Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy

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Summary

Background Computed tomography (CT) must be done before thrombolytic treatment of hyperacute ischaemic stroke, but the significance of early ischaemic change on CT is unclear. We tested a quantitative CT score, the Alberta Stroke Programme Early CT Score (ASPECTS).

Methods 203 consecutive patients with ischaemic stroke were treated with intravenous alteplase within 3 h of symptom onset in two North American teaching hospitals. All pretreatment CT scans were prospectively scored. The score divides the middle-cerebral-artery territory into ten regions of interest. Primary outcomes were symptomatic intracerebral haemorrhage and 3-month functional outcome. The sensitivity and specificity of ASPECTS for the primary outcomes were calculated. Logistic regression was used to test the association between the score on ASPECTS and the primary outcomes.

Findings Ischaemic changes on the baseline CT were seen in 117 (75%) of 156 treated patients with anterior-circulation ischaemia included in the analysis (23 had ischaemia in the posterior circulation and 24 were treated outside the protocol). Baseline ASPECTS value correlated inversely with the severity of stroke on the National Institutes of Health Stroke Scale ($r=-0.56$, $p<0.001$). Baseline ASPECTS value predicted functional outcome and symptomatic intracerebral haemorrhage ($p<0.001$, $p=0.012$, respectively). The sensitivity of ASPECTS for functional outcome was 0.78 and specificity 0.96; the values for symptomatic intracerebral haemorrhage were 0.90 and 0.62. Agreement between observers for ASPECTS, with knowledge of the affected hemisphere, was good (κ statistic 0.71–0.89).

Interpretation This CT score is simple and reliable and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment.

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Introduction

There is evidence that intravenous recombinant tissue plasminogen activator (alteplase) is an important treatment for acute ischaemic stroke. A systematic review of 17 clinical trials suggested that thrombolysis, though associated with an increased risk of symptomatic intracerebral haemorrhage, may increase the proportion of patients with stroke surviving and able to live independently.[1] The most convincing evidence for the efficacy of alteplase comes from the National Institute of Neurological Disorders and Stroke (NINDS) study,[2] which randomised patients within 3 h of stroke. However, there is uncertainty about who to treat—for instance, the elderly, patients with severe strokes, and those with early ischaemic change on computed tomography (CT).

CT in acute stroke is highly sensitive for the detection of intracerebral haemorrhage. Concern has arisen about the reliable detection of early ischaemic change on CT and of its significance in relation to functional outcome and the risk of symptomatic haemorrhage before the administration of thrombolytic therapy. The European Cooperative Acute Stroke Study (ECASS) trials identified the importance of early CT ischaemic changes in predicting benefit with intravenous thrombolysis.[3,4] Patients were eligible only if there was CT ischaemia involving less than a third of the distribution territory of the middle cerebral artery. This method is not reliable, however, and even experienced stroke clinicians have difficulty in recognising and quantifying such changes by currently available methods.[5-9] A system is needed to improve the general reading of CT scans.

The main aim of our study was to assess the validity, reliability, and usefulness of a standardised quantitative CT grading system, the Alberta Stroke Programme Early CT Score (ASPECTS), in acute anterior-circulation ischaemic stroke. We hypothesised that by quantification of early ischaemic change detected on CT scan before the administration of alteplase, outcome in terms of independence, dependence, and symptomatic intracerebral haemorrhage could be predicted. We assumed that other factors may modify the effects of ASPECTS (ie, serum glucose and age).[2,10,11] Such a score, if reliable and practical, could be applied to future clinical trials to identify the most appropriate patients for interventional stroke therapy with thrombolytic or potential neuroprotective drugs.

