Neurology Asia 2016; 21(3) : 209 – 216

ORIGINAL ARTICLES

Time interval between first ever and recurrent stroke in a population hospitalized for second stroke: A retrospective study

Rong Zhu, Ke Xu, Jingpu Shi, Qi Yan

Department of Clinical Epidemiology, Institute of Cardiovascular Diseases, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning China

Abstract

Objectives: The survivors of first-ever stroke are at a high risk of recurrent stroke. The time interval between first-ever stroke and first recurrence of stroke, however, have not been well studied. The aim of the present study was to evaluate the time interval between first-ever and first recurrence of stroke and the risk factors of stroke that were related to the length of time interval. *Methods:* Patients admitted in our hospitals during 2014 with first recurrence of stroke were included in the study. A total of 377 patients were enrolled and a standardized questionnaire was used to collect data in this retrospective study. *Results:* The mean time interval among all the subjects was 58.42 months (median, 36.01 months; range 0.16months to 455.98months). The mean time interval was shorter in hemorrhagic stroke group (56.78 months) than in ischemic stroke group (58.75 months), but the difference was not significant (p=0.819). The median of time interval was similar in the two groups. The associated risk factors to the length of time interval were age over 60 years, subtype of first-ever stroke, the length of history of hypertension. Age was the only associated risk factor to the time interval among patients with first recurrence of hemorrhagic stroke.
Conclusion: Factors associated with the time interval are different among different types of recurrent stroke. This provides the basis for preventive treatment for recurrent stroke after their first-ever stroke.

INTRODUCTION

Stroke is now a major global burden of disease. According to a recent research, ischemic heart disease and stroke were the two most important causes of death between 1990 and 2010.[1] In 2010 as compared to 1990, an estimated 16.9 million cases of incident stroke occurred worldwide with a 25% (13–33%) increase in stroke incidence in population aged 20–64 years.[2] The stroke survivors have a significant risk of stoke recurrence, about 11.1% (95% CI 9.0–13.3) at 1 year, 26.4% (20.1–32.8%) at 5 years, and 39.2% (27.2–51.2%) at 10 years.[3]

Previous studies have been done to observe the short-term and long-term outcomes after first-ever stroke. The majority of these investigations, however, focused on the prognosis and predictors of recurrent stroke in these stroke patients. Detailed studies about the time interval between first-ever and recurrent stroke is still limited.

The aim of the present study was to evaluate the time interval between first-ever and first recurrence of stroke and the contributory factors, which may help in the secondary preventive treatment of stroke.

METHODS

This is a retrospective, hospital-based study was performed involving 1950 stroke patients in the First Hospital of China Medical University between January 2014 and December 2014. All the patients in this study were admitted to the ward from emergency department or outpatient department. Computerized records of discharge diagnoses were searched for a diagnosis of stroke.

The WHO defines stroke as "rapidly developing clinical signs of focal disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin." Diagnosis of stroke was based on clinical symptoms, physical examination, and CT/MRI findings. For the purpose of this analysis, we,

Address correspondence to: Dr. Jingpu Shi, Department of Clinical Epidemiology, Institute of Cardiovascular Diseases, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning 110001, China. Email: sjp562013@126.com

