Kaohsiung Journal of Medical Sciences (2013) 29, 32—36

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

Timing of stroke onset determines discharge-functional status but not stroke severity: A hospital-based study

Li-Min Liou [a], Hsiu-Fen Lin [b,c], Chin-Ling Tsai [a], Ruey-Tay Lin [b,c], Chiou-Lian Lai [b,c,*]

[a] *Department of Neurology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[b] *Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan*
[c] *Department of Master's Program in Neurology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Received 6 January 2012; accepted 17 February 2012
Available online 9 October 2012

KEYWORDS
Circadian variation;
Functional outcome;
Stroke onset

Abstract Circadian variation of the onset time of acute ischemic stroke has been well studied. However, little is mentioned about the circadian variation of discharge-stroke severity and discharge-functional status. This study evaluated the impact of onset time on discharge-stroke severity and the functional status of acute ischemic stroke. Brain magnetic resonance imaging was performed on 274 acute ischemic stroke patients (66.42% male; mean age = 64.81 ± 12.80 years). All times of onset were assigned to 4-hourly periods (six groups) starting from midnight. Stroke severity/functional status was evaluated on admission and discharge using the National Institute of Health Stroke Scale (NIHSS) score/modified Rankin Scale (mRS) and Barthel Index (BI), respectively. Using mRS, but not NIHSS score and BI, it was possible to differentiate the best and worst groups on discharge. Patients in group 2 (4 to <8 AM) and group 6 (8 to <12 PM) had best and worst functional status, respectively. To control other stroke risk factors, multiple logistic regression analyses were conducted to examine the role of onset time in discharge mRS. Aside from age, onset time was a significant indicator in mRS, while gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and current smoking were not. In conclusion, there is also circadian variation of discharge-functional status in patients with acute ischemic stroke when assessed by mRS.

* Corresponding author. Department of Neurology, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung City 807, Taiwan.
E-mail address: liou.lm@gmail.com (C.-L. Lai).

http://dx.doi.org/10.1016/j.kjms.2012.08.005

Introduction

Stroke is the leading cause of disability worldwide and requires significant resources measured in both health-care costs and lost productivity [1]. Associated predictors and stroke outcome are important issues in clinical practice, but unfortunately with discrepant results [2,3]. Circadian variation, which characterizes many normal physiological processes and several cardiovascular disorders such as myocardial infarction, and sudden cardiac death [4–6] may be the factors responsible for stroke onset [4–7]. A review of the related literature clearly shows that circadian rhythm of onset time of ischemic stroke, with a major morning peak and a secondary evening peak, is well studied [4,6,8–10]. Interestingly, ischemic stroke and its subtypes, and hemorrhagic stroke had similar circadian variation of onset time either in Asian or in Western cultures [6,10]. First-ever and recurrent stroke also have a similar circadian rhythm [4,8]. However, little is mentioned about the relationships between onset time and severity/functional status of acute ischemic stroke. The present study prospectively examined the association between onset time and discharge-stroke severity/functional status, with the hypothesis that certain onset time would be associated with more severe discharge-stroke severity/functional status.

Patients and methods

Patients

It was a prospective study. Patients were recruited from the Kaohsiung Municipal Hsiao-Kang Hospital from October 2007 to October 2009 using the following criteria: (1) clinical symptoms of stroke, defined as rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting 24 hours, without any apparent causes other than a vascular origin [11], and (2) no intracranial hemorrhage on computed tomography (CT) or magnetic resonance imaging (MRI) scan. All patients had at least one CT or MRI scan performed within 24 hours of stroke onset.

