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THROMBOLYTIC THERAPY WITH STREPTOKINASE IN ACUTE ISCHEMIC STROKE

THE MULTICENTER ACUTE STROKE TRIAL — EUROPE STUDY GROUP*

ABSTRACT

Background In patients with acute ischemic stroke, early treatment with thrombolytic agents is thought to permit reperfusion of ischemic neurons and to promote recovery of function. The Multicenter Acute Stroke Trial — Europe (MAST-E) was designed to assess the efficacy and safety of streptokinase in patients with acute ischemic stroke.

Methods Patients with moderate-to-severe ischemia in the territory of the middle cerebral artery were randomly assigned to receive streptokinase (1.5 million units over a period of one hour) or placebo within six hours after the onset of stroke. The primary efficacy outcome was a binary criterion combining mortality and severe disability at six months, with severe disability defined as a score of 3 or higher on the Rankin scale. The primary safety outcomes were mortality at 10 days and cerebral hemorrhage.

Results All randomized patients (156 in the streptokinase group and 154 in the placebo group) were evaluated at six months. The incidence of the primary efficacy outcome was similar in the two groups (124 patients in the streptokinase group and 126 in the placebo group died or had a Rankin score ≥ 3). However, the mortality rate at 10 days was significantly higher in the streptokinase group than in the placebo group (34.0 percent vs. 18.2 percent, $P=0.002$). The higher rate in the streptokinase group was mainly due to the hemorrhagic transformation of ischemic cerebral infarcts. At six months, more deaths had occurred in the streptokinase group than in the placebo group (73 vs. 59, $P=0.06$).

Conclusions In patients with acute ischemic stroke, treatment with streptokinase resulted in an increase in mortality. The routine use of streptokinase cannot be recommended in acute ischemic stroke. (N Engl J Med 1996;335:145-50.)

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ALTHOUGH stroke is a leading cause of death and disability in developed countries, there is no established treatment for acute ischemic stroke. Reperfusion is one possible approach. Interest in reperfusion with thrombolytic agents has been renewed following the success achieved with thrombolysis in patients with acute myocardial infarction.^{1,2} The rationale for reperfusion with thrombolytic agents is that early treatment aimed at the recovery of ischemic neurons leads to increased survival and reduced disability. However, thrombolytic therapy carries the risks of symptomatic cerebral bleeding and reperfusion-associated injury.

Since the late 1950s, reports involving over 3000 patients with stroke treated with various thrombolytic agents have been published; most have been reports of individual cases or small series. Only a few small, randomized, controlled trials have been reported, and it is not possible, on the basis of the data from these studies, to determine whether thrombolytic therapy is effective and safe in patients with acute ischemic stroke.^{3,4} The results of larger randomized trials designed to assess the safety and efficacy of thrombolytic therapy in acute ischemic stroke have recently been published.⁵⁻⁸ We have reported the results of the Multicenter Acute Stroke Trial — Europe (MAST-E) with respect to the safety of streptokinase (based on data from 270 patients). The Data Monitoring Committee recommended that recruitment be stopped early because of an increase in mortality due to intracerebral hemorrhage.⁹

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*The members of the study group are listed in the Appendix. The members of the Writing Committee were M. Hommel, C. Cornu, F. Boutitie, and J.P. Boissel.

Here we report the final results, including the outcome at six months for all 310 patients enrolled in the trial before recruitment was stopped.

METHODS

Study Protocol

The protocol has been described elsewhere.¹⁰ Briefly, MAST-E was a multicenter, double-blind, controlled trial with computerized randomization performed by an independent statistics center. All patients who were hospitalized because of the sudden onset of a focal neurologic deficit attributable to ischemia in the territory of the middle cerebral artery and who could be randomly assigned to a treatment group within six hours after the onset of symptoms were eligible for enrollment. The criteria for exclusion were a mild deficit (MAST score, >55 ¹¹); the resolution of symptoms before randomization; a computed tomographic (CT) scan showing cerebral hemorrhage or a nonvascular disorder; a previous hemorrhagic stroke or a previous stroke with clinical sequelae; recent surgery or trauma; another illness known to compromise the prognosis; or known or suspected pregnancy. Randomization was stratified according to the center and the MAST score (<20 , severe deficit, or 20 to 55, moderate deficit). Patients received either 1.5 million units of streptokinase (Kabikinase, Kabi) or an identical-appearing placebo administered by intravenous infusion over a period of one hour.