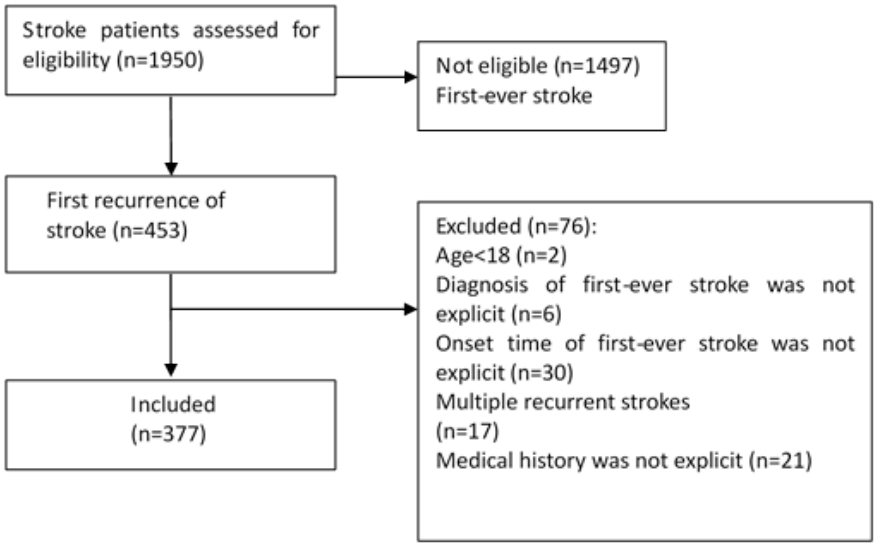

Figure 1. Participant flow chart

like others, defined stroke recurrence as any new event occurring more than 21 days after the index stroke or, if earlier, clearly in another part of the brain.[4] First recurrence of stroke was classified into two categories: ischemic and hemorrhagic stroke[5] according to the brain image findings. The inclusion and exclusion criteria are shown in Figure 1. We finally included a total of 377 subjects.

We designed a standardized questionnaire to collect data from electronic medical record including date and subtype of first-ever stroke, date and subtype of first recurrence of stroke, medical history, possible contributory factors to time interval, previous medication, biochemical examination and brain imaging performed during the hospitalization.

We analyzed the following possible contributory factors which were mostly are risk factors of stroke and listed their definitions: (1). History of hypertension: history of medically diagnosed hypertension (>140/90mmHg, or receipt of antihypertensive medication); (2) Length of history of hypertension in years: the time interval between medically diagnosed hypertension and admission to hospital for recurrent stroke; (3) History of diabetes mellitus (DM): history of medically diagnosed raised plasma blood glucose (fasting blood glucose level ≥6.1mmol/l, 2-hour post-challenge glucose level≥11.1mmol/l, or receipt of antidiabetic medication); (4) Length of history of DM in years: the time interval between medically diagnosed diabetes mellitus and admission to hospital for recurrent stroke; (5) History of heart disease: history of angina pectoris, myocardial infarction, atrial fibrillation, cardiac failure or previous percutaneous transluminal cardiac angioplasty or cardiac angioplasty bypasses graft; (6) Smoking: daily use of cigarettes or pipe; (7) Alcohol consumption: daily intake of 10 g or more of pure alcohol; (8); Systolic blood pressure (SBP): SBP>140mmHg; (9) Fasting blood glucose level (FBG): FBG>6.1mmol/l; (10) Dyslipidemia: high total cholesterol (≥5.72mmol/L) or high low density lipoprotein cholesterol (≥3.64mmol/L) or low high lipoprotein cholesterol (≤5.72mmol/L) or high triglyceride (≥1.70mmol/L).

The statistical analyses were performed with SPSS (version 19.0; SPSS Inc., Chicago, IL, USA). We calculated the mean, standard deviation, median, minimum, maximum, range and quartiles of the time interval. We also classified the subjects into four groups according to the quartiles to compare the intergroup differences in univariate analysis. All contributory factor variables were first examined by univariate analysis to assess the importance of each of them on time interval. Intergroup differences were assessed with the Chi-square test for categorical variables, the one-way ANOVA for continuous normally distributed variables and kruskal-Wallis test for continuous skewed variables. In particular, we chose certain cutoff points of age (50 years, 55 years, 60 years, 65 years, 70 years, 75 years and 80 years) to stratify patients for comparison. When a variable was significant at the 0.1 level, it was chosen to contribute to the multivariate model. Multivariate linear regression was used to examine the correlation between time interval and the contributory factors. The square root

Table 1: The time interval between first-ever stroke and recurrent stroke

	Ischemic group n=314	Hemorrhagic group N=63
Mean(months)	58.75	56.78
Std. deviation	65.85	58.96
Median(months)	36.01	36.01
Minimum(months)	0.99	0.16
Maximum(months)	455.98	240.00
Range(months)	455.00	239.84
quartiles(months)	11.99 36.01 84.01	11.99 36.01 93.99

transformation of time interval produced a more normal distribution (the Kolmogorov-Smirnov Z value changed from 3.37 to 1.87 for ischemic subjects and from 1.53 to 1.06 for hemorrhagic subjects).When a most parsimonious model was obtained by backward elimination, each variable was entered separately into the model to look for further effects. In multiple linear regression, $p<0.05$ was considered significant.

RESULTS

Time interval between first-ever stroke and first recurrent stroke

The subjects in the present study were 377 patients with first recurrence of stroke. Among them, 314 had ischemic recurrent stroke, 63 had hemorrhagic recurrent stroke.

