Neurology Asia 2015; 20(2) : 121 – 127

ORIGINAL ARTICLES

High prevalence of diabetes in stroke patients and its association with lacunar infarction

[1]Zhe Kang Law *MRCP*, [1]Wan Nur Nafisah *MMed*, [1]Ramesh Sahathevan *PhD*, [1]Jee Yong Hing *MD*, [1]Mohd Firdaus Zakaria *MD*, [1]Nurul Munirah Mohd Shuhari *MD*, [1]Nur Fathihah Ahmad *MD*, [1]Teong Kui Ting *MD*, [1]Hui Jan Tan *MMed*, [1]Shahrul Azmin *MMed*, [1]Rabani Remli *MMed*, [2]Azmawati Mohammed Nawi *MPH*, [1]Norlinah Mohamed Ibrahim *MRCP*

[1]Department of Medicine, and [2]Community Health, Universiti Kebangsaan Malaysia Medical Centre, Malaysia

Abstract

Background & Objectives: The burden of stroke is increasing, in part due to increasing prevalence of diabetes mellitus. Given the high prevalence of diabetes in the Malaysian population (22.6%), we aimed to determine the prevalence of diabetes in our stroke population. We also aimed to study the stroke subtype associated with diabetes. We hypothesized that lacunar infarction would be more prevalent in diabetics. *Methods:* We retrospectively reviewed data of consecutive patients with acute ischaemic stroke admitted from October 2004 to December 2010 from our stroke registry. Demographic data, risk factors profile and stroke subtypes were reviewed and analyzed. *Results:* Eight hundred and fifty eight patients were identified from the registry. As high as 59.3% (n=509) of our patients were diabetics, of which 49.2% (n=422) had pre-existing diabetes and 10.1% (n=87) were newly diagnosed. Lacunar infarction was the commonest stroke subtype, comprising 60.6% (n=519) of all strokes. Diabetes was significantly associated with lacunar infarction (OR 1.5, CI 95% 1.16-2.01, p=0.003), particularly in those aged ≤ 55 years (OR 2.29, 95% CI 1.12-4.67) and HbA1C ≥ 6.5% (χ^2=8.77, p=0.003). *Conclusions:* The prevalence of diabetes in our stroke patients is amongst the highest reported. Diabetes mellitus, particularly those with poor glycaemic control is strongly associated with lacunar infarction.

INTRODUCTION

Diabetes mellitus is a major risk factor for stroke, increasing the risk by 1.5 to 3 fold.[1,2] There is an increasing prevalence of diabetes worldwide. In 2012, 371 million people worldwide were affected by diabetes compared to 171 million in 2000.[3,4] Concurrently, the global burden of cardiovascular diseases is on the rise reflected in the 25% increase in stroke incidence worldwide within the same period. In 2010, stroke affected 16.9 million people globally.[5] This increase is attributable to an increasingly aging population and the rise in prevalence of diabetes, hypertension and other cardiovascular risk factors.

Stroke is conventionally classified as a diabetic macrovascular complication alongside coronary artery disease and peripheral artery disease.[6] However, stroke is a more heterogeneous disease with myriad pathophysiological mechanisms, including both large and small vessel disease. There is conflicting evidence whether stroke is a predominantly microvascular or macrovascular complication of diabetes. Diabetes had been shown to be associated with a higher risk of lacunar infarction compared to large vessel disease. Two large population study: the German Stroke Data Bank and The Atherosclerotic Risk in Communities study found that diabetes carried a higher risk for lacunar infarction than non-lacunar infarction or cardioembolic stroke.[7,8] On the other hand, at least one study showed that diabetes was associated with an equal incidence of all ischaemic stroke subtypes.[9]

There is global variation in the prevalence of diabetes and its complications. Some countries have higher prevalence of diabetes and as a result a high burden of diabetic complications.