Methods

Patients

Consecutive stroke patients at two North American teaching hospitals who met established NINDS criteria were treated within 3 h with intravenous alteplase. Only patients thought to
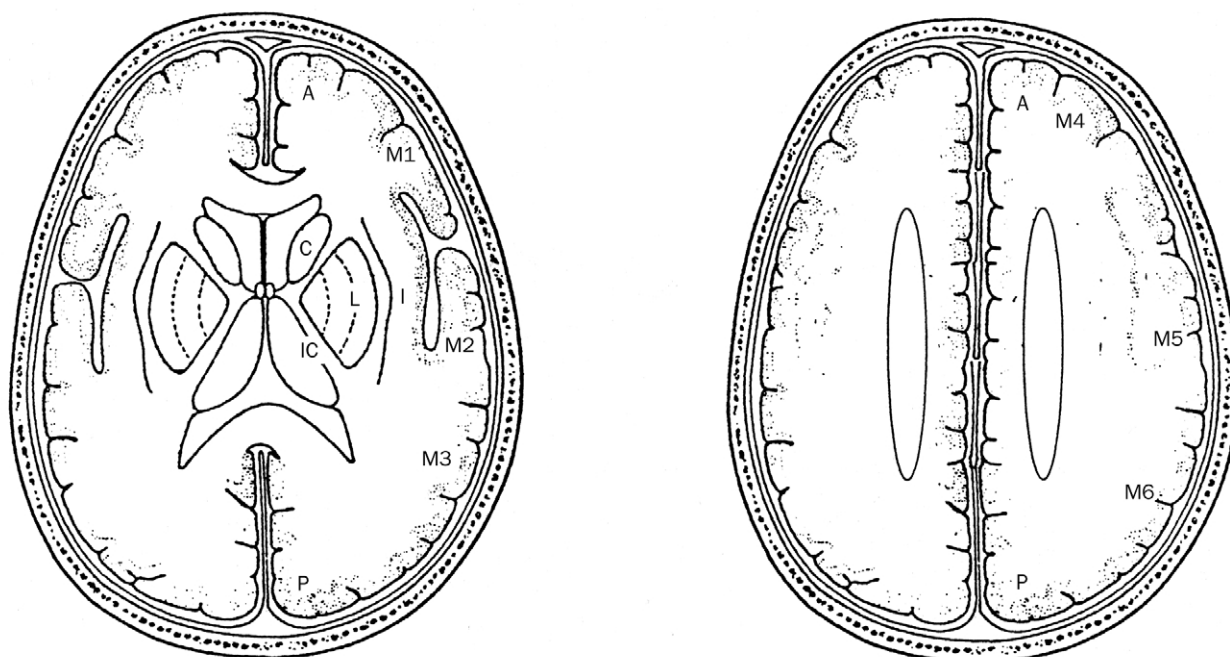
Figure 1: **ASPECTS study form**
A=anterior circulation; P=posterior circulation; C=caudate; L=lentiform; IC=internal capsule; I=insular ribbon; MCA=middle cerebral artery; M1=anterior MCA cortex; M2=MCA cortex lateral to insular ribbon; M3=posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories immediately superior to M1, M2, and M3, rostral to basal ganglia.
Subcortical structures are allotted 3 points (C, L, and IC). MCA cortex is allotted 7 points (insular cortex, M1, M2, M3, M4, M5, and M6).

have anterior-circulation ischaemia (including some severe lacunar strokes), at presentation, were included in the analysis.

Procedures
Before treatment, all patients had a CT brain scan and the score on the National Institutes of Health Stroke Scale (NIHSS) was recorded by a stroke neurologist; in five cases the NIHSS score had to be extrapolated from the medical records.[12] All the CT scans were done on fourth-generation scanners with 10 mm slice thickness without contrast enhancement. The NIHSS score was recalculated just before the follow-up 24 h CT scan. Both the baseline and 24 h NIHSS scores were done without knowledge of the results of baseline or 24 h CT scan or the clinical progress of the patient.

Stroke severity, measured by the NIHSS (an incremental scale, with higher scores indicating a more severe neurological deficit), was categorised into five groups: 0–5, 6–10, 11–15, 16–20, and more than 20. Primary outcome measures were score on the modified Rankin scale at 3 months (independence 0–2 *vs* dependence 3–5 and death), and symptomatic intracerebral haemorrhage. The Rankin scale score at 3 months was assessed by a stroke neurologist or nurse stroke practitioner who was not aware of the results of the baseline CT, baseline NIHSS score, or the acute clinical events.