Data collection and assessment of risk factors

Demographic data and risk factors for stroke were obtained from each study participant. Hypertension was defined as each individual's previous record of at least two blood pressure (BP) readings of 140/90 mmHg or use of antihypertensive medications. Diabetes was defined as fasting blood glucose of 126 mg/dL or use of hypoglycemic medications, and hyperlipidemia as serum levels of total cholesterol of 200 mg/dL. The following information was obtained immediately after hospital admission: age, sex, history of previous transient ischaemic attack (TIA) or stroke, time of onset of symptoms, National Institute of Health Stroke Scale (NIHSS) score, risk factors for stroke, results of laboratory investigations, and findings on CT or MRI of the brain. The NIHSS score, modified Rankin Scale (mRS), and Barthel Index (BI) were evaluated again on discharge. The onset time in the present study was determined by the neurologist, by questioning patients and/or relatives who observed the onset and who were aware of the last seen well/normal (LSN) time. For patients who first noted symptoms on awakening from sleep, the onset time is categorized after LSN time and prior to the time of awakening. When precise timing was not given, or when the original report did not include data from each of the 24-hourly divisions, the individual was excluded from our study. All times of onset were assigned to 4-hourly periods (six groups) starting from midnight.

Assessment of stroke severity/functional status

NIHSS score/mRS and BI were administered as stroke severity/functional outcome evaluation instruments. The NIHSS is a 15-item impairment scale, intended to evaluate neurologic outcome and degree of recovery for patients with stroke. The scale assesses level of consciousness, extraocular movements, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect). These scales are sensitive measures of stroke severity with high inter-rater reliability [12,13]. The BI [14] evaluates 10 basic activities of self-care (i.e., feeding, grooming, dressing, toileting, bathing, and continence of bowel and bladder) and mobility (i.e. transferring, walking, and climbing the stairs) on a total score of 0 (totally dependent) to 100 (totally independent functioning). The mRS [15] is a simplified global assessment of function in which a score of 0 indicates no impairment while a score of 5 indicates severe disability.

Statistical analysis

The Chi-square test along with 95% confidence intervals to evaluate the circadian pattern of stroke onset time was applied to the number of observed versus expected strokes during each 4-hour interval (six groups). The strategy was used to estimate the relative risk of strokes occurring at specific time periods: it was based on a comparison of the observed number of strokes compared with the average for six 4-hour intervals. The Chi-square test evaluated the circadian rhythm of admission, and discharge-stroke severity/functional status was applied to the NIHSS score/mRS and BI of observed versus expected strokes during each 4-hour interval (six groups). By using *post hoc* analysis, we were able to determine the best and worst patient groups. Multiple logistic regression with adjustment for cardiovascular risk factors (e.g., age, gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and current smoking) was used to evaluate the influence of onset time on discharge mRS. We also calculated the impact of age on mRS by simple linear regression test, and the correlation between admission and discharge mRS by Pearson correlation coefficient. A p value of <0.05 was considered statistically significant.

Results

Initially, 302 patients with acute ischemic stroke confirmed by clinical diagnosis and brain CT/MRI results

were included. Sixteen patients were in critical clinical condition and transferred to other hospital from emergency room (ER). Nine patients could not remember the accurate stroke onset and were excluded from the study. Therefore, 277 eligible patients participated in this study at baseline. Three patients were lost to follow-up due to being transferred to another city or because of an unwillingness to participate further. Altogether, 274 study participants completed all assessments.