Address correspondence to: Norlinah Mohamed Ibrahim, Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia. Telephone number: +60391456074, Fax number: +60391456679, E-mail: norlinah@ppukm.ukm.edu.my

An example would be Malaysia, where the prevalence of diabetes in the general population is among the highest in the world. Diabetes effects approximately 22.6% of adults aged more than 30 years old in Malaysia.[10] In stroke patients, the prevalence of diabetes was found to range between 45.7% to 55.2% based on two studies of in-patient stroke.[11,12] This is in contrast to epidemiological studies in other parts of the world, which report a prevalence of diabetes ranging from 21% to 32% amongst stroke patients.[13-15] Previously two comparative studies also showed that the prevalence of lacunar infarction and diabetes is higher in Malaysia compared to Australia. In 1994, a comparative study between University Hospital, a Malaysian teaching hospital and Austin Hospital, Australia demonstrated a higher prevalence of lacunar infarction and diabetes among the Malaysian patients. Thirty percent of the stroke patients were diabetic in Malaysia compared to 13.3% in Australia.[16] In a more recent study in 2010, Tan *et al*. also showed that the Malaysian cohort had more frequent small vessel occlusion (OR 2.59, 95% CI 1.01-6.79, p=0.046) and diabetes (OR 7.25, 95% CI 2.78-19.45, p=0.0007) compared to Australia.[17]

We aimed to study the prevalence of diabetes mellitus amongst our ischaemic stroke patients and its association with stroke subtypes. We hypothesized that there is a high prevalence of diabetes amongst our stroke patients and that diabetes is associated with lacunar infarction.

METHODS

We retrospectively reviewed data from our hospital stroke registry of consecutive patients admitted with acute ischaemic stroke from October 2004 to December 2010. Stroke was defined as a rapidly developing clinical symptoms of focal or global impairment of cerebral function lasting more than 24 hours or leading to death, with no apparent cause other than one of vascular origin.[18] We included patients with acute ischaemic stroke admitted within 7 days after the event, diagnosed based on clinical and radiological (Computed Tomography and/or Magnetic Resonance Imaging) criteria. Hemorrhagic strokes were excluded.

Our stroke registry consists of a standardized data sheet which was used to record the following on admission: demographic profile; preexisting risk factors specifically hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, smoking, past history of stroke or transient ischaemic attack, family history of stroke and ischaemic heart disease; clinical features; stroke subtype; blood pressure and random blood sugar; HbA1c levels; stroke severity upon discharge and complications. For the purpose of this study, we only analyzed the demographic profile, risk factors and stroke subtypes. All data were extracted from the stroke registry report form. In cases of inconsistency or unclear information, patients' case notes were traced for review.

We defined hypertension as previous record of at least 2 readings of blood pressure > 140/90 mmHg or requirement of antihypertensive agent(s).[19] Diabetes mellitus was defined as fasting blood sugar level of > 7.0 mmol/L or random blood sugar of > 11.1 mmol/L or requirement of antidiabetic agent(s).[20] For patients without pre-existing diabetes, HbA1c levels taken within 3 months of stroke were examined; HbA1c level of ≥ 6.5% was considered diagnostic of diabetes.[21] Both type 1 and type 2 diabetes mellitus were included but not classified differently. Dyslipidaemia was defined as abnormal lipid profile needing therapeutic lifestyle modification or lipid-lowering agent(s). Atrial fibrillation was considered present if recorded in the history or captured on ECG during hospital stay. Patients were regarded as smoker if they were current smokers or had ever smoked in the past. Ischaemic heart disease included previous myocardial infarction or angina.

Stroke was categorized as lacunar infarction and non-lacunar infarction. Lacunar infarction was diagnosed if there was a clinical lacunar stroke syndrome with radiological evidence of small subcortical infarctions less than 15mm located in the internal capsule, basal ganglia, thalamus, corona radiata, external capsule, centrum semiovale or brainstem resulting from occlusion of single perforator artery.[22] Clinical lacunar stroke syndrome with normal CT brain imaging was also classified as lacunar infarction. Clinical lacunar stroke syndromes include pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria-clumsy hand syndrome.[23] Non-lacunar infarctions were further classified to middle cerebral artery (MCA) infarction, anterior cerebral artery (ACA) infarction, posterior cerebral artery (PCA) infarction and vertebrobasilar artery (VBA) infarction. MCA, ACA, PCA and VBA infarcts are clinical stroke syndromes resulting from cerebral infarcts in the respective vascular territory. Posterior cerebral artery infarct and vertebrobasilar artery infarct are grouped together as posterior circulation infarcts.

This research was approved by the institutional review board (UKM-FF-002-2011).

