LDL is the main cholesterol transporter in blood (Soeharto, 2004). High of LDL level is related to a high risk factor of ischemic stroke, stroke attack, hypertension, hyperglycemia, etc. Post ischemic stroke condition also causes a high level of initial LDL on ischemic stroke patients so that influence the Unachieved LDL levels.

In the study, we also found that the use of statins is difficult to achieve the targeted-LDL levels if it was used in patients with more than one comorbid and very high initial LDL level condition ( $\geq 190$  mg/dL). Based on the facts, the use of statin in these patients needs to consider the standard lipid management guidelines, type of statins, dosage, patient compliance, combination with other drug and duration of statin treatment.

**Table 1:** The analysis of bivariate chi square regarding to the influence of predictor factors on Unachieved LDL levels (<100 mg/dL).

Predictor Factors	LDL level does not reach <100 mg/dL		P	OR	CI 95%
	Case (%) (n=118)	Control (%) (n=118)			
Gender					
a. Female	57 (55.9)	45 (44.1)	0.115	1.516	0.903 – 2.545
b. Male	61 (45.5)	73(54.5)		Ref.	
Age Group					
a. ≥55 years old	83 (48.8)	87 (51.2)	0.562	0.845	0.478 – 1.493
b. <55 years old	35(53)	31(47)		Ref.	
Comorbid Type (%)					
a. Hypertension history					
- Hypertension	64 (50.4)	63 (49.6)	0.896	1.035	0.620 – 1.726
- Normotensive	54 (49.5)	55(50.5)		Ref.	
b. Dyslipidemia history					
- Dyslipidemia	33 (48.5)	35 (51.5)	0.774	0.921	0.524 – 1.618
- Normal	85(50.6)	83 (49.4)		Ref.	
c. Renal disorders history					
- Renal disorders	21 (46.7)	24 (53.3)	0.619	0.848	0.442 – 1.625
- Normal	97 (50.8)	94 (49.2)		Ref.	
d. Cardiovascular disease history					
- Cardiovascular disease	11 (57.9)	8 (42.1)	0.473	1.414	0.547 – 3.651
- Normal	107 (49.3)	110 (50.7)		Ref.	
e. Diabetes mellitus history					
- Diabetes mellitus	40 (54.8)	33 (45.2)	0.324	1.321	0.759 – 2.299
- Normal	78 (47.9)	85 (52.1)		Ref.	

p (p value),

OR (Odds Ratio),

CI (Confidence Interval 95%)

**Table 2:** The characteristic of ischemic patients based on gender and age in a private hospital in Yogyakarta.

Age	Gender	
	Female (%)	Male (%)
Above 55 years old	76 (44.7)	94 (55.3)
Under 55 years old	26 (39.4)	40 (60.6)

**Table 3:** The analysis of bivariate chi square regarding to the influence of co-medication given to patients on Unachieved LDL level (<100 mg/dL).

Predictor Factors	LDL level does not reach <100 mg/dL		P	OR	CI 95%
	Case (%) (n=118)	Control (%) (n=118)			
a. The treatment of antihypertension					
- Yes	58(50)	58(50)	1.000	1.000	0.600 – 1.666
- No	60(50)	60(50)		Ref.	
b. The treatment of antiplatelet					
- Yes	107 (49.8)	108 (50.2)	0.819	0.901	0.367 – 2.09
- No	11 (52.4)	10 (47.6)		Ref.	
c. The treatment of anticoagulant					
- Yes	31 (40.3)	46 (59.7)	0.037	0.558	0.321 – 0.969
- No	87 (54.7)	72 (45.3)		Ref.	
d. Central NeuroSystem (CNS) Protection					
- Yes	91 (49.2)	94 (50.8)	0.635	0.862	0.463 – 1.601
- No	27 (52.9)	24 (47.1)		Ref.	
e. Antidiabetic oral medicine					
- Yes	30 (58.8)	21 (41.2)	0.115	1.575	0.840 – 2.950
- No	88 (47.6)	97 (52.4)		Ref.	
f. The treatment of insuline					
- Yes	3 (33.3)	6 (66.7)	0.499	0.487	0.256 – 9.674
- No	115 (50.7)	112 (49.3)		Ref.	
g. The treatment of lipid-lowering agent					
- Yes	2 (66.7)	1(33.3)	1.000	2.017	0.180 – 22.553
- No	116(49.8)	117 (50.2)		Ref.	

p (p value)

OR (Odds Ratio)

CI (Confidence Interval 95%)

**Table 4:** The analysis of bivariate chi square regarding to the influence of initial LDL levels on Unachieved LDL level (<100 mg/dL).

Predictor Factors	LDL level do not reach<100 mg/dL		P	OR	CI 95%
	Case (%) (n=118)	Control (%) (n=118)			
Early LDL levels (mg/dL)					
a. Very high (≥190)	48 (64.9)	26 (35.1)	0.003	3.231	1.484 – 7.033
b. High (160-189)	31(50)	31(50)	0.164	1.750	0.794 – 3.858
c. High limit (130-159)	23 (41.1)	33 (58.9)	0.632	1.220	0.541 – 2.750
d. Near Optimal (100-129)	16 (36.4)	28 (23.7)		Ref.	

p (p value)

OR (Odds Ratio)

CI (Confidence Interval 95%)

**Table. 5:** Analysis of bivariate chi square regarding to the influence of comorbid on Unachieved LDL level (<100 mg/dL).