The mean of the time interval among all the subjects was 58.42 months. The period between the first-ever stroke and subsequent recurrent stroke ranged from 0.16 months to 455.98 months. The first and second quartiles of hemorrhagic subjects were the same as ischemic subjects. The third quartile of hemorrhagic subjects was 93.99 months which was longer than that of ischemic subjects.

The detailed time interval of ischemic group and hemorrhagic group of patients are listed in Table 1. The mean time interval was shorter in hemorrhagic group (56.78 months) than in ischemic group (58.75 months), but the difference was not statistically significant ($p=0.819$). The minimum and maximum time interval of hemorrhagic subjects were shorter than that of ischemic subjects which might suggest that recurrent hemorrhagic stroke happened in a shorter time than ischemic stroke.

We divided the patients into different groups according to quartiles of the time interval (Table 2).

Table 2: The frequency and percent of subjects in different time interval groups

	Ischemic group			Hemorrhagic group			
Time interval (months)	Frequency	percent	Cumulative pecent	Frequency	percent	Cumulative percent	p value
＜12	75	23.9	23.9	13	20.6	20.6	0.053
12-36	70	22.3	46.2	18	28.6	49.2	0.100
36-48	86	27.4	73.6	14	22.2	71.4	0.304
＞48	83	26.4	100.0	18	28.6	100.0	0.089
Total	314	100.0		63	100.0		

Table 3: The differences of risk factors in ischemic group of patients

variables	<12 months (Group 1) (n=75) Percentage/ Mean (SD) /Median	12-36 months (Group 2) (n=70) Percentage/ Mean (SD) /Median	36-48 months (Group 3) (n=86) Percentage/ Mean (SD) /Median	>48 months (Group 4) (n=83) Percentage/ Mean (SD) /Median	P value
Gender(male)	68.00%	61.42	61.63%	67.47	0.725
Age[1]	63.51 (11.068)	65.53 (11.768)	64.99 (10.314)	66.01 (10.784)	0.520
Age>60 years	56.00%	62.86%	63.95%	74.70%	0.095
History of hypertension	74.67%	72.86%	61.63%	77.11%	0.122
Length of history of hypertension in years[2]	8.00	10.00	10.00	10.50	0.002
History of DM	36.00%	45.71%	32.59%	24.10%	0.044
Length of history of DM in years[2]	6.50	10.00	6.00	8.50	0.288
History of heart disease	26.67%	21.43%	27.91	28.92%	0.738
Smoking	32.00%	22.86%	24.41%	25.30%	0.596
Alcohol consumption	26.67%	1.57%	10.47%	15.11%	0.050
SBP>140mmHg	44.00%	62.85%	70.00%	69.88%	0.008
FBG>6.1mmol/L	52.00%	62.85%	60.00%	55.42%	0.285
Dyslipidemia	61.33%	60.00%	97.14%	69.88%	0.004

[1] Mean (SD); [2] Median; DM: Diabetes mellitus; SBP: Systolic blood pressure; FBG: Fasting blood glucose

The patients who had ischemic recurrent stroke tend to be in the group with longer time interval. We also compared the differences of constituent ratio of the time interval in different subtypes, the results showed no significant difference.

The analyses of contributory factors related to the time interval

Differences of associated risk factors between different time interval groups in ischemic subjects

The differences of associated risk factors in ischemic group are shown in Table 3. Age was continuous normally distributed variable so that we used one-way ANOVA for comparison. Length of history of hypertension and DM were continuous skewed variables and kruskal-Wallis test were used for comparison. The age in different time interval groups showed no significant difference, however, age > 60 years showed statistically significant difference in different groups. The other risk factors showed differences in ischemic group were length of history of hypertension (years), history of DM, alcohol consumption, dyslipidemia and systolic pressure over 140mmHg.

The subtypes of first-ever stroke in ischemic subjects

The subtypes of first-ever stroke were defined as intracerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction and cerebral embolism, which are shown in Table 4. According to the Chi-square test, the subtype of first-ever stroke were statistically different among different time interval groups.