Statistical analyses

Data were entered, cleaned and analysed using SPSS 21.0 for Windows. We used simple and multiple logistic regression analysis to identify factors which had significant relationship with lacunar infarction using the following steps:

Firstly, we explored all the variables involved to determine descriptive statistics such as frequency and distribution. We then explored the crude relationship between lacunar infarction and each independent variable using simple logistic regression and Chi square i.e. univariate analyses. Pattern of relationship and potential outliers were observed and verified for correctness of outliers with the raw data.

Using automatic variable selection procedures, we identified significant factors by fitting all independent variables into the multiple logistic regression models. In this step, both forward and backward stepwise variable selection procedures were applied with *P* value less than 0.05 as significant variable to be included into the model, and *P* value more than and equal to 0.10 to be excluded from the model. The selected model after this step was considered as "preliminary main-effect model".

In the next step, all possible two-way interactions between independent variables, selected by automatic procedure, were checked by creating interaction terms and fitting the term, one at a time, into the preliminary main-effect model. When the interaction term was significant, we considered that there was a significant interaction between the two tested variables and then, we included the term in the model. The preliminary main-effect model was also checked for multicollinearity by obtaining variance-inflation-factor (VIF) for each independent variable. When VIF was more than 10, it was considered that there was significant multicollinearity. After the tests of interaction and multicollinearity, the model was considered as "preliminary final model" which was then evaluated for model assumptions by assessing the goodness of fit by doing Hosmer-Lemeshow test, Pearson Chi-square goodness of fit, and classification table. The model which met all these required assumptions and without outliers was then considered the "final model" and used to interpret the relationship between lacunar infarction and each significant independent variable. All hypothesis involved were two-sided tests and *P* value less than 0.05 was considered statistically significant.

RESULTS

Demography and risk factors

Nine hundred and thirty six patients were admitted for acute stroke during the study period. Seventy eight patients with hemorrhagic stroke were excluded leaving 858 patients with ischaemic stroke eligible for study inclusion. The mean age of stroke was 65.32±11.9 years. There were slightly more male (n=456) compared to female (n=402) patients with a ratio of 1.1 to 1. The majority of patients were in the 56 to 75 years age group (n=514, 59.9%). The demographic data and prevalence of risk factors are shown in Table 1.

Diabetes was pre-existent in 49.2% (n=422) of patients while 10.1% (n= 87) were newly diagnosed based on a HbA1c cut-off of 6.5%. This makes the overall prevalence of diabetes in our population 59.3%. HbA1c levels were available in 78.7% of all patients (n=675), which include

Table 1: Demography and stroke risk factors

Demography	**N (%)**
Sex	
Male	456 (53.1%)
Female	402 (46.9%)
Ethnicity	
Malay	324 (37.8%)
Chinese	445 (51.8%)
Indian	70 (8.2%)
Others	19 (2.2%)
Age(years)	
≤55	171 (19.9%)
56-75	514 (59.9%)
≥76	173 (20.2%)
Risk Factors	
Hypertension	694(81.6%)
Diabetes mellitus	
Pre-existing	422(49.2%)
Newly diagnosed	87(10.1%)
Overall	509(59.3%)
Dyslipidaemia	374(40.6%)
Smoking	215(23.3%)
Atrial fibrillation	142(16.6%)
Previous stroke	197(21.4%)
Family history of stroke	86(10.0%)
Ischaemic heart disease	118(13.6%)

88.1% (n=372) of patients with pre-existing diabetes and 69.5% (n=303) of patients without known diabetes. About 28.7% of patients screened (87/303) were diagnosed with diabetes. The mean HbA1c of the all diabetic stroke patient was 8.3 ± 2.5%. There were no significant differences in the mean HbA1c between the newly diagnosed (8.67±2.30) % and pre-existing diabetics (8.31±2.56) %, (p=0.232). The proportion of patients with poor glycaemic control (HbA1c ≥6.5%) was 70.3% (n=358). As for the treatment of diabetes, 59.2% (n=250) were on oral antidiabetic agents and 27.2% (n=115) were on insulin.

Stroke subtypes

CT brain was done in 92% of patients and MRI in 8% of patients. Lacunar infarction was the most prevalent stroke subtype, comprising 60.6% (n=519) of all strokes. Non-lacunar infarction was present in 39.4% (n=339) and involved middle cerebral artery territory (28.2%, n=242), posterior cerebral artery and vertebral artery territory (9.3%, n=80), and anterior cerebral artery territory (5.0%, n=43). Approximately 3.0% of the patients had cerebral infarctions in more than one arterial territory.

