



**KEMENTERIAN PENDIDIKAN NASIONAL  
UNIVERSITAS HASANUDDIN  
FAKULTAS KEDOKTERAN  
KOMISI ETIK PENELITIAN KESEHATAN**

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**REKOMENDASI PERSETUJUAN ETIK**  
Nomor : 0372 /H4.8.4.5.31/PP36-KOMETIK/2013

Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Hasanuddin, setelah melalui pembahasan dan penilaian, pada rapat tertanggal **6 Maret 2013**, telah memutuskan, protokol penelitian berjudul:

*Clinical Features of Transient Ischemic Attack (TIA) or Ischemic Stroke (IS) Patient with High Risk of Stokr Recurrence using Essen Stroke Risk Score in Indonesia*

dengan Peneliti Utama: **dr. Akbar.,SpS, PhD**

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yang diterima pada tanggal: **18 Februari 2013**

Perbaikan diterima tanggal: **14 Maret 2013**

**dapat disetujui untuk dilaksanakan di Indonesia.**

Persetujuan Etik ini berlaku sejak tanggal ditetapkan sampai dengan batas waktu pelaksanaan penelitian.

Pada akhir penelitian, **laporan pelaksanaan penelitian** harus diserahkan kepada KEPK Fakultas Kedokteran Unhas. Jika ada perubahan protokol dan /atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian (amandemen protokol).

Makassar, 15 Maret 2013

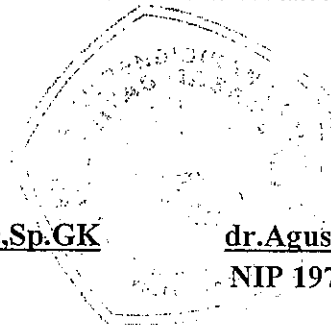
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## ORIGINAL ARTICLES

# Clinical features of transient ischemic attack or ischemic stroke patients at high recurrence risk in Indonesia

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### Abstract

**Background:** In Indonesia, stroke is the leading cause of death. Identification of patients with transient ischemic attack (TIA) or ischemic stroke (IS) at high risk of recurrent stroke is important as part of the disease management. The Essen Stroke Risk Score (ESRS) is one of the predictive scores to identify patients with high or low risk of recurrence. The purpose of this disease registry is to explore clinical profiles of TIA and IS patient with high risk of stroke recurrence using ESRS in Indonesia and to understand how the patients were managed as compared to the National guideline. **Methods:** This is a multicenter, non-interventional, prospective disease registry. The disease registry was designed to mirror real life management of TIA and stroke patients with inclusion criteria of patients 18 years old or older with recent first time TIA or ischemic stroke and with ESRS 3 or more. The follow up period was 3 months. **Results:** Among 395 subjects, 357 of subjects (90.38%) completed the follow up visit. Hypertension was the most prevalent risk factor (92.2%). Majority of subjects had ESRS 3 and 4 (72.2% and 23.3%, respectively). The National guideline was followed in only 32.7% of subjects in baseline and 37.3% at follow up visit. The comparison of parameters between baseline and follow up visit for 357 subjects showed clinical improvement.

**Conclusion:** This registry showed the clinical profiles of TIA and IS in Indonesian patients. An ESRS of 3 was recorded in majority of the subjects. Majority of subjects were not treated according to the National guideline.

**Keywords:** Essen Stroke Risk Score (ESRS); ischemic stroke; transient ischemic attack; disease registry

### INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality worldwide. At the beginning of this millennium, approximately 5.4 million individuals died from stroke worldwide.<sup>1</sup> In ASEAN countries, stroke is one of top four leading causes of death. In Indonesia stroke is the leading cause of death among people above five years of age,

comprising 15.4% of all deaths according to a community-based Basic Health Research survey performed by the Indonesian Ministry of Health on 2007.<sup>1-3</sup>

