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Lessons Learned from Multicenter Randomized Clinical Trials with Intravenous Thrombolysis for Acute Ischemic Stroke

Christopher Lewandowski and Shahram Lotfipour

The idea of thrombolysis for acute ischemic stroke dates back to the 1950s. Many different drugs, dosages, routes of administration, and times to treatment have been investigated through the 1980s. This experience led to the recent large randomized trials of intravenous thrombolysis completed in the 1990s, the decade of the brain. Three of the trials used streptokinase, and four trials used recombinant tissue plasminogen activator (rt-PA). In this review, we examine these seven randomized intravenous acute ischemic stroke treatment trials, summarize their results, and draw lessons that might be useful for patient care and in future trials.
Key Words: Acute ischemic stroke—trials—thrombolysis—streptokinase—rt-PA—lessons.

Acute ischemic stroke is a leading cause of death and disability in developed countries. Until recently, effective treatment during the acute event has been unavailable. Thrombolytic therapy for acute ischemic stroke is an intuitively attractive idea that has been under investigation since the 1950s.[1] The advent of axial computed tomography (CT) of the head was instrumental in patient selection by allowing objective differentiation of hemorrhagic from ischemic infarction.[2] Various approaches, including intra-arterial and intravenous (IV) drug delivery methods have been tried. Local and superselective intra-arterial approaches with relatively low complication rates and high recanalization rates appear promising.[3-9] The initial studies of IV thrombolysis[10-17] for acute stroke accumulated sufficient data to justify further largescale randomized, double-blinded, placebo-controlled studies. During the 1990s, seven large randomized trials of IV thrombolysis have been reported. Three trials used streptokinase (SK) and four used recombinant tissue plasminogen activator (rt-PA). This review will summarize these trials and the important lessons learned as they pertain to patient care and future trials.

The Streptokinase Trials

The streptokinase trials include the Multicenter Acute Stroke Trial-Europe[18] (MAST-E), the Multicenter Acute Stroke Trial-Italy (MAST-I),[19] and the Australian Streptokinase Trial (ASK).[20] These studies were all multicenter, randomized, placebo-controlled trials. All were double-blind studies, except MAST-I, which was an open-label trial that also tested the effect of aspirin (ASA). In all of the studies, the dose of streptokinase was 1.5 million units infused over 1 hour as in previous myocardial infarction trials. Although none of the trials performed a preliminary dose ranging study, the ASK investigators performed a small safety trial at this dose only.[20] The primary outcome measure was the reduction in combined death and disability at 3 months in each of the trials. The results are summarized in Table 1.

MAST-E

The MAST-E Trial,[18] conducted between September 1992 and September 1994 at 48 centers in France and the

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United Kingdom, included 310 patients with moderate to severe ischemic middle cerebral artery (MCA) infarcts treated within 6 hours of symptom onset. There was concomitant treatment with IV heparin in 65% of the SK group and 75% of the placebo group. ASA also was given to 13% of the SK group and 14% of the placebo group in the first 48 hours.

The study was stopped for safety reasons when the 10-day mortality rate in the SK group reached 34% as compared with 18% in the placebo group (relative risk of 2.18, $P = 02$). The majority of the early deaths in the SK group (26 of 33) were caused by fatal intracranial hemorrhage (ICH). There was no statistically significant difference in the combined outcome of mortality plus severe disability (modified Rankin score [mRS] 3 or greater) at 6 months between SK (79.5%) and placebo (81.8%) (see Table 2 for a description of the scores). The survivors of this study had slightly better (but not statistically significant) function at 6 months than placebo according to the mRS ($P = .05$), MAST score ($P = .08$), and Barthel Index (BI) ($P = .06$). Also, patients in the SK group had shorter stays in rehabilitation units or nursing homes (43.2 days versus 67.4 days for placebo).