Based on multiple logistic regression analysis, diabetes was significantly associated with the risk of developing lacunar infarction compared to non-lacunar infarction (OR 1.5, 95% CI 1.17-2.05, p=0.002). None of the other risk factors were significantly associated with lacunar infarction (Table 2). In patients aged 55 years or less, diabetes mellitus conferred a significantly higher risk compared to hypertension (diabetes mellitus OR 2.29, 95% CI 1.12-4.67; hypertension OR 1.83, 95% CI 0.86-3.87). Poorer glycaemic control reflected by a higher HbA1c level was also significantly associated with lacunar infarction (p=0.003) (Table 3).

DISCUSSION

The main findings of this study can be summarised as the following: 1) About 60% of our ischaemic stroke patients are diabetic; 2) Lacunar infarction is the commonest ischaemic stroke subtype, consisting of 60% of all stroke and 3) Lacunar infarction is independently associated with diabetes and poor glycaemic control. In the paragraphs below, we endeavour to provide some explaination of our results.

The prevalence of diabetes amongst ischaemic stroke patients in our centre is at least 2 to 3 times higher than previously reported literature. Approximately 60% of our stroke patients have diabetes. Previous studies have reported the prevalence of diabetes amongst stroke population to be between 1.2% to 32%.[24-26] This may be

Table 2: Risk factors for lacunar infarction

Risk factors	Crude OR	95%CI	p value
Hypertension	1.15	0.79-1.68	0.763
Diabetes mellitus	1.50	1.16-2.01	0.003
Dyslipidaemia	1.01	0.76-1.35	0.970
Atrial Fibrillation	1.27	0.87-1.86	0.065
Smoking	1.26	0.90-1.74	0.175
Family history	1.22	0.75-1.97	0.569
Ischaemic heart disease	1.28	0.85-1.92	0.089
Male	1.03	0.69-1.54	0.879
Age(years)	0.99	0.97-1.01	0.226
Past history of stroke	0.97	0.70-1.35	0.850
Malay[#]	1.08	0.82-1.43	0.574
Risk factors	***Adjusted OR**	**95%CI**	**p value**
Diabetes mellitus	1.55	1.17-2.05	0.002

*Adjusted OR: adjusted odds ratio for other risk factors (hypertension, dyslipidaemia, atrial fibrillation, smoking, family history ischaemic heart disease, age, gender, ethnic and past history of stroke); Forward LR Multiple Logistic Regression model was applied, no multicollinearity and model fitness was checked. [#] compared with non-Malay. [Chinese; crude OR=1.05(95%CI 0.78-1.41), Indian; crude OR=0.98(95%CI 0.58-1.64), others ethnic; crude OR=5.23(95%CI 1.18.23.24)].

Table 3: HbA1c levels and stroke subtypes

	ACA (n, %)	MCA (n, %)	PCA/VBA (n, %)	Lacunar (n, %)
HbA1C (%)				
<6.5	21(58.3)	99(51.8)	39(60.9)	173(43.4)
≥6.5	15(41.7)	92(48.2)	25(39.1)	226(56.6)
χ^2	1.61	1.54	4.71	8.77
p value	0.204	0.215	0.030	0.003
Crude OR (95%CI)*	0.66(033-1.30)	1.24(0.89-1.73)	1.74(1.03-2.95)	1.59(1.16-2.16)
Adjusted OR (95%CI) †	-	-	-	1.57(1.18-2.18)

HbA1c levels: available=675 (78.7%), missing=183 (21.3%); The group with HbA1c and without HbA1c differed significantly in term of diabetes (χ^2=43.2, p<0.001) but not other risk factors (hypertension, ischaemic heart disease, dyslipidaemia, atrial fibrillation, previous stroke and gender). ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA/VBA: posterior cerebral artery/ vertebrobasilar artery (posterior circulation infarct); * Simple logistic regression, †Forward LR Multiple Logistic Regression model was applied with adjusted for age, gender, hypertension, dyslipidaemia, smoking, AF, IHD, ethnicity and past history of stroke, no multicollinearity and model fitness was checked

attributed to the high prevalence of diabetes in the Malaysian population generally. Our findings also affirm the high prevalence of diabetes previously reported in the local stroke population.[11,12] The mean HbA1c of diabetic patients was 8.3 ± 2.5%, indicating a poor glycaemic control which puts them at high risk of diabetic vascular complications.