There are several known risk factors for stroke, such as older age, hypertension, diabetes mellitus, smoking, hyperlipidemia and obesity. A hospital-based survey of 28 hospitals in Indonesia,

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which included 2,065 acute stroke patients, found that mean age of stroke was 58.8 years. Hypertension (73.9%) is the most common risk factors, followed by smoking (20.4%), heart disease (19.9%), history of stroke (19.9%) and diabetes (17.3%).<sup>3,4</sup>

Patients who have transient ischemic attack (TIA) or ischemic stroke (IS) have higher risk of recurrence. It is estimated that the recurrence rate after TIA and IS range from 5–20% per year. The recurrence risk is even higher in the first few days after a TIA or IS. Overall, the cumulative recurrence rates at 1, 5, and 10 years were: 10.0%, 34.1%, and 49.7% after ischemic stroke, respectively.<sup>5</sup> Therefore, identification of patients with TIA or IS at high risk of recurrent stroke is an important aspect of patient's management to prevent future disease burden.<sup>6</sup>

Several predictive scores for cerebrovascular patients have been proposed and some have also demonstrated external validity. The Essen Stroke Risk Score (ESRS) is one of the predictive scores that can be utilized to identify patients with high or low risk of recurrence. The ESRS was derived from the data subset of 6,431 patients with ischemic stroke in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.<sup>7</sup>

In contrast to other validated scales, the ESRS is easy to calculate and shows an almost linear increase of risk. On a 10-point scale, the ESRS could help to predict the 1-year risk of recurrent stroke. Low risk categories (score 0 – 2) and the higher risk category (score  $\geq$  3) can be easily distinguished. The ESRS has been validated in 3 observational studies as well as in the European Stroke Prevention Study-2 (ESPS-2).<sup>7-10</sup>

Recently, the ESRS has been validated in the Chinese stroke population and the overall cumulative 1-year recurrent stroke event rate was 16%. According to Chinese stroke population, IS and TIA Patients with high ESRS stratification (ESRS3–9) were found to have twelve-month cumulative rates of recurrent stroke around 20% and 21%, respectively.<sup>10</sup> This registry, however, was not designed to validate ESRS in the study population.

Several stroke guidelines, including the current National guideline in Indonesia by Indonesian Neurological Association (INA) / Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI) 2011 emphasized the importance of reducing the recurrent risk of stroke in the management of patients with a recent ischemic stroke or TIA. The strategy includes the use of

antiplatelet, management of hypertension, diabetes or dyslipidemia, as well as recommendations to modify any high-risk behavior or life-style such as cigarette smoking, alcohol consumption and physical inactivity.<sup>11</sup>

Along with the above measures, treatment with antiplatelet has important role for medical stroke prevention in patients with TIA or stroke of non-cardio embolic stroke etiology. In patients with TIA or ischemic stroke of non-cardiac origin, antiplatelet drugs can decrease the risk of stroke by 11 – 15%. The composite risk of stroke, myocardial infarction (MI) and vascular death is also reduced by 15 – 22%.<sup>12</sup>

The aim of this disease registry is to explore the clinical feature of TIA and ischemic stroke patients with high risk of stroke recurrence using ESRS in Indonesia. It is also important to understand how the patients were managed by their treating physicians according to the current National guideline.

## METHODS

This is an observational registry study with a multicenter, non-interventional prospective disease registry. The design of the registry mirrors the real life management of TIA and stroke patients in Indonesia. Patients 18 years or older with recent first time clinically-defined TIA or ischemic stroke with ESRS 3 or more were eligible for this registry. Stroke is defined as 'a clinical syndrome consisting of rapidly developing clinical signs of focal (or global in case of coma) disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than a vascular origin'. A TIA is defined as stroke symptoms and signs that resolve within 24 hours.<sup>13</sup> Patients with suspected cerebrovascular disease (CVD) in whom the image studies show cerebral hemorrhagic events or another non-vascular cerebral lesion, cerebrovascular event confirmed to have originated from cardiac source of embolus, cancer, renal insufficiency, cardiac insufficiency, and thrombolytic or other acute intervention is indicated were excluded from the study. For hospitalized subjects, the baseline visit was performed upon hospital discharge. The subjects were followed up by neurologists after 3 months.

