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Clinical characteristics of early and late recurrent ischaemic stroke

Charakterystyka kliniczna wczesnych i późnych nawrotowych udarów niedokrwiennych

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Abstract

Background and purpose: The aim of the study was to search for differences between clinical characteristics of recurrent ischaemic stroke which occurred within the fifth year after the first event or later, and early recurrence, i.e. within the first year after first-ever ischaemic stroke. We also tried to determine prognostic factors of late recurrent ischaemic episodes.

Material and methods: The patients were divided into two groups: group I comprised 124 individuals with recurrence within the first year, and group II – 98 individuals in whom the recurrent episode appeared within the fifth year or later.

Results: A significantly higher percentage of patients in group I demonstrated evident stenosis (70% or more) of internal carotid artery ipsilateral to stroke ($p = 0.023$). In this group more cardioembolic strokes were found compared to group II, while in the latter, predominantly lacunar strokes appeared ($p = 0.046$ and 0.0002, respectively). Group II patients significantly more frequently reported acetylsalicylic acid application, including systematic drug use ($p = 0.001$). No evident differences were found between groups considering other important non-modifiable and modifiable risk factors of stroke.

Conclusions: Small differences between risk factors of ischaemic stroke profiles in patients with early and late recurrent episodes do not allow us to distinguish unequivocally a group of patients with better prognosis regarding the time of recurrent stroke. Use of antiplatelet drugs, either systematic

Streszczenie

Wstęp i cel pracy: Celem opracowania jest wykazanie różnic w charakterystyce klinicznej chorych, u których do kolejnego udaru niedokrwiennego doszło w piątym roku po pierwszym w życiu epizodzie lub później, z osobami, u których nawrót dokonał się w ciągu pierwszego roku. Autorzy analizowali też, czy możliwe jest określenie czynników prognostycznych późnego nawrotu udaru.

Materiał i metody: Chorych podzielono na dwie grupy: grupa I obejmowała chorych z nawrotem do roku (124 osoby), a grupa II – chorych z nawrotem w piątym roku po pierwszym udarze lub później (98 osób).

Wyniki: U znamiennie większego odsetka chorych grupy I stwierdzono zwężenie światła tętnicy szyjnej wewnętrznej tożstronnej do udaru, przekraczające 70% ($p = 0.023$). W grupie tej więcej było udarów pochodzenia sercowo-zatorowego, natomiast w grupie II znamiennie częściej występowały udary zatokowe (odpowiednio $p = 0{,}046$ i $p = 0{,}0002$). Wśród chorych grupy II znamiennie większy był odsetek osób deklarujących przyjmowanie kwasu acetylosalicylowego, w tym systematyczne ($p = 0{,}001$). Nie wykazano istotnych różnic między grupami chorych odnośnie do częstości występowania innych najważniejszych modyfikowalnych i niemodyfikowalnych czynników ryzyka udaru.

Wnioski: Niewielkie różnice w profilu czynników ryzyka udaru niedokrwiennego mózgu między chorymi z wczesnym i późnym nawrotem nie pozwalają na jednoznaczne wyodrębnienie grupy chorych z lepszym rokowaniem co do czasu powtórnego udaru. Przyjmowanie leków przeciwpłytkowych,

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or non-systematic, and lacunar stroke are independent, positive prognostic factors of delay of potential recurrent stroke.

Key words: recurrent stroke, early and late recurrence, prognostic factors.

zarówno systematyczne, jak i niesystematyczne, oraz udar zatokowy są niezależnymi, pozytywnymi czynnikami prognostycznymi opóźnienia potencjalnego nawrotu udaru.

Słowa kluczowe: udary nawrotowe, wczesny i późny nawrót, czynniki prognostyczne.

Introduction

Despite updated evidence-based guidelines related to the secondary prevention of ischaemic stroke [1,2], recurrent stroke remains one of the most important challenges of contemporary medicine, and involves specialists in various medical disciplines. Recent studies indicate even increased incidence of stroke [3,4]. Recurrent stroke comprises 75% of all sequelae of ischaemic stroke [5]. It causes greater neurological deficit and greater mortality than first-ever stroke [6,7]. About 200 000 patients die annually in the USA due to recurrent stroke [4]. It is estimated that the greatest risk of stroke recurrence falls in the first year after stroke, exceeding 20%, and during the subsequent 4 years the risk is 5-8% annually [8-10]. Risk of recurrence within a year after stroke is 15 times greater (and 9 times higher within 5 years after stroke) than in people at the same age and the same sex without stroke [11,12].