Streptokinase and placebo were received in batches at the Drug Supply Center, where they were packaged and numbered non-sequentially. The use of concomitant treatments was left to the discretion of the participating investigators, and details of these treatments were noted on the case-report forms. Quality-control measures included on-site visits and cross-checking of case-report forms and medical records.

The trial was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee in Lyon, France, and the West Ethics Committee in Glasgow, United Kingdom. Patients or family members gave written informed consent. Before its commencement, the trial was registered in the International Society for Thrombosis and Haemostasis Registry, the Ottawa Stroke Trials Registry, and the Major Ongoing Stroke Trials Registry.¹²⁻¹⁴

Outcome Measures and Data Collection

The primary efficacy outcome was a binary criterion combining death and severe disability (Rankin score, ≥ 3) six months after admission. The Rankin scale is a six-point scale that assesses the degree of handicap.¹⁵ The secondary efficacy outcomes were death, recurrent cerebrovascular events, and ischemic events. The Barthel score, on a 20-point scale that assesses the ability to perform 10 activities of daily living, was determined at the six-month visit.¹⁶ The safety outcomes were mortality at 10 days, symptomatic intracranial hemorrhages, and clinically silent intracranial hemorrhages assessed by CT on day 5, or earlier in the event of clinical deterioration.

We calculated that 600 patients should be enrolled to detect a decrease of at least 20 percent in the incidence of the primary efficacy outcome in the streptokinase group, with alpha and beta errors of 5 percent in a two-sided comparison, assuming that the incidence of the primary efficacy outcome in the control group would be 70 percent.

Selection data were collected with the use of a telephone computer system before randomization. Base-line and in-hospital data were collected by the participating investigators and sent to the coordinating center. To ensure a blinded evaluation of the primary efficacy outcome, the six-month follow-up data were collected centrally in France by telephone interviews with each patient, a family member, or the patient's general practitioner by a neurologist unaware of the treatment received by the patient.¹⁷ In the United Kingdom, follow-up data were collected by home visits or

a review of clinic records. These two methods have been shown to be highly correlated in assessing the outcome of stroke.¹⁸ Critical events were documented by the investigators and validated by the Critical Events Committee, which was composed of neurologists not involved in the enrollment or follow-up of patients and unaware of the treatment received.

All CT scans were reviewed independently, with the use of a standard questionnaire, by three neurologists who were unaware of the treatment assignments. CT findings considered to be early signs of stroke included loss of the density contrast of the lentiform nucleus¹⁹; loss of the density contrast of the insular ribbon²⁰; and hemispheric sulcus effacement, either alone or in association with hyperdensity of the middle cerebral artery.²¹ Hemorrhagic transformations were classified as either hemorrhagic infarcts or parenchymal hematomas. Hemorrhagic infarcts have heterogeneous areas of blood with indistinct margins and a speckled or mottled appearance or multiple areas of coalescent hemorrhage within large areas of infarcted tissue, situated in the cortical or basal-ganglia gray matter. Parenchymal hematomas have a homogeneous area of circumscribed hyperdensity, usually with a mass effect and sometimes with ventricular extension.²²

Statistical Analysis

The statistical analysis was performed at the independent Statistics Center, with the use of an intention-to-treat approach. Data from the two treatment groups were compared with Student's *t*-test, Wilcoxon's test, the chi-square test, or Fisher's exact test, as appropriate. For the survival analysis, data were censored at the date of the six-month assessment. The distributions of survival times in the two groups were compared with the log-rank test. A Cox proportional-hazards model was used to make adjustments for the effect of potential confounding variables on in-hospital mortality. All reported *P* values are two-tailed. The Data Monitoring Committee, composed of scientists not involved in the routine running of the trial, reviewed the safety reports each time the 10-day in-hospital assessment had been completed for 50 patients. Two formal interim analyses were planned: the first after the enrollment of 100 patients, and the second after 300 patients had been followed for six months.