Risk factors (diabetes, cardiovascular disease, smoking history, and high blood pressure) were defined as per ESRS criteria. The clinical parameter assessment was assessed by physical examination in 2 visits. Laboratory parameters

that were included in this analysis were blood glucose, HbA1C, total cholesterol, low density lipoprotein (LDL), and high-density lipoprotein (HDL). Compliance to treatment was based on the subjective opinion from treating physicians during subject's visit based on interview with subjects.

Descriptive analysis was performed on the database. Qualitative data were summarized in frequency tables, and quantitative data were summarized in quantitative descriptive statistics (mean, standard deviation, median, and range). Comparisons and statistical tests were performed using 2-tailed test at 5% level of significance.

## RESULTS

The disease registry consists of 395 subjects from 18 participating study centers, with 50.1% of them was diagnosed on the same day. The sex ratio of subject was 1.4 males for every 1 female with an average age of 64.5 years. Anthropometrically the subjects varied highly with a minimum body weight of 40 to a maximum of 134 kilograms, while the waist circumference was ranged from 35 to 174 cm. Two major ethnics were Javanese and Sundanese. The median of stroke onset was 0 day with a range from 0 to 42 days. The majority of subjects (98.7%) had ischemic type of stroke, and only 5 (1.3%) subjects suffered TIA. Most of the subjects were diagnosed using CT (computerized tomography) scan modality (81.8%) and only 18.2% of subjects were diagnosed using MRI (magnetic resonance imaging). Majority of subjects (72.2%) had ESRS 3, 23.3% with score 4, and 4.5% have a score of 5 or more.

Hypertension was the most prevalent risk factor for stroke with 92.2% followed by old age with 81.3%. High cholesterol, diabetes, cardiac diseases, and smoking were other important risk factors with prevalence of 52.7%, 45.6%, 41.5%, and 40% respectively. Less frequent risk factors were physical inactivity (30.4%), family history of stroke (27.1%), and obesity (7.1%). Other factors accounted for 14.0% (see Table 1).

Table 2 shows that 12.9% of subjects were not prescribed an antiplatelet as recommended by the guideline (aspirin 80 – 325 mg or clopidogrel 75 mg or combination of low dose aspirin 25 mg with extended release dipyridamole 200 mg). Antiplatelet drugs were previously prescribed for 98.5% of cases with most of them (89.9%) receiving a single drug type (see Table 1). Clopidogrel was the most common antiplatelet drug previously prescribed (57.7%), followed

by acetyl-salicylic acid (44.8%). Cilostazole was prescribed to 6.1% subjects, warfarin was prescribed for 0.8%, while dabigatran and nimbokinase were prescribed to 0.3% of subjects.

Among patients with hypertension only 75.6% of them received antihypertensive drug according to the guideline, while 71.5% of the patient with hyperlipidemia received drug as recommended by the guideline. Treatment for diabetes risk factor had the least consistency to National guideline with only 15.0% of patients received antidiabetic regimen according to the guideline. Overall, subjects with co-morbid conditions as mentioned in the guideline (hypertension, hyperlipidemia, and diabetes), 129 (32.7%) of them were treated according to the guideline.

At the admission, almost all subjects (92.7%) were hospitalized with an average length of stay of 8.6 days. There were no documented complication in 87.6% of subjects who were hospitalized, while 5.1% of subjects had complications during their hospital stay. Pneumonia was the most prevalent complication, followed by hematemesis and urinary tract infection.