Answers to many apparently simple questions remain vague. Estimations of cumulative 5-year risk of recurrence are very divergent and range from 6 to 42% [2,13]. Risk factors for stroke recurrence were rather arbitrarily divided into so-called risk factors for early recurrence (up to 30 days) and late recurrence (after 30 days). The most important risk factors for early recurrence include hypertension, atrial fibrillation and hypercholesterolaemia [14,15]. Opinions on the importance of factors that predict delay of potential stroke recurrence are, however, diverse. While the importance of advanced age, a non-modifiable factor, is stressed [16], other papers list advanced age as the equivalent to hypertension, atrial fibrillation, type 2 diabetes, smoking, as well as extent and aetiology of the previous stroke [17-20]. It should also be noted that the cause of recurrence in relation to the above-mentioned conventional risk factors cannot be established in numerous patients [21].

The aim of the study was to search for differences in clinical characteristics of patients in whom stroke recurred in the fifth year or later after first-ever stroke in comparison with subjects in whom stroke recurred within the first year after the first-ever stroke. We were also interested whether it is possible to establish predictive factors for better prognosis, in this case later recurrence of stroke.

Material and methods

This prospective study was performed in 1460 patients with ischaemic stroke who were hospitalized in the Department of Neurology, Pomeranian Medical University during 2005-2008 and in whom the required data were available. Recurrent stroke was diagnosed in 442 patients: it was the first recurrence in 357 patients (75.5%), the second in 76 subjects (23.03%), the third in 4 patients (1.21%), and the fourth in 1 patient (0.3%). Patients with the first recurrence and complete clinical data were selected and further divided into 2 groups according to the time to the recurrence. The first group included 124 patients with the stroke recurrence within 1 year after the first-ever stroke. The second group included 98 patients with the stroke recurrence in the fifth year after first-ever stroke or later. A total of 222 patients (62.2% of patients with the first recurrence of stroke) was analysed.

It was assumed that patients suffered from hypertension or type 2 diabetes according to the history, medical records and/or medications used. Blood pressure (BP) was measured during the hospital stay at least twice daily; in ambulant patients it was measured in a sitting position after at least 10 minutes' rest. Incident hypertension was diagnosed if systolic BP (SBP) was ≥ 140 mm Hg and/or diastolic BP (DBP) was ≥ 90 mm Hg twice after the acute period of stroke [22]. In doubtful cases, 24-hour BP recording was performed.

Each patient had the glycaemia profile assessed, starting on admission. Glycaemia was measured 4 times daily. Incident diabetes was diagnosed if fasting glucose was ≥ 126 mg/dL twice or if the random glucose independently of meals was ≥ 200 mg/dl after the acute phase of stroke. An alternative criterion for the diagno-

sis of diabetes was glycaemia ≥ 200 mg/dL measured 2 hours after oral load with 75 g of glucose (oral glucose tolerance test) [23]. In patients with the diabetes diagnosed before their stroke or in doubtful cases, the level of haemoglobin A1C was measured.

Atherogenic dyslipidaemia was defined as LDL cholesterol level > 114 mg/dL, HDL cholesterol level < 40 mg/dL in men or < 46 mg/dL in women, or triglyceride level > 150 mg/dL [24]. Blood lipids were measured after admission within the first day of stroke.

Patients were divided into smokers and non-smokers. Marked alcohol abuse was noted with the ICD-10 criteria for addiction. Weekend alcohol drinking in amounts markedly greater than doses assumed to be prophylactic ones was also considered as alcohol abuse.

ECG and laboratory studies (troponin T level and MB isoenzyme of creatine kinase) were assessed on admission to rule out acute myocardial infarction concurrent with stroke. Ischaemic heart disease was diagnosed also in patients with the ECG signs of previous myocardial infarction or myocardial ischaemia.

The dynamics of stroke was analysed. Only patients with progressive stroke (signs increase up to the third day and then stabilize) were included because most patients were discharged before day 21, which is the term that determines qualification of patients to the group of reversible stroke (signs disappear within 21 days) or completed stroke (signs persist longer than 21 days). Patients with transient ischaemic attack were excluded.