The mean age of the 274 participants was 64.81 ± 12.80 years, and 66.42% of them were males. The duration of hospitalization was 9.38 ± 4.37 days. For stroke risk factors, the percentages of diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation, old stroke, and current smoking were 51.5, 81.00, 57.30, 11.70, 43.75 and 43.80, respectively. Table 1 shows patient numbers/percentage in six onset time segments. Group 2 (4 to <8 hours) had most patients with ischemic stroke, while group 1 (0 to <4 hours) had least patients. The admission- and discharge-stroke severity/functional status in six 4-hour time intervals were shown in Table 2. Table 3 shows the relationships between stroke severity and functional status and six 4-hour time intervals. When discharge-functional status was assessed by mRS, there was a significant difference: group 6 and group 2 had the highest and the lowest scale, respectively, on admission. When stroke severity and functional status were assessed by NIHSS/BI, there was no significant difference the between the six groups. To control other stroke risk factors, multiple logistic regression analyses were conducted, using mRS, to examine the role of onset time in discharge-stroke functional status. Multiple logistic regression with adjustment for the cardiovascular risk factors (e.g., age, gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and current smoking) was used to evaluate the influence of onset time on discharge mRS. Aside from age, onset time interval, especially in groups 2 and 6, was a significant indicator in mRS on discharge, while gender, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and current smoking were not risk factors in this control analysis. While group 2 (4 to <8 AM) was associated with favorable functional status, group 6 (8 to <12 PM) had the worst functional status. Simple linear regression test was used to test the correlation between age and discharge mRS. The estimated parameter for age was 0.028296 ($p < 0.0001$, $t = 4.68$). Pearson correlation coefficient was used to find the correlation between the admission and discharge mRS. The correlation coefficient is 0.8480 ($p < 0.0001$).

Discussion

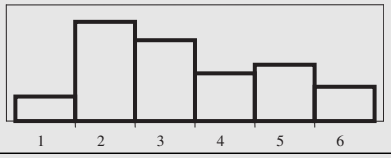
The present study demonstrated that, when evaluated by mRS, circadian rhythm of onset functional status of acute ischemic stroke with the best function was seen in group 2 (4 to <8 AM) and that with the worst function was seen in group 6 (8 to <12 PM) on discharge. When evaluated by NIHSS, either on admission or on discharge, there was no difference between these groups. In addition, there was circadian variation of onset time of stroke with a morning peak (4 to <8 AM).

No single factor is likely to explain the circadian variation (morning peak and afternoon peak) of onset time of stroke [16]. Critical alternation of hemostatic functions (the body's thrombotic/antithrombotic balance, and the brain's susceptibility to ischemia) and BP were the two most acceptable explanations for the "morning peak".

Hematologic alternations would predispose to thrombus formation, including increases in the levels of hematocrit, platelet aggregation, hypercoagulability [5,7,8], plasma catecholamines (epinephrine peaks at 11:00 hours and norepinephrine at 11:00–13:00 hours), cortisol (peaks at 07:00 hours) [4,6,17], and central dopamine activity [7,18,19] in the morning, which would promote ischemic events. BP, which manifests circadian variations and shows a bimodal pattern, may correspond to an increase in morning stroke onset [4–6,8]. Interestingly, Cheung et al. [4] demonstrated a similar pattern of BP diurnal variation in both Chinese and Caucasian populations. Although perhaps not enough, these findings may help explain why Asian and Western studies showed similar circadian variation of stroke onset time [10].

Siesta, a traditionally accepted Greek habit (a kind of afternoon sleep, mostly between 3 and 4 PM), may explain the afternoon peak of stroke onset (between 4 and 6 PM). Recent studies have identified a decline in BP during siesta to levels similar to those of night sleep. Because cardiovascular and cerebrovascular events cluster after awakening from night sleep, while changes from nocturnal baseline are maximal, a second peak of such events after an additional sleep period during the day could be

Table 1 Group stratification by 4-hour intervals of stroke onset time.

Onset time	0 to <4	4 to <8	8 to <12	12 to <16	16 to <20	20 to <24	Total
Group	1	2	3	4	5	6	
Patient number (%)	20 (7.3)	79 (28.8)	64 (23.4)	38 (13.9)	45 (16.4)	28 (10.2)	274 (100)
RR	43.8	173.0	140.2	83.2	98.6	61.3	
95% CI (%)	32.4–55.2	163.0–183.0	129.8–150.6	72.2–94.2	87.8–109.4	50.1–72.5	
Timing of stroke onset separated by groups 1–6							

CI = confidence interval; RR = relative risk.

Table 2 Admission- and discharge-stroke severity and discharge-functional status in 4-hour intervals assessed by BI, mRS, and NIHSS.