The follow-up chart shows that only 357 stroke patients completed 3-months follow up. Thirty-three subjects were lost to follow up. Three subjects withdrew their consent and the other two subjects died during the follow-up period (Figure 1). Subjects who dropped out from the study were included in the analysis for baseline visit. These subjects were on average younger than the overall study population (less than 55 years: 21.1% vs 17.0%) and generally had lower incidence of diabetes (31.6% vs 45.6%) and smoking history (28.9% vs 40.0%). However, the difference was not statistically significant indicating that the baseline characteristics of subjects who dropped out were in general similar to the overall study population, except for the "others" group with combined other risk factors (Table 1).

The disease registry found that 94.4% of subjects were prescribed with single antiplatelet drug at the follow up visit. A combination of antiplatelet regimen was prescribed to 4.2% of subjects. There were 5 subjects (1.4%) who were not given any antiplatelet.

For those who completed the follow up visit, the treatment still did not entirely conform to the National guidelines.<sup>10</sup> Table 2 shows that 7.8% of subjects were not prescribed antiplatelet drug according to the guidelines. For patients with hypertension, only 84.5% of them received the recommended antihypertensive drug regimen,

**Table 1: Demographic and Baseline of the study subjects (n = 395)**

Variables	Overall study population	Dropped out (n = 38)	p value
Female patients, n (%)	165 (41.8)	17 (44.7)	0.73
Age (years)	64.5 +/- 10.1	63.2 +/- 10.4	0.45
Age group, n (%)			
Less than 55 years	67 (17.0)	8 (21.1)	
55 – 64 years	109 (27.6)	12 (31.6)	
65 – 74 years	160 (40.5)	14 (36.8)	
Over 74 years	59 (14.9)	4 (10.5)	
Length of diagnosis, n (%)			
The same day	198 (50.1)	22 (57.9)	0.36
1 – 7 days	142 (36.0)	12 (31.6)	0.59
Over 1 week	55 (13.9)	4 (10.5)	0.56
Types of stroke, n (%)			
Ischemic	390 (98.7)	36 (94.7)	0.06
TIA	5 (1.3)	2 (5.3)	0.06
Essen Stroke Risk Score, n (%)			
Score 3	285 (72.2)	28 (73.7)	0.08
Score 4	92 (23.3)	9 (23.7)	0.96
Score 5 and over	18 (4.5)	1 (2.6)	0.58
Previous antiplatelet drug, n (%)			
Combined drugs	34 (8.6)	5 (13.9)	0.28
Single drug	355 (89.9)	33 (86.8)	0.55
No medication	6 (1.5)	0 (0)	0.45
Risk Factors, n (%)			
Hypertension	364 (92.2)	37 (97.4)	0.24
Over 55 Years	321 (81.3)	29 (76.3)	0.45
High Cholesterol	208 (52.7)	20 (52.6)	0.99
Diabetes	180 (45.6)	12 (31.6)	0.09
Cardiac	164 (41.5)	17 (44.7)	0.70
Smoking	158 (40.0)	11 (28.9)	0.18
Inactivity	120 (30.4)	8 (21.1)	0.23
Family History	107 (27.1)	7 (18.4)	0.24
Obesity	28 (7.1)	2 (5.3)	0.68
Others (PAD, HHD, hyperuricemia, etc)	55 (14.0)	10 (26.3)	0.04