MAST-I

The MAST-I Trial,[19] conducted between May 1991 and February 1995 at 70 centers in three countries, included 622 patients treated within 6 hours of symptom onset and was randomized by an open-label protocol to receive SK, ASA (300 mg), both, or neither (control). If the time of symptom onset was unknown (such as found after waking from sleep), it was considered the midpoint in time from last known normal to the time the neurologic deficit was discovered. Concomitant treatment with IV heparin was not allowed for 10 days except as subcutaneous deep venous thrombosis (DVT) prophylaxis.

MAST-I was stopped before the planned enrollment of 1,500 patients because of safety concerns over increased early mortality in the SK groups. The SK-plus-ASA group had an increased 10-day mortality of 34%, significantly higher than the 19% in the SK-alone group, or the 13% rate in the control group. The 10-day mortality in the groups that received SK (either alone or with ASA) was 27% as compared with 12% without SK (ASA or placebo), odds ratio 2.7 (95% confidence interval [CI] = 1.7-4.4). Symptomatic cerebral hemorrhages were more frequent in the SK-plus-aspirin and SK-alone groups than in the group given neither drug (10% and 6%, respectively, versus 0.6%).

The rate of death or severe disability at 6 months was not significantly different among any of the groups. The SK-plus-ASA group had the highest fatality rate (44%) and lowest severe disability rate (20%), and, conversely, the ASA-alone group had the lowest fatality rate (20%) and the highest severe disability rate (42%).

ASK

The ASK Trial,[20] conducted between June 1992 and Decemer 1994 at 40 centers from four Australian states, included 340 patients (initial goal 600) with moderate and severe strokes, randomized within 4 hours of symptom onset. ASA (100 mg) was given to all patients within 4 hours of SK administration. An a priori hypothesis stated that patients treated within 3 hours would fare better than those treated after 3 hours of symptom onset and 79% were randomized after 3 hours.

The trial was suspended in December 1994 after a safety analysis of the first 300 patients. Those treated with SK after 3 hours had an early mortality of 43% with SK compared with 22% with placebo (relative risk [RR] = 2.11, 95% CI, 1.25-3.57). Those treated after 3 hours tended to a have an unfavorable outcome, 52.7% with SK and 43.1% with placebo (RR = 1.22, 95% CI, 0.80-1.86). Those treated within 3 hours (n = 70) showed a nonsignificant trend in favor of SK, 34.1% unfavorable outcome with SK versus 51.7% with placebo (RR = 0.66, 95% CI, 0.28-1.58). There were more symptomatic ICHs in the SK group (12.6% versus 2.4%) as well as more hemorrhagic transformations (19.0% versus 13.0%).

rt-PA Trials

The trials involving rt-PA were all multicenter, randomized, double-blind, and placebo-controlled. The European Cooperative Acute Stroke Study Trial (ECASS 1)[21] and the Second European-Australian Cooperative Acute Stroke Study Trial (ECASS 2)[22] treated patients in the 6-hour window. The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke Trial (ATLANTIS)[23] treated most patients in the 3-to-5 hour window though it began as a 6-hour trial. The National Institute of Neurological Disorders and Stroke rt-PA Studies (NINDS)[24] were the only ones treating within 3 hours of symptom onset. Antiplatelet and antithrombotic agents were withheld in all studies during the first 24 hours. Of the rt-PA trials, only the Atlantis was stopped before completion, after a futility analysis showed no potential for benefit with rt-PA. The results are summarized in Table 3.

ECASS 1

The ECASS Trial conducted between late 1992 and early 1994 entered 600 patients at 75 centers in 14 European countries. Patients with moderate to severe deficit were treated with rt-PA (1.1 mg/k, limit of 100 mg) or placebo. The baseline National Institutes of Health, Stroke Scale (NIH-SS) score was 13 in the placebo group and 12 in the treatment group. The outcome measures of the trial were mortality, ICH, and disability. Improvement in disability was defined as a 15-point improvement