Aetiology of stroke was assessed according to the TOAST classification: A – stroke due to large artery disease, B – cardioembolic stroke, C – stroke due to small vessel disease (lacunar strokes), D – stroke due to other, rare causes, and E – unclassified stroke. Lacunar stroke was defined as stroke without current or previous territorial strokes, as assessed with computed tomography [25].

Brain CT was performed once, within the first hours of hospitalization in the Department of Imaging Diagnostics and Interventional Radiology, Pomeranian Medical University (Head: Professor Anna Walecka) with a Picker PQ5000 machine with 10-mm slices (lamp parameters: 120 kV and 250 mA, 512 × 512 array).

Statistical analysis

Continuous variables were characterized by median, minimum value, maximum value and standard deviation (SD). Continuous variables had skewed distribution ($p < 0.05$, Shapiro-Wilk test) and therefore non-parametric tests were used. Comparisons between more than two groups were carried out with Kruskal-Wallis ANOVA, and comparisons between two groups were performed with Mann-Whitney *U*-test. Nominal variables were compared with chi-square test or with Fisher's exact test (for 2 × 2 tables). Logistic regression was used to perform univariate and, afterwards, multivariate analysis of odds ratio (OR) with 95% confidence interval (95% CI). *P*-value of less than 0.05 was considered as significant. Statistical calculations were performed with Statistica 7.1.

Results

Patients in both groups were of similar age: median age was 69 in group I and 73 in group II ($p = 0.23$). Men were more prevalent in both groups: 60.5% in group I and 54.1% in group II, but the difference was non-significant ($p = 0.34$)

Groups did not differ significantly regarding the prevalence of hypertension: 77.4% in group I and 80.6% in group II; $p = 0.4$; hypertension, however, lasted significantly longer in patients from group II. Median duration of hypertension was 17 years in group II (range: 2-40 years, SD = 7.3) and 9 years in group I (range: 1-31 years, SD = 5.44) ($p = 0.03$). A similar percentage of patients in both groups reported systematic use of antihypertensive medications: 76% in group I and 68% in group II ($p = 0.17$).

Groups did not differ significantly regarding the percentages of patients with ischaemic heart disease (group I – 53.2% and group II – 53.1%). History of myocardial infarction was recorded in 8.1% of patients from group I and in 3.1% of patients from group II ($p = 0.14$).

Atrial fibrillation was diagnosed in 26.5% of patients from group I and in 22.4% of patients from group II ($p = 0.53$). There was no difference in percentages of patients with paroxysmal and permanent atrial fibrillation. Diabetes was found in 32.3% of patients from group I and in 26.5% of patients from group II ($p = 0.38$). Mean HbA_{1c} level was 5.58 in group I and 5.9 in group II ($p = 0.89$).

Atherogenic dyslipidaemia was found in 25.8% of patients from group I and in 22.4% of patients from group II ($p = 0.58$). No significant difference was noted between groups regarding smoking. Alcohol abuse was reported in similar percentages of patients in both groups (25% and 28.6%, respectively; $p = 0.65$).

Stenosis > 70% of ipsilateral internal carotid artery was found significantly more frequently in patients from group I (22.6%) than in group II (9.2%, $p = 0.023$). Stenosis > 70% of contralateral internal carotid artery was found in similar percentages of patients in both groups: 12.1% (group I) and 9.2% (group II) ($p = 0.77$). Ipsilateral and contralateral occlusion of that artery was also found in similar percentages of patients in both groups.

Patients from group II significantly more often reported use of acetylsalicylic acid (ASA): 16.1% (group I) and 52.5% (group II; $p = 0.001$), including the systematic use of ASA (12% in group I and 42.3% in group II; $p = 0.001$). Among patients in group I, 83.9% did not use ASA at all, and 4.1% took that drug irregularly.

The percentage of patients with progressive stroke diagnosed up to the time of discharge or to death was similar in both groups: 11.5% (group I) and 13.2% (group II) ($p = 0.76$). The case fatality was similar in both groups (12.7% and 12.8%, $p = 0.99$).