PAD: peripheral artery disease; HHD: hypertensive heart disease

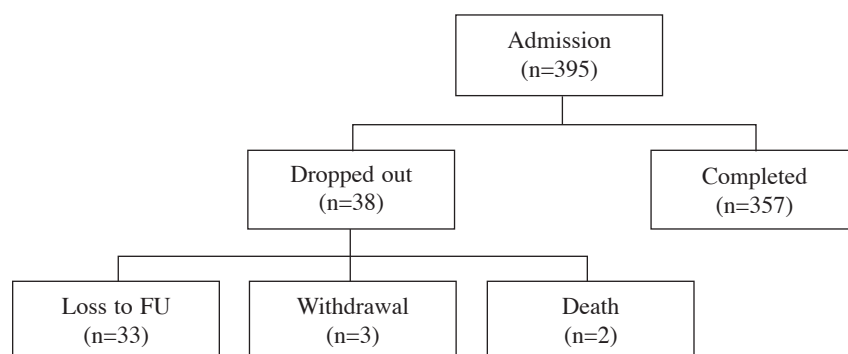


Figure 1. Completion rate of study and reasons for drop out

**Table 2: Distribution of treatment according to National guideline at baseline**

evaluation basis	Baseline (n=395)			Follow Up Visit (n=357)		
	n	Followed	Not followed	n	Followed	Not followed
		n (%)	n (%)		n (%)	n (%)
Antiplatelet medication	395	344 (87.1)	51 (12.9)	357	329 (92.2)	28 (7.8)
Antihypertension treatment	373	282 (75.6)	91 (24.4)	335	283 (84.5)	52 (15.5)
Antihyperlipidemic drug	214	153 (71.5)	61 (28.5)	193	131 (67.9)	62 (32.1)
Antidiabetic medication	213	32 (15.0)	181 (85)	198	34 (17.2)	164 (82.8)
Total evaluation	395	129 (32.7)	266 (67.3)	357	133 (37.3)	224 (62.7)

while 67.9 % of the subject with hyperlipidemia received medication according to the guideline. Treatment for diabetes was the least consistent with the guideline recommendation with only 17.2% of subjects received antidiabetic regimen as stated in the guidelines. Overall, for subjects with co-morbid conditions as mentioned in the guidelines, 133 (37.3%) of them were treated according to the guidelines.

The compliance rate for stroke therapy was evaluated during follow up visit, with 76.8% of subjects showed good compliance, 20.7% showed moderate compliance, and only 2.5% of subjects showed poor compliance as classified by investigators. Due to the small number of subjects, the poorly compliant subjects were combined with moderate compliant subjects to be compared to those with good compliance.

The patients' compliance to the treatment was

not influenced by either gender type or the length of diagnosis. The statistical difference between gender was not significant (p value = 0.268) while the length of diagnosis has a p value of 0.071. However, older patients, especially patients aged more than 75 years old, had significantly (p=0.015) lower compliance compared to younger patients (Table 3).

The comparison of all clinical and laboratory parameters between baseline and follow up visit for 357 patients showed clinical improvement. Table 4 shows that systolic blood pressure was improved most with 14.7%, followed by blood glucose tests. Total cholesterol showed good improvement, but LDL and HDL cholesterol showed rather lesser improvement.

Table 4 also shows significant reduction of clinical signs and symptoms among subjects who completed follow up visit. Complaints regarding

**Table 3: Distribution of subjects according to compliance and factors (n=357)**

Determinant	Compliance		p value
	Poor/Moderate (n=83)	Good (n=274)	
Gender type			
Male	44	164	0.268
Female	39	110	
Age group			
<55 year	11	48	0.015
55 – 64 year	19	78	
65 – 74 year	31	115	
75 + year	22	33	
Length of diagnosis			
The same day	50	126	0.071
1-7 days	23	108	
Over one week	10	40	

Note: Chi Square test

**Table 4: Change of clinical and laboratory parameters from baseline to follow up visit**

Parameters	N	Mean	S.D.	% change
<b>Laboratories</b>				
Systolic (mmHg)	357	25.46	22.20	- 14.7%
Diastolic (mmHg)	357	8.38	11.74	- 7.9%
Post prandial blood glucose (mg/dL)	147	38.18	64.57	- 13.9%
Fasting blood glucose (mg/dL)	171	27.74	51.49	- 12.3%
Random blood glucose (mg/dL)	92	35.45	64.66	- 12.6%
HbA1C (%)	103	0.97	1.48	- 10.1%
Total cholesterol (mg/dL)	219	28.12	48.05	- 10.4%
LDL cholesterol (mg/dL)	219	19.46	40.54	- 7.6%
HDL cholesterol (mg/dL)	215	-0.74	12.80	+ 5.5%
<b>Clinical Parameters (n=357)</b>				
Dysarthria				- 30.5%
Sensory				- 19.9%
Motor disability				- 17.6%
Vertigo				- 11.3%
Dysphagia				- 11.3%
Aphasia				- 6.1%
Ataxia				- 2.3%
Visual				- 0.9 %
Others				- 2.2 %

dysarthria showed the largest improvement, followed by sensory disturbances and motor disability. Visual complaints showed the least improvement with only 0.9% change from baseline.