To detect intracerebral haemorrhage, CT scans were done 24 h after the onset of stroke and when the patient's neurological state had deteriorated. A haemorrhage was classified as symptomatic if it had not been seen on a previous CT scan and there had subsequently been a decline in the neurological status.

The baseline CT scan was subsequently assessed with knowledge of the side affected but without knowledge of the baseline stroke severity, 24 h CT scan, or the clinical outcome by a panel of CT reviewers consisting of stroke neurologists (PAB, AMD, AMB) and experienced neuroradiologists (RJS, WYH, MEH) for the presence of haemorrhage, parenchymal hypoattenuation in the territories of the anterior, middle, and posterior cerebral arteries and the vertebrobasilar artery distribution, focal swelling, and a hyperdense middle-cerebral-artery sign. The 24 h scan was assessed under the same

conditions. Parenchymal hypoattenuation was defined as a region of abnormally low attenuation of brain structures relative to attenuation of other parts of the same structures or of the contralateral hemisphere. Focal brain swelling was defined as any focal narrowing of the cerebrospinal-fluid space due to compression by adjacent brain structures such as effacement of the cortical sulci or ventricular compression.

The affected territory of the middle cerebral artery was graded by a systematic quantitative scoring system, ASPECTS, and according to the rule of one-third or less or more than a third of the territory affected by ischaemia,[5] done at the same time. The ASPECTS value was calculated from two standard axial CT cuts, one at the level of the thalamus and basal ganglia, and one just rostral to the ganglionic structures.

For ASPECTS, the territory of the middle cerebral artery is allotted 10 points (figure 1). 1 point is subtracted for an area of early ischaemic change, such as focal swelling, or parenchymal hypoattenuation, for each of the defined regions. A normal CT scan has an ASPECTS value of 10 points. A score of 0 indicates diffuse ischaemia throughout the territory of the middle cerebral artery.

As a separate part of the study, the reliability within and between observers for detection and quantification of early CT ischaemia was assessed between three pairs of clinicians: stroke neurologists (PAB, AMD), radiology trainees (JNS, DK), and experienced neuroradiologists (WYH, MEH) on a sample of 68 scans. Each clinician assessed the baseline CT scan in isolation at a viewing box initially without access to any clinical information and then at least 3 weeks later with the benefit of only the knowledge of the affected hemisphere.

Statistics
Spearman's rank correlation coefficient was used to test the association between baseline ASPECTS value and baseline NIHSS score, ASPECTS value at 24 h, and functional outcome. A review of the data suggested that baseline ASPECTS value in two categories ($\leqslant 7$ and >7) discriminated independence from dependence and death. Similarly, previous studies[1] have suggested that more severe stroke is associated with greater risk of poor outcome and symptomatic
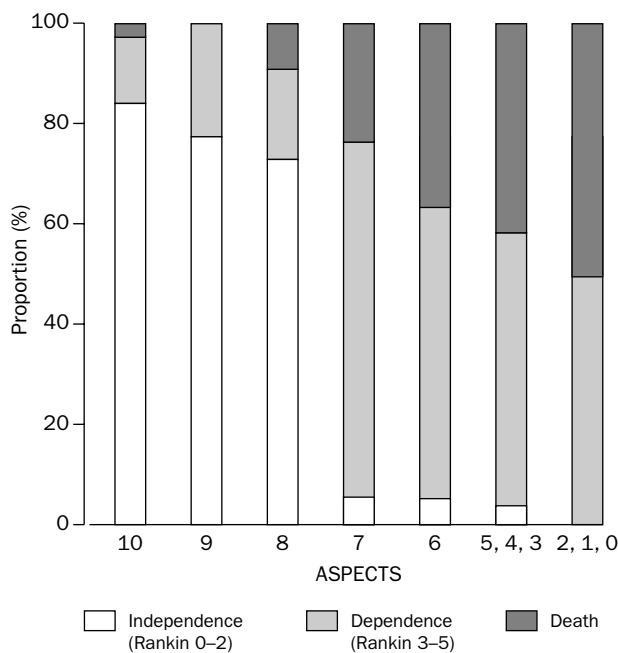
Figure 2: **ASPECTS and functional outcome**
Spearman correlation coefficient –0·69, p<0·001.