Table 1. *Streptokinase (SK) trials*

Study (number of patients)	Study group	Time to treatment (mean)	Sx ICH rate	Early mortality (10-day)	Late mortality	Primary outcome	Comment
MAST-E[18]		4.5 hrs				D + SD	Survivors in the SK group showed a trend
(n = 310)						@6 mos	toward less disability by mRS (P = .05) and
(156)	SK		21.2%	34.0%	46.8%	79.5%	BI (P = .06). Severe disability was
(154)	PL		2.6%	18.2%	38.3%	81.8%	considered a mRS ≥3 at 6 months.
							Recruitment was stopped early because of an
							increase in 10-day mortality due to ICH.
MAST-I[19]		74% >3 hrs				D + SD	Study was stopped early due to increased 10-day
(n = 622)						@6 mos	mortality. As in Mast-E, rate of D + SD at 6
(157)	SK		6%	19%	28%	62%	months was not significantly different among
(153)	ASA		2%	10%	20%	61%	the groups.
(156)	SK + ASA		10%	34%	44%	63%	
(156)	PL		0.6%	13%	29%	68%	
	All SK		8%	27%	36%	63%	
ASK[20] (n = 340)		79% >3 hrs				D + SD	In ASK 79% of the patients were treated >3
						@3 mos	hours, with a mean of 3 hours and 28
ITT (174)	SK		12.6%	36.2%		48.3%	minutes. Disability was considered a barthel
(166)	PL		2.4%	20.5%		44.6%	index of <60 at 3 months. For patients treated
0-3 hrs (n = 70)							within 3 hour, there was a significant trend
(41)	SK		9.8%	27%		34.1%	toward favorable outcome with SK. This
(29)	PL		0%	24%		51.7%	study also was stopped early because of
3-4 hrs (n = 270)							increased early mortality. Those treated after 3
(133)	SK		14.3%	39%		52.6%	hours tended to have an unfavorable outcome.
(137)	PL		3.6%	20%		43.1%	

NOTE. All SK trials used a combined outcome of death plus severe disability.
Abbreviations: Sx ICH, symptomatic intracerebral hemorrhage; PL, placebo; ASA, aspirin; D, death; SD, severe disability.

Table 2. *Stroke scales*

Stroke Severity Scales	
NIH Stroke Scale (NIHSS)	A 42-point scale that assesses neurologic deficit in 11 categories. A normal function without deficit would give a score of zero, with a severe stroke being a score >20. The scale uses 0 as completely normal and 1 as a single minimal deficit. An overall score of 1-5 would show a mild deficit, 5-15 moderate, 15-20 moderate to severe, and >20 would be a severe deficit.
Scandinavian Stroke Scale (SSS)	A 60-point scale, in which 60 is normal function. The assessed components include consciousness, orientation, speech, eye movement, facial palsy, gait, motor strength, and paresis. A score of <20 would be severe and moderate stroke is between 20 and 40.
Functional Stroke Scales	
Modified Rankin Score (mRS)	A simplified overall assessment of function. It is a 6-point scale (0-5) that assesses the degree of handicap and overall function. Zero is absence of disability, 1 is no significant disability, 2 is slight disability but fully independent, 3 is moderate disability requiring some help, 4 is assistance with all bodily functions, and 5 is severe disability requiring constant nursing care.
Barthel Index (BI)	Assesses the ability to perform 10 activities of daily living over a 100-point scale. A score of 100 would be an individual completely able to care for himself or herself. Points are awarded in increments of 5 or 10, for activities of daily living such as feeding, bathing, grooming, dressing, bladder/bowel control, transferring, and ambulation on level surface and stairs.
Glasgow Outcome Scale (GOS)	A 5-point global assessment of function. A score of 1 is good recovery, 2 moderate disability, 3 severe disability, 4 is survival but in vegetative state, and 5 is death. The original GOS scale had the reverse order with score of 1 as death, but it was reversed in the NINDS studies to better correlate with the other stroke scales.

on the BI or a one-point improvement on the mRS at 90 days. Patients with major early infarct signs on initial CT (such as hypodensity, effacement, or diffuse swelling of more than one third of the MCA distribution) or the most severe hemispheric stroke syndromes were excluded. In anticipation of major protocol violations (predicted 20%, actual 17%), the patients were divided into two groups for analysis, the intention to treat analysis (ITT) (n = 620) and the target population (TP) (n = 511), consisting of those that met the strict inclusion criteria. The most common enrollment violation was CT evidence of major early infarction.