Approximately 60% of our ischaemic stroke are of the lacunar infarction subtype, which is much higher than 20.5% to 29% reported in previous studies.[7,27,28] Our data showed that diabetes is the only significant and independent risk factor of lacunar infarction. All other risk factors including hypertension, were determined to have a similar association for both lacunar infarction and non-lacunar infarction. The higher prevalence of diabetes in the Malaysian population, might explain the higher proportion of lacunar infarction in our study.

Lacunar infarction is classically thought to be a small vessel disease caused by fibrinoid necrosis, lipohyalinolysis and formation of microthrombi.[22] Endothelial dysfunction which is seen in diabetic microvascular disease is also a feature of lacunar infarction.[29] Therefore, lacunar infarction may be a spectrum of diabetic microvascular disease. However, atherosclerosis of large intracranial vessels has recently been demonstrated as a cause of lacunar infraction, using high resolution MRI that demonstrated occlusion of the perforator artery by atheroma or artery-to-artery embolism.[30] It is beyond the scope of this study to determine the mechanism of lacunar infarction in our patients. Advanced brain imaging was not available to determine if the lacunar infarctions were predominantly small vessel disease only or if there were concurrent large vessel diseases as well. A high prevalence of other diabetic microvascular diseases i.e. diabetic nephropathy, retinopathy and neuropathy may support the notion of lacunar infarction as a microvascular complication. However these data were not collected in our patients.

Hypertension was the most prevalent risk factor, affecting 81.6% of our patients. Hypertension is a known risk for all ischaemic stroke subtypes. However, logistic regression analysis did not show significant association between hypertension and lacunar infarction. This does not mean that hypertension was not a risk factor for lacunar infarction but rather that hypertension contributed similarly to non-lacunar infarction as well.

The strengths of our study are that we defined diabetes based on case history, fasting plasma glucose and HbA1c level. We were thus able to identify patients with pre-existing and newly diagnosed diabetes. Using HbA1c in reaching a diagnosis of diabetes was more accurate than random or fasting blood sugar alone, which is influenced by stress hyperglycaemia seen in acute stroke. Secondly, our results were based on data captured over a reasonable period of time which reflect the epidemiological trends of stroke in our centre.

There are also several limitations of this study, as there was some missing data in the stroke registry. HbA1c results were not available in 21.3% of the patients. The patients with HbA1c levels were more likely to have pre-existing diabetes but otherwise did not differ from those without HbA1c in terms of other risk factors. The statistical analysis of HbA1c association with stroke subtype is more depictive of patients with pre-existing diabetes, which is the population group of interest. The registry data collected did not include details of other diabetic microvascular complications. MRI is a better imaging modality than CT scan in determining stroke subtype, however most of our patients did not have a MRI due to the high cost and limited availability. Being a retrospective study, the relation between diabetes and stroke we have demonstrated is at best associative or attributable rather than causal.

In conclusion, we report a high prevalence of diabetes in our population of stroke patients, consisting a combination of pre-existent disease and newly diagnosed cases. We also found a significant association between the presence of diabetes and lacunar infarction especially in younger patients of <55 years and in those with poor glycaemic control. Our findings support the association between diabetes and lacunar infarction reported previously. A large population based prospective analysis would be the best means to determine if lacunar infarction is a micro or macrovascular complication of diabetes.

ACKNOWLEDGEMENT

We would like to thank Dr Amy Brodtmann for her constructive comments.