Onset time	0 to <4	4 to <8	8 to <12	12 to <16	16 to <20	20 to <24	Total
Group	1	2	3	4	5	6	
Admission NIHSS	4.35 ± 3.22	4.04 ± 3.45	4.81 ± 4.00	5.50 ± 4.84	5.16 ± 4.23	6.61 ± 4.84	4.89 ± 4.07
Discharge NIHSS	3.70 ± 3.05	2.97 ± 2.79	3.83 ± 4.54	4.87 ± 4.86	4.08 ± 4.34	4.36 ± 3.70	3.81 ± 3.95
Discharge mRS	2.25 ± 1.16	2.14 ± 1.17	2.47 ± 1.37	2.68 ± 1.38	2.56 ± 1.39	3.04 ± 1.35	2.46 ± 1.32
Discharge BI	78.00 ± 27.31	80.00 ± 25.94	74.84 ± 30.26	68.82 ± 30.32	72.67 ± 30.65	60.36 ± 33.44	73.89 ± 29.62

BI = Barthel Index; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale.

hypothesized [10]. In addition, nocturnal low BP itself is a risk factor for ischemic stroke [20]. The prominent afternoon peak was not found in our study. This might be because most of the patients did not have the habit of having an afternoon sleep between 3 and 4 PM, unlike those in countries with a habit of siesta.

BP has a great impact on acute ischemic stroke and its prognosis. Either too low or too high BP is associated with worse outcomes, which obeys a U-shaped relationship [21]. Not only hypertension is a risk factor of ischemic stroke, but also an elevated BP during stroke can result in further vascular damage, increasing the risk of hemorrhagic transformation and early recurrent stroke. Hypotension is also an important issue for acute ischemic stroke. Aggressive treatment of elevated BP could result in secondary reduction of perfusion in the area of ischemia and expand the size of the infarction [22]. Nakamura et al. [20] also found that patients who developed a recurrent attack during sleep had a nocturnal BP dip pattern prior to the attack.

The circadian BP rhythm might possibly explain why group 2 (4—8 AM) and group 6 (8 PM—12 AM) in our study had better and worse outcome, respectively. The circadian BP rhythm is disrupted and a transient elevation of BP is observed in up to 80% of patients with acute ischemic stroke [23,24]. Poststroke hypertension may aim to enhance the perfusion in the penumbra [25]. In a healthy population, circadian BP rhythm has the lowest values during 1—5 AM and highest values during 9 AM to 6 PM. While from 5 to 9 AM, BP tends to increase, from 6 PM to 1 AM, it tends to decrease [26]. Therefore, one may assume that when acute ischemic stroke occurs during 5—9 AM, it is much easier to achieve the perfusion in the penumbra, which results in better outcome because the BP tends to increase physiologically. On the contrary, when acute ischemic stroke occurs during 6 PM to 1 AM, the BP tends to decrease; it would lead to a worse outcome.

Table 3 Relationships between admission and discharge severity/functional status of acute ischemic stroke and six 4-hour time intervals on admission.

Functional status	Onset time—group	*p*
Admission NIHSS[a]	6 (H), 2 (L)	0.078
Discharge NIHSS[a]	—	0.220
Discharge mRS[a]	6 (H), 2 (L)	0.036*
Discharge BI[a]	2 (H), 6 (L)	0.053

*$p < 0.05$.
BI: Barthel Index; H = groups with highest score; L = groups with lowest score; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale.
[a] By chi-square test with *post hoc* analysis.

Although mRS and BI are all indicators of functional stroke outcome, there are still differences between them. While mRS [15] is a simplified global assessment of function, BI [14] further emphasizes on self-care. Liou et al. reported that cerebral white matter lesions can predict functional stroke outcome. They found that peripheral white matter lesions were associated with mRS and BI, and subcortical white matter lesions were related to mRS but not to BI [27]. It appears that mRS is more related to physiology than BI. Takekawa et al. found that the pattern of circadian rhythm during the acute stage of stroke is a predictor of functional prognosis when assessed by mRS. The circadian rhythm was evident in patients who were ambulatory without assistance (mRS $\leq$3), whereas infradian rhythm was evident in patients who were unable to walk without assistance (mRS >4) [28]. These may explain why circadian rhythm of stroke onset time was correlated with functional outcome assessed by mRS in our study. Furthermore, our results should be cautiously interpreted because of a potential type I error due to different diversity data in the two functional outcome parameters.