Differences of associated risk factors between different time interval group in hemorrhagic group

As in ischemic group, we examined age as a continuous variable and as categorical variables by choosing cutoff points of 55 years, 60 years, 65 years, 75 years, 80 years and 85 years of age. The results of hemorrhagic group are quite different

Table 4: The subtype of first-ever stroke in different time interval groups of recurrent ischemic patients

Group of time interval	Subtype of first-ever stroke				Total
	ICH	SAH	CI	CE	
＜12months (group 1)	5	0	70	0	75
12-36months (group 2)	5	0	65	0	70
36-48months (group 3)	8	0	77	1	86
>48months (group 4)	11	4	67	1	83
Total	29	4	279	2	314

Chi-square value=16.086, p=0.065
ICH: intracerebral hemorrhage. SAH: subarachnoid hemorrhage. CI: cerebral infarction. CE: cerebral embolism

from ischemic group (Table 5). Age, dyslipidemia and length of history of DM were significantly different among four time interval groups.

The subtype of first-ever stroke in hemorrhagic subjects

There were only two subtypes of first-ever stroke that we identified in hemorrhagic patients, intracerebral hemorrhage and cerebral infarction (Table 6). The subtype of first-ever stroke showed no significant difference in different time interval groups.

Table 5: The difference of risk factors in hemorrhagic group

Variables	＜12 months (Group 1) (n=21) Percentage/Mean (Std. deviation) /Median	12-36 months (Group 2) (n=10) Percentage/Mean (Std. deviation) /Median	36-94 months (Group 3) (n=16) Percentage/Mean (Std. deviation) /Median	>94 months (Group 4) (n=16) Percentage/Mean (Std. deviation) /Median	P value
Gender(male)	76.19%	30.00%	56.25%	75%	0.056
Age[1]	59.29 (9.991)	65.20 (10.443)	58.94 (10.878)	70.06 (12.662)	0.014
Age>60 years	42.86%	70.0%	31.25%	75.00%	0.169
History of hypertension	76.19%	60.00%	75.00%	81.25%	0.676
Length of history of hypertension(years)[2]	7.50	20.00	9.50	10.00	0.191
History of DM	4.76%	0	12.50%	12.50%	0.559
Length of history of DM(years)[3]	10.00 (---)	---	4.00 (1.414)	10.00 (0.000)	0.044
History of heart disease	14.29%	10.00%	18.75%	12.50%	0.929
Smoking	23.81%	0	12.50%	25.00%	0.307
Alcohol consumption	23.81	0	6.25%	18.75%	0.228
SBP>140mmHg	66.67%	60.00%	81.25%	75.00%	0.642
FBG>6.1mmol/L	52.38%	50.00%	62.50%	43.75%	0.696
Dyslipidemia	28.57%	50.00%	62.50%	25.00%	0.005

[1] Mean (SD); [2] Median; [3] DM: Diabetes mellitus; SBP: Systolic blood pressure; FBG: Fasting blood glucose

Table 6: The subtype of first-ever stroke in different time interval group of recurrent hemorrhagic

Group of Time interval	Subtype of first-ever stroke ICH	CI	Total
<12months (group 1)	12	9	21
12-36months (group 2)	6	4	10
36-48months (group 3)	8	4	16
>48months (group 4)	9	7	16
Total	35	28	63

Chi-square value=0.305, p=0.959
ICH: intracerebral hemorrhage. CI: cerebral infarction

Correlation between associated risk factors and time interval in ischemic patients and hemorrhagic patients

To define the correlation between the contributory factors and time interval in different recurrent-type groups, we performed multivariate linear regressions (Table 7 and Table 8) using time interval as a continuous variable and the statistically significant contributory factors in univariate analysis. In multivariate analyses of ischemic subjects, age of 60 years, subtype of first-ever stroke and the length of history of hypertension appeared to be independent factors related to the time interval in regression model. The coefficients (SE) for other factors were 1.137 (0.561), -0.014 (0.446) and 0.095 (0.027) respectively. Age appeared to be the only factors related to the time interval in regression model of hemorrhagic group (P=0.002). The coefficient (SE) of age in linear regression model is 0.123 (0.039).

DISCUSSION

This is the first study, to the best of our knowledge, to evaluate time interval of first-ever stroke and first recurrence of stroke as well as the associated risk factors to the time interval. In this study, 23.9% of patients with recurrent ischemic stroke and 20.6% of patients with recurrent hemorrhagic stroke had history of their first stroke in the first year. This percentage dropped as the time interval rose. 10.19% and 2.87% of patients with recurrent ischemic stroke and 7.94% and 3.17% of patients with recurrent hemorrhagic stroke had history of their first stroke in the second years and tenth years. This may indicate that these patients were most vulnerable during the first year after their first stroke. The unique feature of our study is a wide range of time interval. 48 cases involved in our study had a long time interval which was over 10 years and the longest time interval in the present study was 455.98 months. These data may provide important reference value as few studies recruited patients with a long time interval.