intracerebral haemorrhage, and therefore, NIHSS scores of 15 or less (less severe) and more than 15 (more severe) were used. The validity of ASPECTS (≤7 vs >7), NIHSS score (≤15 vs >15), and a third or less versus more than a third of middle-cerebral-artery territory were assessed by calculation of the sensitivity and specificity for functional outcome and symptomatic haemorrhage. Logistic regression was used to examine the predictive ability of ASPECTS (≤7 vs >7) in terms of functional outcome (independence vs dependence and death) and symptomatic haemorrhage, in the presence of other potential risk factors that may modify the effect of ASPECTS (ie, age and serum glucose).

κ statistics[13] were used to assess the clinicians' agreement with each other for the presence of early CT ischaemic change and for the quantification of early CT ischaemia according to the one-third middle-cerebral-artery territory rule and ASPECTS. A κ value of 0 indicates agreement no better than chance, and a value of 1 indicates perfect agreement. The within-rater agreement was measured for each individual observer.

Results

Of 203 consecutive patients treated with intravenous alteplase, 23 were identified clinically to have sustained ischaemia in the posterior circulation, and 24 were treated outside the established NINDS protocol,[14] and were prospectively excluded from the analysis. Four patients who presented within the 3 h treatment window were excluded from treatment on the basis that the baseline CT scan revealed ischaemic changes too extensive to treat with alteplase. At 3 months, all were dependent or had died. The main reasons for treatment to be withheld from patients presenting with cerebral ischaemia within 3 h were non-disabling or mild symptoms and rapidly improving deficit.

The final analysis included 156 patients (mean age 68 years [SD 14]; 72 women and 84 men) treated within 3 h of stroke onset with intravenous alteplase between March, 1996, and May, 1999. 117 (75%) of the 156 patients had evidence of early ischaemic change on baseline CT and 141 (90%) had such features on the 24 h scan.

Among the 154 patients with NIHSS scores at presentation, five (3·2%) had scores of 0–5, 41 (26·6%) scores of 6–10, 35 (22·7%) scores of 11–15, 41 (26·6%) scores of 16–20, and 32 (20·8%) scores above 20. In total, 31 (19·9%) of these 154 patients had intracerebral haemorrhage confirmed by the 24 h CT; in ten (6·4%) this haemorrhage was associated with neurological deterioration. For two patients, NIHSS and Rankin scores at 3 months were not available but neither had a symptomatic intracerebral haemorrhage. At 3 months, of the remaining patients, 74 (48·1%) were independent, 54 (35·1%) were dependent, and 26 (16·9%) had died.

The median baseline ASPECTS value was 8. The baseline ASPECTS correlated with the baseline NIHSS score ($r=-0·56$ [95% CI $-0·46$ to $-0·78$], p<0·001), the ASPECTS at 24 h ($r=0·88$ [0·84 to 0·91], p<0·001); functional outcome at 3 months ($r=-0·69$ [$-0·57$ to $-0·75$], p<0·001). A baseline ASPECTS of 7 or less sharply discriminated independence, dependence, and death at 3 months (65 patients had scores of 7 or less, and 89 had scores of more than 7; figure 2).

The sensitivity and specificity of the baseline ASPECTS value, NIHSS score, and the one-third middle-cerebral-artery rule in terms of functional outcome (independence vs dependence and death) and symptomatic intracerebral haemorrhage are shown in table 1. Because there were very few symptomatic haemorrhages, the data for ASPECTS and for the one-third middle-cerebral-artery rule were identical.

In logistic regression analysis, baseline ASPECTS value was a significant predictor of both functional outcome (odds ratio 82 [95% CI 23–290], p<0·001) and symptomatic haemorrhage (14 [2–117], p=0·012). Age (≤78 vs >78 years) was a significant predictor of

Test	Functional outcome					Symptomatic haemorrhage				
	Independent	Dependent or dead	Sensitivity	Specificity	Odds ratio (95% CI)	Yes	No	Sensitivity	Specificity	Odds ratio (95% CI)
NIHSS										
≤15 (n=81)	56	25	0·69	0·76	6·8 (3·4–14)	6	75	0·40	0·52	0·7 (0·2–2·7)
>15 (n=73)	18	55				4	69			
ASPECTS										
≤7 (n=89)*	71	18	0·78	0·96	82 (23–290)	1	90	0·90	0·62	14 (1·8–117)
>7 (n=65)	3	62				9	56			
MCA rule										
≤1/3 (n=89)*	67	22	0·73	0·91	25 (10–63)	1	90	0·90	0·62	14 (1·8–117)
>1/3 (n=65)	7	58				9	56			

*n=91 for symptomatic haemorrhage analysis.