Predictor Factors	LDL level do not reach <100 mg/dL		P	OR	CI 95%
	Case (%) (n=118)	Control (%) (n=118)			
- More than One comorbid	82 (59.9)	55 (40.1)	0.032	2.361	1.061 – 5.250
- One comorbid	24 (35.3)	44 (64.7)	0.743	0.864	0.359 – 2.077
- No comorbid	12 (38.7)	19 (61.3)		Ref.	

p (p value)  
OR (Odds Ratio)  
CI (Confidence Interval 95%)

**Table. 6:** The analysis of bivariate chi square regarding to the influence of predictor factor on characteristics of statin treatment.

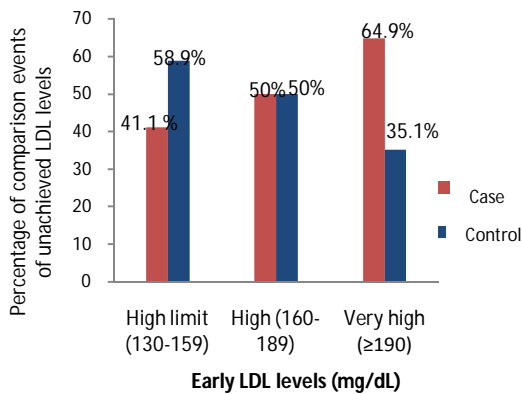
Predictor Factors	LDL level do not reach <100 mg/dL		P	OR	CI 95%
	Case (%) (n=118)	Control (%) (n=118)			
a. Type of statin					
- Simvastatin	90 (49.7)	91 (50.3)	1.000	0.989	0.240 – 4.076
- Atorvastatin	24 (51.1)	23 (48.9)	1.000	1.043	0.233 – 4.673
- Rosuvastatin	4 (50)	4 (50)		Ref.	
b. DDD statin					
- <1 DDD	98 (49.5)	100 (50.5)	0.723	0.882	0.440 – 1.767
- ≥1 DDD	20 (52.6)	18 (47.4)		Ref.	
c. Simvastatin dosage					
- Simvastatin 10 mg	79 (48.2)	85 (51.8)	0.170	0.465	0.152 – 1.419
- Simvastatin 20 mg	10 (66.7)	5 (33.3)		Ref.	
d. Atorvastatin dosage					
- Atorvastatin 10 mg	8 (47.1)	9 (52.9)	0.760	0.830	0.250 – 2.752
- Atorvastatin 20 mg	15(51.7)	14 (48.3)		Ref	
e. Medication Possession Ratio (MPR)					
- <50%	49 (43.8)	63 (56.2)	0.190	0.652	0.344 – 1.239
- 50 – 80%	38(56.7)	29 (43.3)	0.795	1.099	0.540 – 2.237
- >80%	31 (54.4)	26 (45.6)		Ref.	
f. Statin Use Dosage					
- <4 weeks	106 (50.7)	103 (49.3)	0.540	1.286	0.575 – 2.880
- ≥4 weeks	12 (44.4)	15 (55.6)		Ref.	

p (p value)  
OR (Odds Ratio)  
CI (Confidence Interval 95%)

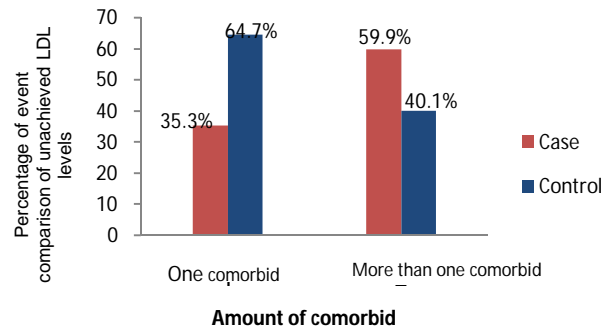
**Table. 7:** Multivariate analysis logistic regression based on the results of analysis of bivariate chi square

Predictor Factors	Coefficient	P	OR	CI 95%
Anticoagulant	-0.557	0.060	0.573	0.321 – 1.023
<b>Very high early LDL</b>	<b>0.962</b>	<b>0.003</b>	<b>2.618</b>	<b>1.398 – 4.904</b>
<b>More than one comorbid</b>	<b>1.118</b>	<b>0.006</b>	<b>3.058</b>	<b>1.376 – 6.796</b>
Constants	-0.516	0.123	0.597	

p (p value)  
OR (Odds Ratio)  
CI (Confidence Interval 95%)



**Fig. 1:** The percentage of Unachieved LDL level between the case and control groups against initial LDL level of ischemic stroke patients who treated with statin in a private hospital in Yogyakarta.



**Fig. 2:** The percentage of Unachieved LDL level between case and control groups against the amount of comorbid on ischemic patients who treated with statin in a private hospital in Yogyakarta.

## CONCLUSION

The predictor factors which playing significant role in Unachieved LDL level in ischemic stroke patients were patients with a very high initial LDL level ( $\geq 190$  mg/dL) and patients with more than one comorbid. Therefore, these ischemic stroke patients treated with statins need to consider the standart lipid management guidelines, type of statins, dosage, patient compliance, combination with other drug and duration of statin treatment.

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