There was a higher 90-day mortality in the ITT group with rt-PA (22.4%) than with placebo (15.8%). This difference did not exist in the TP (19.4% versus 14.8%) because the mortality rate among those excluded because of major protocol violations was higher with rt-PA (n = 20, 33.3%) than with placebo (n = 9, 22.1%). There was no significant mortality difference at 30 days in either analysis. The rates of parenchymal hemorrhage (PH) were greater with t-PA (19.8% versus 6.5% for ITT, 19.4% versus 6.8% for TP; $P < .001$). A decrease in the duration of in-hospital stay by 4 days (ITT: 21 versus 17 days; $P = .002$; TP: 21 versus 17 days; $P = .004$) was found among those treated with rt-PA unrelated to early mortality. The study failed to show a significant improvement on the BI at 90 days in either analysis. There was an improvement on the mRS in the target population (TP) (median score 2 for rt-PA group and 3 for the placebo group, $P = .035$), but not in the ITT analysis. More TP subjects were independent at 90 days when treated with rt-PA, (40.9% versus 29.2% of the placebo TP; odds ratio [OR] = 1.29, 95% CI, 1.09-1.54). The 90-day median Scandinavian Stroke Scale (SSS) score was better with rt-PA in the TP ($P = .03$), but not the ITT analysis ($P = .54$). Treatment with rt-PA provided benefit in both the ITT analysis (P = .003) and the TP ($P < .001$) when measured by the combined BI-mRS score at 90 days. ECASS 1 was a negative trial according to its primary endpoints.

A post-hoc analysis of those treated under 3 hours from symptom onset[25] showed a Rankin Score of 0 to 1 in 46% of the rt-PA treatment group versus 21% in placebo (mortality was 26% versus 21%, respectively). Odds ratio for favorable outcome with rt-PA was 1.5 (95% CI, 1.1-2.0, $P = .008$).

ECASS 2

Based on success in the NINDS trial and the secondary and post-hoc analyses of ECASS 1, a second ECASS trial

Table 3. *rt-PA (recombinant tissue-Plasminogen Activator) trials*

Study (number of patients)	Study group	Time to treatment (mean)	Sx ICH rate	Early mortality	Late mortality	Primary outcome	Comments
ECASS 1[21]		4.4°				BI/RS	17% of the enrolled patients had major protocol violations (predicted 20%) in the ITT with the most common being CT evidence of major early infarction. rt-PA provided benefit in the ITT and TP when measured by combined BI-mRS score (secondary endpoint) at ninety days. This benefit was not present according to the primary endpoints (BI or mRS).
(n = 620)							
ITT	t-PA-313		19.8%	17.9%	22.4%	85/3	
(n = 620)	PL-307		6.5%	12.7%	15.8%	75/3	
TP	t-PA-247		19.4%	14.6%	19.4%	90/2	
(n = 511)	PL-264		6.8%	11.7%	14.8%	80/3	
EACSS 2[22]		>3°					ECASS 2 used a lower dose of rt-PA at 0.9 mg/kg and was aggressive in excluding patients with CT evidence of major early infarction. The median NIHSS score at entry was low (11). The primary outcome measure was the proportion of patients with mRS = 0 or 1. There was no significant difference from placebo. Post-hoc analysis showed benefit for rt-PA using mRS of ≤2 as the outcome measure.
Total	t-PA-409		11.8%	6.1%	22.4%	40.3%	
(n = 800)	PL-391		3.1%	4.9%	15.8%	36.6%	
0-3 hours	t-PA-81		8.6%		14%	42%	
(n = 158)	PL-77		5.2%		8%	38%	
3-6 hours	t-PA-309		9.5%		9.5%	40.2%	
(n = 642)	PL-314		2.6%		11.3%	36.9%	
ATLANTIS[23]						NIHSS score of 0, 1 at 90d	No significant t-PA benefit on the 90-day efficacy endpoints in the patients between 3-5 hours. Primary outcome measure was NIH-SSS ≤1 at 90 days. It is the only rt-PA trial to be stopped prior to completion due to the futility analysis showing no potential for benefit with drug treatment.
TP, 3-5 hr	t-PA-272	4 hr 28 min	7.0%	7.0%	11.0%		
(n = 547)	PL-275	4 hr 28 min	1.1%	4.4%	6.9%	33.8%	
ITT 0-6 hr	t-PA-307		6.7%	7.6%	10.9%	32.0%	
(n = 613)	PL-306		1.3%	4.2%	6.9%	34.5%	
						34.0%	
NINDS[24]		90 min				Global outcome score at 90d	This was the only trial that treated patients only within three hours of symptom onset. Part 1 and Part 2 were identical studies except for the primary outcome measure. Part 1 focused on 24 hour neurologic improvement and Part 2 focused on long term function. The global statistic combines the 90-day function by using a favorable outcome on the NIHSS score, BI, mRS and GOS. Significant benefit for rt-PA was found on each of the 4 scales in each part of the 2 studies at 90 days.
(n = 624)							
Part 1/Part 2	t-PA-312		6.4%		17%	O.R. 1.9,	
combined	PL-312		0.6%		21%	C.I. 1.2-2.9	
Part I	t-PA-144		6%			O.R. 2.1,	
(n = 291)	PL-147		0%			C.I. 1.3-3.2	
Part 2	t-PA-168		7%			O.R. 1.7,	
(n = 333)	PL-165		1%			C.I. 1.2-2.6	