Table 1: **Sensitivity, specificity, and odds ratio for NIHSS score, baseline ASPECTS value, and one-third middle-cerebral-artery (MCA) rule for functional outcome and symptomatic haemorrhage**

	κ statistic for agreement between two observers		
	Stroke neurologists	Radiology trainees	Experienced neuroradiologists
Without knowledge of clinical information			
Evidence of early ischaemia	0·25	0·52	0·20
Side of lesion	0·34	0·58	0·35
Evidence of focal brain swelling	0·25	0·41	0·36
≤1/3 vs >1/3 MCA	0·49	0·14	0·37
ASPECTS ≤7 vs >7	0·69	0·39	0·47
With knowledge of affected hemisphere			
Evidence of early ischaemia	0·45	0·34	0·33
Evidence of focal brain swelling	0·24	0·23	0·42
≤1/3 vs >1/3 MCA	0·61	0·64	0·52
ASPECTS ≤7 vs >7	0·85	0·71	0·89

Table 2: **Assessment of agreement between observers**

functional outcome (6·4 [2–20], p=0·002) but not of symptomatic haemorrhage, after inclusion of ASPECTS value and serum glucose in the model (p=0·68). Serum glucose (≤ 10 *vs* >10 mmol/L) was a significant predictor of symptomatic haemorrhage (4·9 [1–21], p=0·032) but not functional outcome, after inclusion of ASPECTS value and age in the model (p=0·36). No interactions were observed between ASPECTS value and age (p=0·86) or serum glucose (p=0·83). Therefore, two multiple logistic regression models were developed. The model that provided the best prediction of functional outcome included ASPECTS value and age; the model that provided the best prediction of symptomatic intracerebral haemorrhage included ASPECTS value and serum glucose. After control for ASPECTS value in the two models, the probability of dependence and death was higher for patients older than 78 years than for those aged 78 years and younger, and the probability of symptomatic haemorrhage was higher for patients with serum glucose higher than 10 mmol/L than for those with concentrations of 10 mmol/L or lower.

Table 2 shows the agreement between observers. The within-rater reliability ranged from 0·26 to 0·76 for the one-third middle-cerebral-artery rule and from 0·67 to 0·82 for ASPECTS.

Discussion

Early ischaemic changes identified on CT during the first few hours after stroke onset represent early cytotoxic oedema and possibly the development of irreversible injury.[15] Attempts to assess the prognostic value of these early ischaemic changes on CT in terms of functional outcome and the risk of intracerebral haemorrhage before administration of thrombolytic therapy have had misleading results.[5] Many have cited the potential superiority of diffusion-weighted magnetic resonance imaging over CT, but discrimination of salvageable from irretreviably injured brain tissue with MRI is not yet possible.[16] Although diffusion-weighted magnetic resonance imaging may become the imaging method of choice, most physicians treating stroke will depend on CT because it is more accessible.

We have shown that a systematic approach to quantification of early CT ischaemic change can improve the identification of cerebral ischemia and is of prognostic value even before treatment is administered. For patients treated with alteplase, as the ASPECTS value decreases, the probabilities of dependence, death, and symptomatic intracranial haemorrhage increase. ASPECTS is a predictor for both functional outcome

and symptomatic haemorrhage. For patients with identical ASPECTS values, inclusion of age and serum glucose in the model further improved the predictive ability. ASPECTS has high sensitivity and specificity for both functional outcome and symptomatic intracerebral haemorrhage. For example, in an individual with an ASPECTS value of 7 or less, the risk of symptomatic intracerebral haemorrhage with alteplase is 14 times that of patients with a score greater than 7. In patients with scores above 7 the rate of symptomatic intracerebral haemorrhage is 1%, slightly higher than the frequency of symptomatic ischaemic haemorrhagic transformation in the placebo group in the NINDS trial (0·6%).[2]

ASPECTS is simple and quick and has good between-observer reliability. However, the results of our study should not be misinterpreted as showing that patients who have an ASPECTS of 7 or less should be excluded from thrombolysis, since we cannot know how these patients would have done if they had not received treatment. Validation of this score in a randomised controlled study is needed.