RESULTS

From September 17, 1992, to September 26, 1994, 310 patients were enrolled at 48 centers in France and the United Kingdom. The recommendation of the Data Monitoring Committee to stop recruitment has been reported elsewhere.⁹ We report here the results for the 310 patients already enrolled when recruitment was stopped (156 in the streptokinase group and 154 in the placebo group). There was no significant difference in the base-line characteristics of the two groups, except for the number of patients with diabetes mellitus ($P=0.05$) and the frequency of right-sided brain infarction ($P=0.003$), which were higher in the streptokinase group (Table 1). The median delay from the onset of stroke to treatment was 4.58 hours (first and third quartiles, 3.75 and 5.25 hours) in the streptokinase group and 4.50 hours (first and third quartiles, 3.67 and 5.25 hours) in the placebo group. A total of 148 patients in the streptokinase group and 152 in the placebo group received the full dose. Sixty-five percent of the patients in the streptokinase group and 75 percent in the placebo group received concomitant treatment with heparin, and in 31 percent and 12 per-

TABLE 1. BASE-LINE CHARACTERISTICS OF 310 PATIENTS WITH ACUTE ISCHEMIC STROKE ASSIGNED TO RECEIVE STREPTOKINASE OR PLACEBO.*

CHARACTERISTIC	STREPTOKINASE (N=156)	PLACEBO (N=154)
Male sex (% of patients)	56.4	56.5
Age (yr)		
Mean	68.7	69.8
Range	22-92	28-94
Blood pressure (mm Hg)		
Systolic	153.3±1.8	154.0±1.9
Diastolic	84.2±1.1	86.0±1.0
Atrial fibrillation (% of patients)	32.1	26.6
Right-sided ischemia (% of patients)	53.9†	37.0
MAST score	26.1±1.0	23.9±0.9
MAST score <20 (% of patients)	30.1	29.9
Normal Rankin score before stroke (% of patients)	87.2	81.2
History of hypertension (% of patients)	51.9	43.5
History of diabetes mellitus (% of patients)	14.1‡	7.1
Previous stroke with clinical sequelae (Rankin score ≥3) (% of patients)	5.8	8.4
Previous transient ischemic attack (% of patients)	12.2	9.7

*Plus-minus values are means ±SE.

†P=0.003 for the comparison with the placebo group.

‡P=0.05 for the comparison with the placebo group.

cent, respectively (P=0.04), heparin was administered within 12 hours of randomization. Twenty-one patients in each group received aspirin within 48 hours.

The safety and efficacy outcomes are shown in Table 2. A similar number of patients in the two groups had died or were severely disabled at six months. No patients were lost to follow-up. In-hospital deaths and symptomatic cerebral hemorrhages occurred more frequently in the streptokinase group; 26 of the symptomatic cerebral hemorrhages in the streptokinase group were fatal, as compared with 2 in the placebo group (P=0.001). After adjustment of the proportional-hazards model for the MAST score and the side of brain damage, the rate of in-hospital deaths remained significantly higher in the streptokinase group (hazard ratio, 2.18; 95 percent confidence interval, 1.37 to 3.46; P<0.001). At six months, the mortality rate was higher (but not significantly so) in the streptokinase group than in the placebo group, with a relative risk of 1.22 (95 percent confidence interval, 0.94 to 1.58) (Fig. 1). There was a trend toward less severe disability, as indicated by the Rankin score (P=0.05) and the Barthel score (P=0.06) among the survivors in the streptokinase group (Table 3). Among these pa-

tients, the mean (±SE) length of hospitalization was similar in the two groups (35.9±3.5 days in the streptokinase group and 30.3±3.0 days in the placebo group), but the patients in the streptokinase group had shorter stays in rehabilitation units or nursing homes (43.2±5.6 days vs. 67.4±5.6 days, P=0.003).

The CT findings at base line and subsequently (between day 1 and day 5) are shown in Table 4. All 310 patients had either no abnormalities on the CT scan or signs suggestive of acute cerebral ischemia on the initial scan. As compared with the placebo group, significantly fewer patients in the streptokinase group had only an infarct on the subsequent CT scan (P<0.001) and more had scans showing any hemorrhage (P<0.001), hemorrhagic infarction (P=0.03), or parenchymal hematoma (P<0.001).