Abbreviations: Sx ICH, symptomatic intracerebral hemorrhage; PL, placebo; ITT, intention to treat; TP, target population.

was undertaken using a lower dose of rt-PA, 0.9 mg/kg (limit 90 mg) within 6 hours of symptom onset. The ECASS 2 Trial[22] entered 800 patients with moderate to severe ischemic stroke (median NIH-SS score of 11) at 108 centers in Europe, Australia, and New Zealand between October 1996 and January 1998. Patients were analyzed by time to treatment, 0 to 3 hours and 3 to 6 hours. Strict exclusionary CT criteria again were applied. The primary endpoint was favorable outcome (mRS score of 0 to 1) at 90 days. Secondary endpoints were the change from baseline to days 30 on the NIHSS (see Table 1) and the combination of BI and RS at day 90.

The 72 (9.0%) protocol violations were mostly caused by a breech of the CT criteria. These were excluded from the ITT analysis (n = 800) group and analyzed as TP. There was no significant difference in favorable outcome by mRS (0 to 1); it was 40.3% [CI 35.6%-45.4%] with rt-PA and 36.6% [CI 31.8%-41.6%] with placebo. However, in a post-hoc analysis, treatment with rt-PA increased the proportion of independent patients (mRS score 0, 1, 2; 54.3% versus 46.0%; $P = .024$). By day 30, the median NIHSS score improved more in the rt-PA group ($P = .035$). Mortality did not differ between the two groups. No benefit was found among the 20% of patients treated in the 0-to-3–hour window.

ATLANTIS

The ATLANTIS Trial,[23] conducted between December 1993 and July 1998 in 140 university and community hospitals in North America, included 613 patients (ITT population) with a mean baseline NIHSS score of 11. The target population of 547 patients, enrolled between 3 and 5 hours of symptom onset, were randomized to receive 0.9 mg/kg of rt-PA (n = 272) or placebo (n = 275). The study began as a 0-to-6 hour trial and was modified because of safety concerns in the 5 to 6–hour window and Food and Drug Administration (FDA) approval of rt-PA in the 0-to-3–hour window. A total of 39 (6.4%) patients were treated within 3 hours, 547 (89.2%) within 3 to 5 hours (the target population), and 24 (3.9%) patients were treated after more than 5 hours. The primary outcome measure was NIHSS score of 1 or less at 90 days; secondary end points of BI, mRS, and Glasgow Outcome Scale (GOS) at 30 and 90 days (Table 1).