This scoring method has implications for the design of future stroke trials. It also underlines the arbitrary nature of use of rigid time windows as the basis for treatment decisions. This concept is supported by the observation from ECASS II of no significant difference in outcome between patients treated at 0–3 h and at 3–6 h.[4] Definition of an arbitrary treatment window ignores evidence of wide variation among individuals in potentially salvageable brain tissue.[17] Future "tissue-window" studies could assess how a systematic approach to early CT ischaemic change, such as ASPECTS, can be used to redefine time windows. For instance, a patient with a persistent deficit presenting after the defined time window but with a CT scan that shows only a small area of early ischaemic change (and therefore a high ASPECTS value) might be considered for thrombolytic therapy. In addition to determining trial eligibility, the ASPECTS system has the potential to be used as a surrogate endpoint to provide objective evidence in placebo-controlled neuroprotective trials.

References

1 Wardlaw JM, Yamaguchi T, del Zoppo G. Thrombolytic therapy versus control in acute ischaemic stroke. In: Cochrane Library, issue 4. Oxford: Update Software, 1999.

2 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333:** 1581–87.

3 Hacke W, Kaste M, Fieschi C, et al., for the ECASS Study Group. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; **274:** 1017–25.

4 Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998; **352:** 1245–51.

5   von Kummer R, Allen KL, Holle R, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology* 1997; **205:** 327–33.

6   Dippel DWJ, Du RY, van Beest Holle M, et al. The validity and reliability of early infarct signs on CT in acute ischaemic stroke. *Cerebrovasc Dis* 1997; **7** (suppl 4): 15 (abstr).

7   Schriger D, Kalafut M, Starkman S, et al. Cranial computed tomography interpretation in acute stroke. Physicians' accuracy in determining eligibility for thrombolytic therapy. *JAMA* 1998; **279:** 1293–97.

8   Grotta J, Chiu D, Lu M, et al. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA. *Stroke* 1999; **30:** 1528–33.

9   Wardlaw JM, Dorman PJ, Lewis SC, Sandercock PAG. Can stroke physicians and neurologists identify signs of early cerebral infarction on CT? *J Neurol Neurosurg Psychiatry* 1999; **67:** 651–53.

10 The NINDS rt-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA for ischemic stroke. *Stroke* 1997; **28:** 2109–18.

11 Demchuk AM, Morgenstern LB, Krieger D, et al. Is baseline serum glucose a predictor of hemorrhage after rtPA therapy in acute stroke? *Stroke* 1999; **30:** 34–39.

12 Kasner S, Chalela JA, Luciano JM, et al. Reliability and validity of estimating the NIH stroke scale score from medical records. *Stroke* 1999; **30:** 1534–37.

13 Armitage P, Berry G. Statistical methods in medical research. Oxford: Blackwell Scientific Publications, 1987.

14 Buchan AM, Barber PA, Newcommon NJ, et al. Effectiveness of t-PA in acute ischemic stroke: outcome relates to appropriateness. *Neurology* 2000; **54:** 679–84.

15 del Zoppo GJ, von Kummer R; Hamann GF. Ischaemic damage of brain microvessels: inherent risks for thrombolytic treatment in stroke. *J Neurol Neurosurg Psychiatry* 1998; **65:** 1–9.

16 Baird AE, Warach S. Magnetic resonance imaging of acute stroke. *J Cereb Blood Flow Metab* 1998; **18:** 583–609.

17 Baron JC, von Kummer R, del Zoppo GJ. Treatment of acute ischemic stroke: challenging the concept of a rigid and universal time window. *Stroke* 1995; **26:** 2219–21.