DISCUSSION

The results of this study do not demonstrate that streptokinase is beneficial in the treatment of acute ischemic stroke, since the incidence of the primary efficacy outcome (death or severe disability at six months) was similar in the two groups. In addition, the mortality rate was higher in the streptokinase group, mainly because of hemorrhagic transformation of cerebral infarcts. Imbalances in important prognostic factors at base line are not likely to have influenced the results, since they remained unchanged after adjustment for these factors. In another clinical trial involving patients with acute stroke, hypotension was thought to be the cause of the high mortality rate, because of the loss of autoregulation of cerebral blood flow.²³ This is an unlikely explanation

TABLE 2. EFFICACY AND SAFETY OUTCOMES IN THE STREPTOKINASE AND PLACEBO GROUPS.

OUTCOME	STREPTOKINASE (N=156)	PLACEBO (N=154)	P VALUE
	no. of patients (%)		
Mortality or Rankin score ≥3 at 6 mo	124 (79.5)	126 (81.8)	0.60
Mortality at 10 days	53 (34.0)	28 (18.2)	0.002
Cerebral hemorrhage in hospital			
Symptomatic	33 (21.2)	4 (2.6)	<0.001
Asymptomatic*	63 (45.3)	57 (41.3)	0.50
Unadjusted mortality			
At 3 mo	70 (44.9)	53 (34.4)	0.06
At 6 mo	73 (46.8)	59 (38.3)	0.13

*Data are based on CT scans from 139 of the patients in the streptokinase group and 138 in the placebo group. CT was not performed in 18 patients who died early (12 in the streptokinase group and 4 in the placebo group) or were discharged before CT could be performed (1 in each group); scans were not available or were of insufficient quality in 11 patients (3 in the streptokinase group and 8 in the placebo group); and CT was performed too late (i.e., more than five days after enrollment) in 4 patients (1 in the streptokinase group and 3 in the placebo group).

of our results, since only 0.6 percent of the patients in our study had hypotensive reactions.

The majority of the patients in both groups received concomitant heparin, although fewer patients in the streptokinase group received this agent, possibly because the early occurrence of hemorrhagic transformation dissuaded the investigators from using heparin. However, concomitant treatment with heparin may partly explain the higher rate of hemorrhagic transformations in the streptokinase group, if it is assumed that heparin potentiates the hemorrhagic effect of streptokinase. The patients enrolled in our trial had a very poor prognosis, with a mortality rate of 38.3 percent and a combined rate of mortality and severe disability of 81.8 percent in the placebo group at six months. It is possible that hemorrhagic transformation induced by thrombolytic therapy occurs more frequently in patients with severe stroke than in those with less severe stroke. To test the hypothesis that there is an interaction between the severity of the stroke and treatment, however, data from less severely affected patients are required.

At the six-month visit, survivors in the streptokinase group, as compared with those in the placebo group, had a greater improvement in function, as judged by their MAST and Barthel scores. Also, fewer patients in the streptokinase group were very severely disabled and more were judged to have normal function on the Rankin scale. One possible explanation for the improved functional status of the survivors in the streptokinase group is that treatment with streptokinase really does improve func-

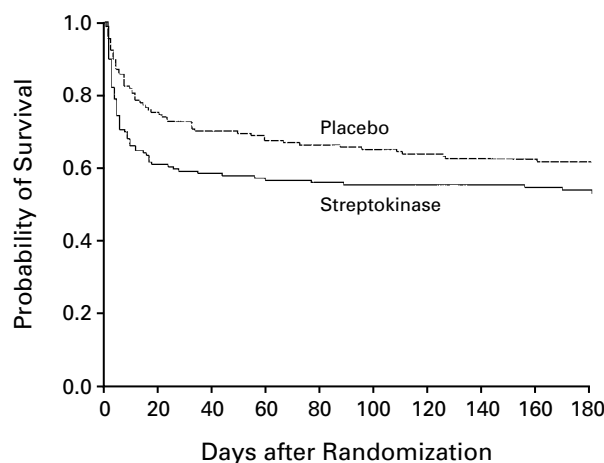


Figure 1. Probability of Survival over a Period of Six Months among Patients with Acute Ischemic Stroke Assigned to Receive Streptokinase or Placebo.

There were more deaths at six months in the streptokinase group than in the placebo group (73 vs. 59; $P = 0.06$ by the log-rank test).

TABLE 3. DISABILITY RATINGS AT SIX MONTHS.