Our study had several limitations that are worth noting. First, the time of stroke onset in patients with stroke on awakening was not accurate. Most authors support the existence of circadian variation of stroke onset time despite redistributing patients over the previous 8 or 6 hours [10]. One author reported that, when considering onset time of waking state and on awakening together, there was still a circadian variation [29]. To date, there is no marker that can indicate the accurate onset time of stroke [8]. Concurrent use of the concept of LSN can increase the accuracy. Second, our study was based on data from a single regional hospital and concerned only hospitalized patients. Patients with severe stroke were transferred to a medical center. There was also no information from patients who were not admitted, died prior to or soon after admission, and were not seen by the Department of Neurology. However, Ricci et al. reported similar results of circadian variation of onset time of stroke in community- and hospital-based studies [30]. Third, in the present study, the data did not allow for a firm conclusion on overall stroke functional outcome because there was only the discharge-stroke severity/functional survey, which might

not be sufficient to represent overall functional status after stroke. Furthermore, in a related literature review, functional admission score has been found to be positively correlated with functional outcome in most studies [31—36]. Thus, the findings in our study still have predictive and clinical values.

Also, circadian variation of discharge-stroke functional status was observed in patients with acute ischemic stroke when assessed by mRS. Group 2 (4 to <8 AM), although with most patients, was associated with favorable functional status, whereas group 6 (8 to <12 PM), with the least number of secondary patients, had the worst functional status. We should seriously consider providing selected medical and social resources according to this circadian phenomenon.

References

[1] Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, et al. Heart disease and stroke statistics—2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25—146.

[2] Friday G, Alter M, Lai SM. Control of hypertension and risk of stroke recurrence. Stroke 2002;33:2652—7.

[3] Kissela B, Lindsell CJ, Kleindorfer D, Alwell K, Moomaw CJ, Woo D, et al. Clinical prediction of functional outcome after ischemic stroke: the surprising importance of periventricular white matter disease and race. Stroke 2009;40: 530—6.

[4] Cheung RT, Mak W, Chan KH. Circadian variation of stroke onset in Hong Kong Chinese: a hospital-based study. Cerebrovasc Dis 2001;12:1—6.

[5] Sloan MA, Price TR, Foulkes MA, Marler JR, Mohr JP, Hier DB, et al. Circadian rhythmicity of stroke onset. Intracerebral and subarachnoid hemorrhage. Stroke 1992;23:1420—6.

[6] Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. Stroke 1998;29:992—6.

[7] Marsh 3rd EE, Biller J, Adams Jr HP, Marler JR, Hulbert JR, Love BB, et al. Circadian variation in onset of acute ischemic stroke. Arch Neurol 1990;47:1178—80.

[8] Lago A, Geffner D, Tembl J, Landete L, Valero C, Baquero M. Circadian variation in acute ischemic stroke: a hospital-based study. Stroke 1998;29:1873—5.

[9] Ince B. Circadian variation in stroke. Arch Neurol 1992;49:900.

[10] Spengos K, Vemmos KN, Tsivgoulis G, Synetos A, Zakopoulos NA, Zis VP, et al. Two-peak temporal distribution of stroke onset in Greek patients: a hospital-based study. Cerebrovasc Dis 2003;15:70—7.

[11] Bonita R. Epidemiology of stroke. Lancet 1992;339:342—4.

[12] D'Olhaberriague L, Litvan I, Mitsias P, Mansbach HH. A reappraisal of reliability and validity studies in stroke. Stroke 1996; 27:2331—6.