The causes of stroke among patients in group I, according to the TOAST classification, were as follows: stroke due to large artery disease – 16.1%, cardioembolic stroke – 34.7%, lacunar stroke – 11.3% and unclassified stroke – 37.9% of patients. The respective aetiology of stroke among patients in group II was as follows: 14.3%, 22.4%, 32.7%, and 30.6%. None of the patients was diagnosed with a rare cause of stroke. As one may conclude from the above data, cardioembolic strokes were more prevalent in group I, and lacunar strokes were more common in group II ($p = 0.046$ and $p = 0.0002$, respectively).

Within the subgroup of patients who died after their stroke, stroke itself was considered as the cause of death in 75% of patients from group I and in 83.3% of patients from group II ($p = 0.7$). Other patients died because of acute heart failure, myocardial infarction, gastrointestinal bleeding, or pulmonary embolism. Median time between admission and death was similar in both groups: 9 days in group I (range: 1-39, SD = 7.8 days), and 7 days in group II (range: 1-30 days; SD = 7.7 days); $p = 0.84$.

Detailed clinical characteristics of patients are presented in Table 1.

Univariate logistic regression analysis was performed to establish predictors of better prognosis, i.e. later recurrence of stroke. Results of that analysis are shown in Table 2. Significant predictors included: use of ASA in general (OR = 3.56; 95% CI: 1.49-3.86; $p = 0.0001$), systematic use of ASA (OR = 2.02; 95% CI: 1.39-2.94; $p = 0.0001$) and lacunar stroke (OR = 3.81; 95% CI: 1.88-7.68; $p = 0.0002$). Among factors that decrease chances for later recurrence of stroke were: cardioembolic stroke (OR = 0.54; 95% CI: 0.29-0.99; $p = 0.042$) and significant stenosis of ipsilateral internal carotid artery (OR = 0.35; 95% CI: 0.15-0.778; $p = 0.001$). Variables established as predictive factors for late recurrence of stroke in univariate analysis were then entered into multivariate analysis. Results of that analysis are shown in Table 3. Strong and independent predictors of late recurrence of stroke included: stroke due to small vessel disease (lacunar one), general use of ASA and systematic use of ASA.

Discussion

We studied consecutive stroke patients in whom it was possible to collect all necessary data to analyse the characteristics of patients with early (within a year) and late (within the fifth year or later) recurrent ischaemic stroke. We recognize the limitation of the study related to completion of data in 62% of patients only. Stroke recurrence was noted in 34.7% of patients, as evident from the data presented. That value is closer to the data of Sarzyńska-Długosz, who noted recurrent episodes, mostly ischaemic strokes, in 26.2% of patients within the year after first-ever stroke [10]. Other authors report rates of 6-14% [9,12,26]. Those figures include data from the 1980s and 1990s. The increased number of recurrences may result both from the increased incidence of first stroke and from better chance of survival in the era of stroke units [27].

Despite numerous studies, it was impossible to establish a certain panel of risk factors for recurrent ischaemic stroke. The most commonly cited risk factors include the following non-modifiable factors: advanced age, history of transient ischaemic attack or stroke, and male sex; modifiable risk factors include hypertension, atrial fibrillation, ischaemic heart disease, myocardial infarction, type 2 diabetes, significant carotid stenosis, and post-stroke dementia [10,26,28]. As is evident from the above, all the most important risk factors for ischaemic stroke are also relevant for recurrence. This leads to the justified opinion that each stroke survivor, irrespectively of his/her vascular risk factor profile, should be considered as a person with a high risk of stroke recurrence.

Table 1. Clinical characteristics of patients with early (group I) and late (group II) ischaemic stroke recurrence