Similar to the ECASS-1 study, patients with CT findings of hypodensity, loss of gray/white distinction, and/or effacement of cerebral sulci involving more than a third of the MCA territory were excluded. The TP population had a significantly greater rate of major neurologic recovery (11 point improvement in NIHSS) with rt-PA, 40% versus 31% with placebo ($P = .02$) on day 30, and 45% with rt-PA versus 36% with placebo ($P = .03$) on day 90. This similar improvement was found only in the ITT group at day 30 (41.1% versus 32.2% [$P = .02$]). In the ITT and TP rates of ICH in the treatment group were significantly increased as compared with placebo (symptomatic ICH: 7.0% with rt-PA versus 1.1% with placebo; $P < .001$). Those treated after 5 hours suffered significantly higher rates of ICH and death. This trial was stopped before completion when an interim futility analysis revealed no hope for a positive outcome based on the primary endpoint.

NINDS

The NINDS rt-PA Stroke Trial[24] represents two consecutive trials that differed only in the definition of their primary and secondary outcome measures. They enrolled 624 patients (median baseline NIHSS score of 14) from January 1991 through October 1994 at 8 centers in the United States to receive 0.9 mg/kg (10% as a bolus, followed by a 1-hour infusion, 90 mg limit) or placebo within 3 hours of symptom onset. The patients were further divided into two groups based on the time from symptom onset to the start of infusion of rt-PA or placebo (0 to 90 minutes and 91 to 180 munutes). Part 1 (n = 291), from 1991 to 1993, tested whether rt-PA had early clinical activity, as indicated by the proportion of patients with major neurologic improvement (MNI), an improvement of 4 points or more over baseline NIHSS score, or resolution of symptoms (NIHSS score = 0 or 1) within 24 hours. Part 2 (n = 333), from 1992 to 1995, also known as the pivotal efficacy study, primarily assessed functional outcome at 90 days, a secondary endpoint in Part 1. Patients were dichotomized into favorable or unfavorable 90-day outcomes (favorable defined as NIHSS score of 0 or 1, BI of 95 or more, mRS of 0 or 1, GOS of 1).

Patients were excluded if there was evidence of ICH on the baseline CT scan, but not for major early ischemic changes as in the ECASS studies. Further, a BP of more than 185/110 mm Hg at the time of treatment was exclusionary. After treatment began, blood pressure was maintained in prespecific values. All analyses were based on the intention to treat.

In Part 1, the proportion of patients with MNI was similar in both rt-PA and placebo groups; however, a statistically significant improvement in median NIHSS scores at 24 hours was observed (eight in the rt-PA group and 12 in the placebo group, with a median baseline NIHSS score of 14 in both groups), providing post-hoc evidence of early activity. Functional outcome of 3 months (the secondary endpoint) in Part 1 showed an absolute increase of 15% to 20% in the proportion of rt-PA treated patients with a favorable outcome. The global statistic showed an odds ratio of 2.1 (95% CI, 1.3-3.2) in favor of treatment using rt-PA as compared with placebo on the secondary endpoint.

In part 2, there was an absolute increase of 11% to 13% in the proportion of patients with a favorable outcome,

using rt-PA as compared with placebo, confirming the findings from Part 1. The global statistic showed that the odds ratio for improvement with rt-PA was 1.7 (95% CI, 1.3-3.1) and each of the 4 outcome measures at 90 days showed benefit for the rt-PA group. The positive effect found in both parts of the NINDS study was independent of age, baseline NIHSS score, stroke subtype, and ASA use before treatment.

No significant difference in outcome according to the time to treatment (dichotomized between 0 and 90 minutes versus 91 to 180 minutes) in either Part 1 or Part 2 was found in the initial analysis. There was no significant difference in mortality between the groups by day 90 (rt-PA 17% versus 21% of placebo; $P = .30$). Symptomatic ICH during the first 36 hours occurred significantly more often in treatment patients (Part 1: rt-PA 6% versus placebo 0%; Part 2: rt-PA 7% versus placebo 1%; $P < .001$). Patients with symptomatic ICH had a more severe baseline neurologic deficit (median NIHSS score of 20) compared with the study population as a whole (median NIHSS score of 14).