DISCLOSURE

Conflict of interest: None

REFERENCES

1. Stegmayr B, Asplund K. Diabetes as a risk factor for stroke. A population perspective. *Diabetologia* 1995; 38(9):1061-8.
2. Kissela BM, Khoury J, Kleindorfer D, *et al*. Epidemiology of ischemic stroke in patients with diabetes: the greater Cincinnati/Northern Kentucky Stroke Study. *Diabetes care* 2005; 28(2): 355-9.
3. Guariguata L. By the numbers: new estimates from the IDF Diabetes Atlas Update for 2012. *Diabetes Res Clin Pract* 2012; 98(3):524-5.
4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5):1047-53.
5. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014; 383(9913): 245-54.
6. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clinical Diabetes* 2008; 26: 77-82.
7. Grau AJ, Weimar C, Buggle F, *et al*. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke* 2001; 32(11): 2559-66.
8. Ohira T, Shahar E, Chambless LE, Rosamond WD, Mosley TH, Jr., Folsom AR. Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities study. *Stroke* 2006; 37(10): 2493-8.
9. Iso H, Rexrode K, Hennekens CH, Manson JE. Application of computer tomography-oriented criteria for stroke subtype classification in a prospective study. *Ann Epidemiol* 2000; 10(2): 81-7.
10. Wan Nazaimoon WM, Md Isa SH, Wan Mohamad WB, *et al*. Prevalence of diabetes in Malaysia and usefulness of HbA1c as a diagnostic criterion. *Diabetic Medicine* 2013; 30(7): 825-8.
11. Nazifah SN, Azmi IK, Hamidon BB, Looi I, Zariah AA, Hanip MR. National Stroke Registry (NSR): Terengganu and Seberang Jaya experience. *Med J Malaysia* 2012; 67(3): 302-4.
12. Hamidon BB, Raymond AA. Predictors of in-hospital mortality after an acute ischemic stroke. *Neurol J Southeast Asia* 2003; 8:5-8.
13. Wong KS. Risk factors for early death in acute ischemic stroke and intracerebral hemorrhage: A prospective hospital-based study in Asia. Asian Acute Stroke Advisory Panel. *Stroke* 1999; 30(11): 2326-30.
14. Seet RC, Lim EC, Chan YH, Chan BP, Quek AM, Ong BK. Can demographic and admission laboratory variables be useful to identify long-stay patients with acute ischemic stroke? A hospital-based cohort study in Singapore. *Neurol Sci* 2009; 30(4): 275-80.
15. Icks A SM, Genz J, Giani G, Glaeske G, Hoffmann F. Stroke in the diabetic and non-diabetic population in Germany: relative and attributable risks, 2005-2007. *J Diabetes Complications* 2011; 25(2): 90-6.
16. Ng WK, Goh KJ, George J, Tan CT, Biard A, Donnan GA. A comparative study of stroke subtypes between Asians and Caucasians in two hospital-based stroke registries. *Neurol J Southeast Asia* 1998; 3: 19-26.
17. Tan KS, Tan CT, Churilov L, Mackay M, Donnan GA. Ischaemic stroke in young adults: A comparative study between Malaysia and Australia. *Neurology Asia* 2010; 15(1): 1-9.
18. World Health Organisation MONICA Project Investigators. The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. *J Clin Epidemiol* 1988; 41(2): 105-14.
19. Chobanian AV, Bakris GL, Black HR, *et al*. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42(6): 1206-52.
20. American Diabetes Association. Position Statement on Standards of Medical Care in Diabetes - 2009. *Diabetes Care* 2009; 32: S13-S61.
21. Higgins T. HbA1c for screening and diagnosis of diabetes mellitus. *Endocrine* 2013; 43(2): 266-73.
22. Fisher CM. Lacunar infarcts: a review. *Cerebrovasc Dis* 1991; 1: 311-20.
23. Fisher CM. Lacunar strokes and infarcts: a review. *Neurology* 1982; 32(8): 871-6.

24. O'Donnell MJ, Xavier D, Liu L, *et al*. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010; 376(9735): 112-23.
25. Towfighi A, Markovic D, Ovbiagele B. Current national patterns of comorbid diabetes among acute ischemic stroke patients. *Cerebrovasc Dis* 2012; 33(5): 411-8.
26. Venketasubramanian N. The epidemiology of stroke in ASEAN countries - A review. *Neurol J Southeast Asia* 1998; 3: 9-14.
27. Yip PK, Jeng JS, Lee TK, *et al*. Subtypes of ischemic stroke. A hospital-based stroke registry in Taiwan (SCAN-IV). *Stroke* 1997; 28(12): 2507-12.
28. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke* 1999; 30(12): 2513-6.
29. Knottnerus IL, Ten Cate H, Lodder J, Kessels F, van Oostenbrugge RJ. Endothelial dysfunction in lacunar stroke: a systematic review. *Cerebrovasc Dis* 2009; 27(5): 519-26.
30. Khan A KS, Lynn MJ, Chimowitz MI. Risk factors and outcome of patients with symptomatic intracranial stenosis presenting with lacunar stroke. *Stroke* 2012; 43: 1230-3330.