	Patients with early stroke recurrence (n = 124)	Patients with late stroke recurrence (n = 98)	P-value
Age, years; median (range); SD	69 (36-96); 11.59	73 (44-93); 9.85	0.23
Sex			
men	75 (60.5%)	53 (54.1%)	0.34
women	49 (39.5%)	45 (45.9 %)	
Hypertension			
yes	96 (77.4%)	79 (80.6%)	0.4
no	20 (16.1%)	19 (19.4%)	
not available	8 (6.5%)		
systematically treated	73 (76%)	54 (68.35%)	0.17
duration, years; median (range); SD	9 (1-31); 5.44	17 (2-40); 7.3	**0.03**
Ischaemic heart disease	66 (53.23%)	52 (53.1%)	1.0
History of myocardial infarction	10 (8.1%)	3 (3.1%)	0.14
Atrial fibrillation	33 (26.5%)	22 (22.4%)	0.53
paroxysmal	12 (9.6%)	10 (10.2%)	
permanent	21 (16.9%)	12 (12.2%)	0.58
Diabetes mellitus	40 (32.3%)	26 (26.5%)	0.38
HbA_{1c} level	5.58 (N = 76)	5.9 (N = 60)	0.89
increased HbA_{1c} level, n (%)	11 (14.5%)	10 (16.7%)	0.45
Atherogenic dyslipidaemia	32 (25.8%)	22 (22.4%)	0.58
Smoking	37 (29.8%)	27 (27.6%)	0.77
Alcohol abuse	31 (25%)	28 (28.6%)	0.65
Stenosis of ipsilateral internal carotid artery	28 (22.6%)	9 (9.2%)	**0.02**
Stenosis of contralateral internal carotid artery	15 (12.1%)	9 (9.2%)	0.77
Use of ASA			
no	104 (83.9%)	47 (48%)	**0.001**
yes	20 (16.1%)	51 (52%)	
systematic	15 (12%)	41 (41.8%)	**0.001**
irregular	5 (4.1%)	10 (10.2%)	
Dynamics			
progressive stroke	14 (11.5%)	13 (13.2%)	0.762
TOAST classification of stroke			
large vessel disease	20 (16.1%)	14 (14.3%)	0.46
cardioembolic	43 (34.7%)	22 (22.4%)	**0.046**
lacunar	14 (11.3%)	32 (32.7%)	**0.0002**
unclassified	47 (37.9%)	30 (30.6)	0.32
Death	16 (12.7%)	12 (12.8%)	0.99
cause of death			
stroke	12 (75%)	10 (83.3%)	0.7
other causes*	4 (25%)	2 (16.7%)	
Time from admission to death, median (range); SD	9 (1-39 days); 7.8	7 (1-30); 7.67	0.84

**(acute heart failure, pulmonary embolism, gastrointestinal bleeding, renal failure), SD – standard deviation*

Table 2. Prognostic factors of late recurrent ischaemic stroke (in fifth year or later) in univariable analysis of logistic regression

	OR	95% CI	*P*-value
Sex	0.77	0.44-1.36	0.34
Age	1.02	0.99-1.05	0.09
Hypertension	0.61	0.31-1.19	0.45
Inadequate treatment of hypertension	0.94	0.47-1.87	0.85
Ischaemic heart disease	1.02	0.65-1.60	0.94
History of myocardial infarction	1.01	0.74-1.35	0.34
Atrial fibrillation	0.84	0.56-1.24	0.37
Diabetes mellitus	0.69	0.35-1.33	0.49
Atherogenic dyslipidaemia	0.75	0.68-1.22	0.64
Smoking	0.89	0.49-1.62	0.71
Alcohol drinking	1.20	0.65-2.22	0.55
Use of ASA	3.56	1.49-3.86	**0.0001**
Systematic use of ASA	2.02	1.39-2.94	**0.0001**
Significant stenosis of ipsilateral internal carotid disease	0.35	0.15-0.78	**0.001**
Significant stenosis of contralateral internal carotid disease	1.23	0.32-1.45	0.24
Stroke due to large artery disease	0.87	0.41-1.83	0.71
Cardioembolic stroke	0.54	0.29-0.99	**0.0422**
Lacunar stroke	3.81	1.88-7.68	**0.0002**
Unclassified stroke	0.72	0.41-1.27	0.26

OR – odds ratio, CI – confidence interval

Table 3. Prognostic factors of late recurrent ischaemic stroke (in fifth year or later) in multivariable analysis of logistic regression

	OR	95% CI	*P*-value
Lacunar stroke	3.58	1.22-4.31	**0.03551**
Use of antiplatelet drugs	1.96	1.12-2.61	**0.00213**
Systematic use of antiplatelet drugs	1.88	1.24-2.89	**0.00341**

Nevertheless, some patients experience recurrent stroke shortly after the first episode, and other patients have the recurrent stroke only after several years. We were interested whether any difference exists in the clinical picture of early and late recurrence, and moreover, whether it is possible to establish risk factors for later recurrence, i.e. for better prognosis.