RATING	STREPTOKINASE	PLACEBO	P VALUE
Barthel score — mean \pm SE*	14.8 \pm 0.6	13.0 \pm 0.7	0.06†
MAST score — mean \pm SE‡	70.5 \pm 2.7	63.9 \pm 2.6	0.08
Rankin disability rating — no. of patients (%)§			0.05¶
None	11 (13.3)	7 (7.4)	
Slight	11 (13.3)	10 (10.5)	
Moderate	10 (12.0)	11 (11.6)	
Moderately severe	20 (24.1)	22 (23.2)	
Severe	24 (28.9)	25 (26.3)	
Very severe	7 (8.4)	20 (21.1)	

*Data were available for 81 patients in the streptokinase group and 94 in the placebo group.

†The Wilcoxon rank-sum test was used.

‡Data were available for 80 patients in the streptokinase group and 92 in the placebo group. Data were analyzed with the Wilcoxon rank-sum test.

§Data were available for 83 patients in the streptokinase group and 95 in the placebo group.

¶The chi-square test for trend was used.

tioning; another possible explanation is simply that the more severely affected patients died early because of complications of thrombolytic therapy.

In clinical trials involving patients with acute stroke, mortality is obviously not the only relevant measure of efficacy, since stroke is the leading cause of disability in adults.²⁴ Therefore, combining the disability and mortality rates provides a simple indicator of efficacy in the analysis of results.⁸ However, when the values for the two components of this combined outcome are in opposite directions, as in our trial, the global estimate of the treatment effect is difficult to interpret. One alternative is to integrate death into a categorical scale of disability, with death considered to be the worst state of disability, but this is a questionable assumption.²⁵

Among the five recent trials of thrombolytic therapy in patients with acute stroke, the only trial reporting no increase in mortality at three months was the National Institute of Neurological Disorders and Stroke (NINDS) trial of recombinant tissue plasminogen activator.⁸ In the Australian Streptokinase (ASK) trial, the preliminary analysis showed a 96.4 percent increase in mortality⁵; in the European Cooperative Acute Stroke Study (ECASS), there was a 40.9 percent increase⁶; and in the Multicenter Acute Stroke Trial — Italy (MAST-I), there was a 46.9 percent increase at six months.⁷

Differences in the designs of the trials may explain the differences in results. The same dose of streptokinase was used in MAST-E, MAST-I, and the ASK trial, whereas tissue plasminogen activator was used in ECASS but at a higher dose than that used in the NINDS trial. In addition, the time from the onset of stroke to treatment was four hours in the ASK tri-

TABLE 4. FINDINGS ON INITIAL AND SUBSEQUENT CT SCANS.

FINDING	STREPTOKINASE	PLACEBO	P VALUE
	no. of patients (%)		
Initial scan*			
Early infarction	2 (1.4)	0	0.50
Hemorrhage	0	0	—
Early signs only†	96 (66.7)	89 (61.8)	0.39
No early signs‡	46 (31.9)	55 (38.2)	0.27
Subsequent scan (day 1 to day 5)‡			
Infarction only	37 (26.6)	73 (52.9)	<0.001
Hemorrhage§	93 (66.9)	60 (43.5)	<0.001
Hemorrhagic infarction	75 (54.0)	56 (40.6)	0.03
Parenchymal hematoma	30 (21.6)	4 (2.9)	<0.001
None of the above findings	9 (6.5)	5 (3.6)	0.28

*Data were available for 146 patients in the streptokinase group and 145 in the placebo group. Scans from 19 patients were unavailable or considered to be of insufficiently good quality.

†Early signs were not readable on scans from two patients in the streptokinase group and one in the placebo group.

‡Data were available for 139 patients in the streptokinase group and 138 in the placebo group. See Table 2 for an explanation of the missing data.

§This category consists of hemorrhagic infarction, parenchymal hematoma, or both.

al and six hours in MAST-E, MAST-I, and ECASS, as compared with less than three hours in the NINDS trial. The risk profiles of the study populations also differed among the trials, since the frequency of hemorrhagic transformation in the control group was much lower in the NINDS trial (3.5 percent) than in the other trials (10.9 percent in MAST-I, 36.8 percent in ECASS, and 39.6 percent in MAST-E). The increase in symptomatic intracranial hemorrhage in the treated group, as compared with the placebo group, was similar in all trials. In the NINDS trial, however, this increase did not lead to a higher mortality rate, possibly because of the low risk profile of these patients.