[13] Goldstein LB, Samsa GP. Reliability of the National Institutes of Health Stroke Scale. Extension to non-neurologists in the context of a clinical trial. Stroke 1997;28:307—10.

[14] Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61—5.

[15] van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604—7.

[16] Gallerani M, Manfredini R, Ricci L, Cocurullo A, Goldoni C, Bigoni M, et al. Chronobiological aspects of acute cerebrovascular diseases. Acta Neurol Scand 1993;87:482—7.

[17] Turton MB, Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. Clin Chim Acta 1974;55:389—97.

[18] Globus MY, Ginsberg MD, Harik SI, Busto R, Dietrich WD. Role of dopamine in ischemic striatal injury: metabolic evidence. Neurology 1987;37:1712—9.

[19] Periodicity of ischemic stroke. Stroke 1989;20:1590—1.

[20] Nakamura K, Oita J, Yamaguchi T. Nocturnal blood pressure dip in stroke survivors. A pilot study. Stroke 1995;26:1373—8.

[21] Spence JD. New treatment options for hypertension during acute ischemic or hemorrhagic stroke. Curr Treat Options Cardiovasc Med 2007;9:242—6.

[22] Powers WJ. Acute hypertension after stroke: the scientific basis for treatment decisions. Neurology 1993;43(3 Pt 1): 461—7.

[23] Dawson SL, Evans SN, Manktelow BN, Fotherby MD, Robinson TG, Potter JF. Diurnal blood pressure change varies with stroke subtype in the acute phase. Stroke 1998;29: 1519—24.

[24] Bath P, Chalmers J, Powers W, Beilin L, Davis S, Lenfant C, et al. International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. J Hypertens 2003;21:665—72.

[25] Mattle HP, Kappeler L, Arnold M, Fischer U, Nedeltchev K, Remonda L, et al. Blood pressure and vessel recanalization in the first hours after ischemic stroke. Stroke 2005;36:264—8.

[26] Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978;1:795—7.

[27] Liou LM, Chen CF, Guo YC, Cheng HL, Lee HL, Hsu JS, et al. Cerebral white matter hyperintensities predict functional stroke outcome. Cerebrovasc Dis 2010;29:22—7.

[28] Takekawa H, Miyamoto M, Miyamoto T, Yokota N, Hirata K. Alteration of circadian periodicity in core body temperatures of patients with acute stroke. Psychiatry Clin Neurosci 2002; 56:221—2.

[29] Omama S, Yoshida Y, Ogawa A, Onoda T, Okayama A. Differences in circadian variation of cerebral infarction, intracerebral haemorrhage and subarachnoid haemorrhage by situation at onset. J Neurol Neurosurg Psychiatry 2006;77:1345—9.

[30] Ricci S, Celani MG, Vitali R, La Rosa F, Righetti E, Duca E. Diurnal and seasonal variations in the occurrence of stroke: a community-based study. Neuroepidemiology 1992;11: 59—64.

[31] Carroll D. The disability in hemiplegia caused by cerebrovascular disease: serial studies of 98 cases. J Chronic Dis 1962;15: 179—88.

[32] Hertanu JS, Demopoulos JT, Yang WC, Calhoun WF, Fenigstein HA. Stroke rehabilitation: correlation and prognostic value of computerized tomography and sequential functional assessments. Arch Phys Med Rehabil 1984;65: 505—8.

[33] Ahlsio B, Britton M, Murray V, Theorell T. Disablement and quality of life after stroke. Stroke 1984;15:886—90.

[34] Bourestom NC. Predictors of long-term recovery in cerebrovascular disease. Arch Phys Med Rehabil 1967;48:415—9.

[35] Drake Jr WE, Hamilton MJ, Carlsson M, Blumenkrantz J. Acute stroke management and patient outcome: the value of Neurovascular Care Units (NCU). Stroke 1973;4:933—45.

[36] Granger CV, Greer DS, Liset E, Coulombe J, O'Brien E. Measurement of outcomes of care for stroke patients. Stroke 1975;6:34—41.