It was concluded that despite the increased risk of symptomatic ICH, treatment with rt-PA provided consistent improvement in functional outcome at 3 months and without increasing morbidity or mortality. These have been the only major trials to show benefit with rt-PA and served as the basis of FDA approval of rt-PA for acute ischemic stroke within 3 hours of stroke onset in 1996.

Lessons Learned

Significant experience has been gained in the conduct of the trials reviewed above. This section will discuss some of the lessons learned that might allow for better patient care and may impact future study design.

Time Is Not on Your Side!

The only positive thrombolytic trials for acute ischemic stroke was conducted in a very short time window, 0 to 3 hours, with nearly half of the patients being treated in the 0-to-90–minute window. The mean time to treatment was 4.4 hours for ECASS 1, and only 20% of the ECASS 2 patients were treated under 3 hours. In the ATLANTIS trial, the time to treatment was 4.5 hours after the 5-to-6–hour window was closed because of increased early ICH and mortality. Among the SK trials, MAST-E treated patients 4.6 hours after stroke onset, and MAST-I only treated 25% of patients within 3 hours. The protocol in MAST-I allowed for extrapolation of the time of onset; therefore some patients might have been treated as long as 9 hours after stroke onset. The ASK trial treated within a mean time of 3.46 hours in a 4-hour protocol, with 20.6% of patients treated under 3 hours. Poor outcomes were confined to those treated beyond 3 hours (including a higher death rate, RR = 1.98). Better outcomes were related to earlier treatment ($P = .04$).

Initial analysis of the NINDS data did not reveal a difference in treatment effect between those treated early and those treated later within the 3-hour window. Further post-hoc analysis found that there was a difference between the 0-to-90– and 91-to-180–groups but that it was hidden by a covariate, the baseline NIHSS score.[26] The baseline NIHSS score in the earlier group was 15.2 and 13.5 in the later group. After adjusting for this difference, a relationship between outcome and time to treatment was uncovered. Patients treated very early (less than 60 minutes from onset of symptoms) had an odds ratio for favorable outcome of nearly 4.0. Meanwhile, patients treated near the minute 180 had an odds ratio for favorable outcome approaching 1.0 (Fig 1).