## DISCUSSION

This registry showed that 92.2% of patients had hypertension as risk factor followed by age over 55 years old (older age). Motor disability was the most prevalent clinical sign followed by dysarthria and sensory disability. Majority of the subjects had ESRS of 3 (72.2%). The finding of ESRS distribution in this registry is markedly different to a nationwide Danish cohort study. The mean ESRS in Danish cohort study was 2.4 (SD 1.4) with majority of patients had ESRS of 2, 3, and 1 (26.3%, 25.9%, and 20.8%, respectively).<sup>14</sup>

Stroke patients with high risk of stroke recurrence using ESRS tend to be influenced by various risk factors. Hypertension was the most frequent risk factor followed by older age, dyslipidemia, diabetes, cardiac disease, smoking,

lack of physical exercise, family history, and obesity. The distribution of risk factors found in this registry was similar to other registry conducted in developing country, with hypertension being the most frequent risk factor in more than 80% of stroke patients.<sup>15</sup> Motor disability was the most prevalent clinical sign found among stroke patients, followed by dysarthria, and sensory disability.

The National guidelines clearly mentioned the importance of antiplatelet drugs and other treatments to prevent stroke recurrence. This disease registry found that there was high inconsistency between the recommendations in the guideline and current clinical practice in Indonesia, even though the guideline clearly showed the benefit of antiplatelet, anti-hypertension, antidiabetic, and antihyperlipidemic in preventing stroke recurrence. This disease registry found that most of the subjects received antiplatelet as recommended by the guideline, however a high percentage of subjects with diabetes did not receive recommended medications. This finding highlights the importance of education of

National guideline among physicians in Indonesia. This disease registry also found that although majority of the treatment given did not entirely follow the National guideline, we still observe the improvement of signs and symptoms.

Evaluation for the first 3 months of treatment showed good treatment compliance in majority of subjects. However, this needs to be further clarified in 'real-world' practice rather than relying only on the assessment from the treating physicians. The treatment compliance is critical to the treatment goal, especially during period after diagnosis. Despite low compliance to the National guideline, evaluation of stroke patients after receive 3 months of treatment showed significant improvement of all types of clinical signs and symptoms.

Almost all patients received an antiplatelet with clopidogrel as the most prescribed anti-platelet drug, followed by acetyl-salicylic acid. The compliance rate for the first 3 months of treatment could be considered satisfying. Younger patients tend to had better compliance. The use of other anti-diabetic and anti-dyslipidemia medication showed deviation from the guideline.

Further survey of the possible use of traditional, herbal or supplemental medicine among Indonesian patients to control their stroke risk factors, might be considered to better understand their role as preventive medicine in stroke patients.

Of the limitations in this study, compliance to the treatment was based on the subjective opinion from treating physicians. This needs to be confirmed using actual patient's data. The improvement of clinical parameter in this registry is merely assessed by their existence during study visit. The use of more comprehensive tool, such as NIH Stroke Scale (NIHSS), will better quantifies stroke severity.

In conclusion, this registry described the clinical profiles of TIA and IS in Indonesian patients as well as medical practice. The registry also showed that an ESRS of 3 was recorded in majority of the subjects, majority of patients were prescribed clopidogrel as single antiplatelet, and satisfying compliance rate for the first 3 months of treatment. Majority of subjects were not treated according to the National guideline.

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