Overall, the results of our trial show an increase in mortality among patients receiving thrombolytic therapy as compared with those receiving placebo, but also provide some evidence that the survivors are less severely disabled. Similar results have been reported in MAST-I⁷ and ECASS.⁶ Only the NINDS trial reported less severe disability without an increase in the mortality rate due to intracranial hemorrhages. The possibility cannot be ruled out that the results of the NINDS trial are due to chance; the results of a single trial do not provide sufficient evidence of the efficacy and safety of a drug, especially when similar trials have conflicting results.

Another possible explanation is that the treatment group in the NINDS trial represented a subgroup of responders (i.e., patients more likely to survive and have less severe disability with treatment), but the specific characteristics of such patients have not yet been identified. Until these characteristics are known,

the widespread use of thrombolytic therapy in patients with acute stroke cannot be recommended. Since more information must be gleaned from the existing data, the decision has been made to conduct a meta-analysis of the data from the patients in all five trials, in order to identify the subgroup likely to benefit from treatment. This analysis is warranted on both scientific and ethical grounds before an additional, very large trial is undertaken to confirm the results of the NINDS trial.

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APPENDIX

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REFERENCES

1. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
2. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12 490 patients with acute myocardial infarction. *Lancet* 1990;336:65-71.
3. Wardlaw JM, Warlow CP. Thrombolysis in acute ischemic stroke: does it work? *Stroke* 1992;23:1826-39.
4. Hommel M, Bogousslavsky J. Thrombolytics in acute cerebral ischaemia. *Expert Opin Invest Drugs* 1994;3:1011-20.
5. Donnan GA, Davis SM, Chambers BR, et al. Trials of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:578-9.
6. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;274:1017-25.
7. Multicenter Acute Stroke Trial — Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995;346:1509-14.
8. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
9. Hommel M, Boissel JP, Cornu C, et al. Termination of trial of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:57.
10. The MAST Group. Protocol for the Multicenter Acute Stroke Trial-Thrombolysis study. *Clin Trials Metaanal* 1993;28:329-44.
11. Orgogozo JM, Asplund K, Boysen G. A unified form for neurological scoring of hemispheric stroke with motor impairment. *Stroke* 1992;23:1678-9.
12. Boissel JP, Bossard N. Registry of Multicenter Clinical Trials: twelfth and thirteenth report — 1990-1991. *Thromb Haemost* 1992;68:752-78.
13. The OSTR Collaborative Group. The Ottawa Stroke Trials Registry Collaborative Group and the development of the Ottawa Stroke Trials Registry (OSTR). *Control Clin Trials* 1994;15:503-11.
14. Major ongoing stroke trials. *Stroke* 1994;25:1317.
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. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14(2):61-5.
17. Jaillard-Serradj A. Value of phone interview in stroke outcome assessment. *Cerebrovasc Dis* 1995;5:269.
18. Candelise L, Pinardi G, Aritzu E, Musicco M. Telephone interview for stroke outcome assessment. *Cerebrovasc Dis* 1994;4:341-3.
19. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction: obscuration of the lentiform nucleus. *Radiology* 1988;168:463-7.
20. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri N, Norman D. Loss of the insular ribbon: another early CT sign of acute middle cerebral artery infarction. *Radiology* 1990;176:801-6.
21. Tomsick TA, Brott TG, Chambers AA, et al. Hyperdense middle cerebral artery sign on CT: efficacy in detecting middle cerebral artery thrombosis. *AJNR Am J Neuroradiol* 1990;11:473-7.
22. Moulin T, Crépin-Leblond T, Chopard JL, Bogousslavsky J. Hemorrhagic infarcts. *Eur Neurol* 1994;34:64-77.
23. Wahlgren NG, MacMahon DG, De Keyser J, Indredavik B, Ryman T. Intravenous Nimodipine West European Stroke Trial (INVEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis* 1994;4:204-10.
24. Modan B, Wagener DK. Some epidemiological aspects of stroke: mortality/morbidity trends, age, sex, race, socioeconomic status. *Stroke* 1992;23:1230-6.
25. Solomon NA, Glick HA, Russo CJ, Lee J, Schulman KA. Patient preferences for stroke outcomes. *Stroke* 1994;25:1721-5.

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