A number of studies have evaluated the risk factors associated with poor outcomes after first-ever stroke and the results of these studies are quite different.[6-10] According to the linear regression of our study, the associated risk factors that may influence the length of time interval were different between the ischemic and hemorrhagic recurrent stroke patients.

Table 7: Multivariate linear regression of time interval of ischemic subjects

variables	Time interval (ischemic group)				
	Coefficients (SE)	t	P value	95% Confidence Interval	
				Lower bound	Upper bound
Age＞60 years	1.137 (0.561)	2.025	0.044	0.030	2.244
Subtype of first-ever stroke	-0.014 (0.446)	-2.275	0.024	-1.893	-0.135
Length of history of hypertension	0.095 (0.027)	3.529	0.001	0.042	0.149

Table 8: Multivariate linear regression of time interval of hemorrhagic subjects

	Time interval（hemorrhagic group）				
variable	Coefficients (SE)	t	P value	95% Confidence Interval	
				Lower bound	Upper bound
age	0.123 (0.039)	3.163	0.002	0.045	0.201

The factors related to the time interval of recurrent ischemic stroke

Subtype of first-ever stroke

Several studies have suggested that the subtypes of past stroke may be predictive of the subtype of recurrent strokes[4,11-13] and the majority of recurrent stoke were of the same subtype.[4] In the present study, most of the subjects (90.45% n=284) with first recurrence of ischemic stroke, including cerebral infarction and cerebral embolism, also had ischemic stroke for their first-ever stroke. Besides, the median time interval among recurrent ischemic patients with 4 different subtypes of first-ever stroke showed differences. The median time interval was the shortest in subjects with first-ever cerebral infarction (54.15months), followed by intracerebral hemorrhagic patients with 80.01months and cerebral embolic patients with 114.01months. The median time interval was the longest (197.99 months) in patient whose first-ever stroke was due to subarachnoid hemorrhage. Although previous study indicated that hemorrhagic stroke on first time may be a negative prognostic factor for recurrent stroke[13], the median time interval between first-ever stroke and recurrent stroke was longer in subjects with hemorrhagic stroke for the first time than those with ischemic stroke for the first time.

Length of history of hypertension

Hypertension is the most prominent modifiable risk factor for ischemic stroke.[14] Chronic hypertension leads to hypertrophy of large cerebral arterial walls and arteriolar walls. It also impairs vasodilator response by alter endothelium mediated dilation. Therefore, chronic hypertension increases susceptibility of cerebral infarction.[15] Our results suggest that the subjects who had hypertension in earlier years tend to have recurrent ischemic stroke in a shorter period. A possible reason is that chronic hypertension alters cerebral vascular morphology, cerebral blood flow (CBF), cerebrovascular reactivity, and increases susceptibility to neurological disorders.[16] SBP>140mmHg was statistically significant in Chi-square test, but not in multivariable linear regression. The reason may be that the variable systolic pressure over 140mmHg was influenced by the length of the history of hypertension.

Age of 60 years

In the univariate analysis, we performed the one-way ANOVA to examine the difference of age in different time interval group, but the results showed that age was not statistically significant(p=0.520) as a continuous variable. We then examined every cutoff point to stratify patients for comparison. Age of 60 years was the only cutoff point that was statistically significant in Chi-square test and in multivariable linear regression. Therefore, age of 60 years may be the demarcation point for stroke patients in predicting the time of recurrent ischemic stroke. The median time interval among subjects who were under 60 years in ischemic group was 55.00 months and the median time interval among subjects who were over 60 years was 70.00 months. According to previous researches, the stroke incidence increases with age[17] and older patients have a higher rate of stroke recurrence and mortality.[8] Our study is consistent with previous studies for 64.6% of patients who had recurrent ischemic stroke were over 60 years of age. On the other hand, our result indicates that the patients who had recurrent ischemic stroke over 60 years of age had a longer time interval from first attack than those who was under 60 years of age. A possible reason is that risk factors and etiology of ischemic stroke in younger patient differ significantly from older patients.[18] A broader spectrum of etiologies and a high percentage of unknown stroke etiologies in young adults may be the reason for the difference of time interval between young and old stroke patients.