Our analysis did not show any significant difference between patients with early and late recurrence regarding prevalence of the most important modifiable and non-modifiable risk factors. This was true for age, gender, hypertension, atrial fibrillation (both paroxysmal and permanent), ischaemic heart disease, diabetes, atherogenic dyslipidaemia, smoking and alcohol use. A similar percentage of patients reported systematic treatment of hypertension, levels of glycated haemoglobin in diabetics were similar in both groups, and the percentage of patients with increased level of glycated haemoglobin was also similar. Patients did not differ also regarding other clinical characteristics of early and late recurrent strokes: general case fatality, case fatality due to the stroke, and survival time during the acute stroke period.

Significant differences, however, were noted in the antiplatelet treatment. Significantly more patients in group II reported use of ASA, including systematic use of ASA. This result confirms the efficacy of ASA used in secondary prevention of ischaemic stroke right from the beginning of the first vascular episode and justifies its recommended use for that type of prevention, at level A according to the EBM standards [1,29,30]. ASA is not only effective, but also seems to be the safest antiplatelet drug in secondary prevention of stroke; while some studies suggest bet-

ter efficacy of combined use of ASA and dipyridamole [31,32], others indicate an increased risk of bleeding with that combined therapy [33].

Another significant difference between the two analysed groups was the greater percentage of patients with significant stenosis of internal carotid artery among patients in group I. This finding confirms the indication for early carotid endarterectomy or endovascular procedures within those arteries after the first-ever stroke [34-37].

Still another difference between the two groups was the cause of stroke assessed according to TOAST criteria. Cardioembolic strokes were more prevalent in patients from group I, and strokes due to small vessel disease were more often seen in patients from group II. This may be explained from the pathogenetic point of view. Assuming that thrombus within the heart develops over a prolonged period, it is unknown why the release of embolic material causing clinical signs occurs at a point in time that is difficult to predict. It is known, however, that the risk of release of other thrombus parts in the form of embolic material is very high soon after the first episode [38]. This provides an explanation for the increased number of early recurrences after cardioembolic stroke. On the other hand, it might be expected that small vessel disease without the concurrent atherosclerosis of large vessels would have less dynamic progression and, consequently, give a better chance for later recurring stroke. We assumed that this mechanism of "delayed" recurrent episode was present in our patients from group II.

Multivariate logistic regression analysis revealed that the use of ASA, both systematic and irregular, is a strong predictor of later stroke recurrence. This might be explained by the prolonged effect of ASA due to the permanent blockage of platelet cyclooxygenase activity [39]. This effect extends for several days, i.e. for the time of survival of platelets subjected to the activity of ASA. Therefore the short-lasting omission of ASA dose (within a week or so), reported by patients, should not immediately affect the risk of stroke, giving a beneficial preventive effect comparable to those who reported systematic use of ASA. Diagnosis of lacunar stroke was the third predictor of late recurrence, i.e. better prognosis. Diagnosis of small vessel disease was established during hospitalization due to the recurrent stroke, but we assumed that the first strokes in those patients were also lacunar ones, given the fact that the pathomechanism of recurrent stroke is the same as the first-ever stroke in most cases [11], and having the results of the CT that showed abnormalities typical for small vessel disease only, without concurrent lesions suggesting previous strokes of type A or B according to TOAST.

Our study revealed little difference in the clinical profile of patients with early versus late recurrence of ischaemic stroke. It fully supports the classification of all stroke survivors into the group at high risk of recurrence. It also suggests a need for systematic secondary prevention of stroke in all patients after a first-ever ischaemic episode, although ischaemic stroke due to small vessel disease gives a better chance of late recurrence than cardioembolic stroke or stroke due to significant stenosis of the internal carotid artery. In the light of these studies, prophylactic use of antiplatelet drugs, even non-systematic ones, is an unquestionable independent positive prognostic factor. The value of that predictor is even greater because it is fully modifiable by the patients at risk of recurrent stroke.

Conclusions

1. Small differences in the profile of risk factors for ischaemic stroke between patients with early and late recurrence of stroke do not enable unequivocal separation of a group of patients with a better prognosis regarding the time to recurrent stroke.
2. Use of antiplatelet drugs, both systematic and irregular, and lacunar stroke are independent positive predictors of delay of potential recurrent stroke.

Disclosure

Authors report no conflict of interest.

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