The factors related to the time interval of recurrent hemorrhagic stroke

In contrast with ischemic subjects, age (p=0.014)

showed significant differences in hemorrhagic subjects instead of age of 60 years. Age was also statistically significant (p=0.001) as a continuous variable in linear model. The time interval increased with age in hemorrhagic group. However, unlike ischemic subjects, the age influenced the length of time interval without an explicit demarcation point. According to our study, those who experienced their first recurrent stroke at younger age tend to have a shorter time interval compared to people who had their first recurrent stroke at older age. Previous studies have shown that, compared with stroke in older people, stroke in the young has a disproportionately large economic impact by leaving victims disabled during their most productive years. Of concern are data indicating an increasing incidence of stroke in younger age groups.[19] In conclusion, more attention should be paid to young patients in prevention of recurrent stroke.

We acknowledge the following limitations of our study. First, this was a hospital-based study; the characteristics may differed from those of the general population. Second, this was a retrospective study. We conducted an analysis not only based on a computerized database created during the period of patient hospitalization, but also based on the previous diagnosis and medical history from other hospital, which may lead to the information bias.

In conclusion, we evaluate the time interval between first-ever stroke and first recurrence of stroke. The median time interval was 36.01 months. We also identified the possible associated risk factors to time interval in patients with recurrent ischemic and hemorrhagic stroke. It may provide the evidence for physicians and patients to predicting the time of recurrent stoke develop strategies to prevent recurrent stroke.

ACKNOWLEDGEMENT

We appreciate the support of Department of Clinical Epidemiology of The First Affiliated Hospital of China Medical University.

DISCLOSURE

Conflict of interest: None.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; 380: 2095-128.
2. 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: 245-54.
3. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke* 2011; 42: 1489-94.
4. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 1994; 25: 333-7.
5. Albertson M, Sharma J. Stroke: current concepts. *S D Med* 2014; 67: 455, 7-61, 63-5.
6. Lakshminarayan K, Schissel C, Anderson DC, et al. Five-year rehospitalization outcomes in a cohort of patients with acute ischemic stroke: Medicare linkage study. *Stroke* 2011; 42: 1556-62.
7. Pennlert J, Eriksson M, Carlberg B, Wiklund PG. Long-term risk and predictors of recurrent stroke beyond the acute phase. *Stroke* 2014; 45: 1839-41.
8. Sun Y, Lee SH, Heng BH, Chin VS. 5-year survival and rehospitalization due to stroke recurrence among patients with hemorrhagic or ischemic strokes in Singapore. *BMC Neurol* 2013; 13: 133.
9. Ray BK, Hazra A, Ghosal M, *et al.* Early and delayed fatality of stroke in Kolkata, India: results from a 7-year longitudinal population-based study. *J Stroke Cerebrovasc Dis* 2013; 22: 281-9.
10. Lv Y, Fang X, Asmaro K, *et al.* Five-year prognosis after mild to moderate ischemic stroke by stroke subtype: a multi-clinic registry study. *PloS One* 2013; 8: e75019.
11. Yoon Y, Lee DH, Kang DW, et al. Stroke recurrence patterns are predicted by the subtypes and mechanisms of the past, non-cardiogenic stroke. *Eur J Neurol* 2013; 20: 928-34.
12. Jones SB, Sen S, Lakshminarayan K, Rosamond WD. Poststroke outcomes vary by pathogenic stroke subtype in the Atherosclerosis Risk in Communities Study. *Stroke* 2013; 44: 2307-10.
13. Hankey GJ, Jamrozik K, Broadhurst RJ, *et al*. Long-term risk of first recurrent stroke in the Perth Community Stroke Study. *Stroke* 1998; 29: 2491-500.
14. Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. *Neurotherapeutics* 2011; 8: 319-29.
15. Muller JE, Tofler GH, Stone PH. Circadian variation and triggers of onset of acute cardiovascular disease. *Circulation* 1989; 79: 733-43.
16. Muller JE, Abela GS, Nesto RW, Tofler GH. Triggers, acute risk factors and vulnerable plaques: the lexicon of a new frontier. *J Am Coll Cardiol* 1994; 23: 809-13.
17. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121: e46-e215.
18. Goeggel Simonetti B, Mono ML, Huynh-Do U, et al. Risk factors, aetiology and outcome of ischaemic stroke in young adults: the Swiss Young Stroke Study (SYSS). *J Neurol* 2015.
19. Smajlovic D. Strokes in young adults: epidemiology and prevention. *Vasc Health Risk Manag* 2015; 11: 157-64.