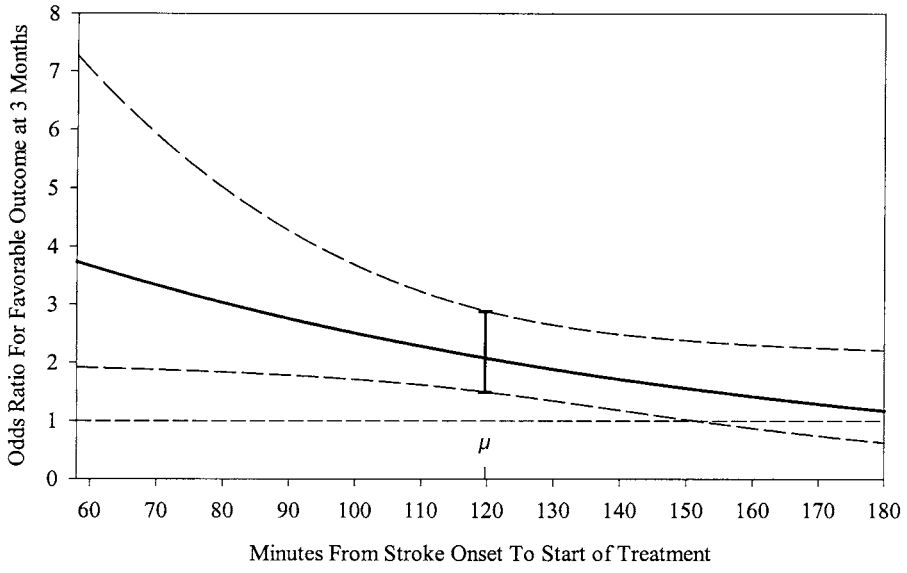

Figure 1. *Graph of model estimating odds ratio for favorable outcome at three months in rt-PA-treated patients compared with placebo-treated patients by time from stroke onset to treatment (OTT) with 95% confidence intervals, adjusting for the baseline NIHSS. Odds ration g 1 indicates greater odds that rt-PA treated patients will have a favorable outcome at the 3 months compared with the placebo-treated patients. Range of time from stroke onset to treatment start was 58 to 180 minutes with a mean (μ) of 119.7 minutes (reprinted with permission[26]).*

The time window for successful thrombolytic treatment of acute ischemic stroke is clearly limited. Whether a 3-hour time window applies to all patients is unknown and might depend on individual factors, such as collateral circulation and severity of ischemia. Longer time windows for thrombolytic trials might have been chosen to increase the number of patients treated and the feasibility of treatment, but not based on the underlying pathophysiology. Earlier time windows are supported by both laboratory and clinical trials,[27,28] showing that longer time to treatment increases the risk of ICH and decreases the chance of a favorable outcome. Thus, it is critical to treat patients as early as possible to resist the tendency to delay treatment until the last minute.

More Might Not Be Better

When it comes to the dose, more might not be better. The question of the correct dose has not been completely answered. In SK trials, the dose was determined by adopting the dose used for acute myocardial infarctions. There were no dose ranging trials for SK, although the ASK investigators did conduct a limited safety trial. All of the SK trials were stopped for safety reasons. The failure of the SK trials might be caused, in part, by issues regarding dose or a combination of factors such as the dose, late treatment time and high stroke severity.

Dose ranging studies were conducted for rt-PA. In ECASS 1, a dose ranging study did not show any evidence of a dose response in regard to efficacy[29]; therefore, a dose similar to acute myocardial infarction (MI) doses was used. In the NINDS trial, dose-ranging studies[16,17] found a dose effect in regard to safety, that higher dose produced more ICHs. This is consistent with thrombolysis trials for acute myocardial infarction in which overdosing, especially in those with low body mass, is a well-established risk factor for ICH.[30]

The dose chosen for the NINDS trial was the greatest dose that did not result in any ICH in the pilot studies. Doses from 0.35 mg/kg to 1.08 mg/kg were administered within 90 minutes of symptom onset in the first pilot study. Two of 22 patients that received a dose of 0.95 mg/kg suffered an ICH, whereas none of the patients treated with 0.85 mg/kg suffered an ICH. Whether this is also the smallest dose that is effective is unknown. The amount of thrombolysis needed might be related to the clot burden. Future trials require customized reperfusion strategies based on the severity of the stroke or the clot burden.

Heparin Might Be Harmful

At this time, there is no evidence to show that heparin is beneficial for the primary treatment of acute ischemic stroke (AIS).[31,32] Heparin in the setting of thrombolysis for AIS might contribute to the risk of hemorrhage. In MAST-E, 65% of SK-treated patients and 75% of placebo patients received full heparinization. The symptomatic ICH rate was 21.2% with SK and 2.6% with placebo. The rate of symptomatic ICH in the placebo group was similar to that found in other trials, but the rate in the MAST-E SK group was much higher than in ASK (12.6%) or MAST-I (6%). Although this might be confounded by factors such as stroke severity, blood pressure control, or time to treatment, data from the intra-arterial trial Prolyse in Acute Cerebral Thromboembolism I (PROACT I)[33] would support the notion of a dose-dependent increase in ICH when heparin is combined with thrombolysis. During the PROACT I trial (intra-arterial thrombolysis within 6 hours of onset), the heparin infusion was decreased from 100 U/kg bolus with 1000 U/hr to a 2000-U bolus with 500 U/hr because of increased ICH. The symptomatic ICH rate dropped from 27% to 6.7%, but the rate of recanalization also dropped, from 82% to 40%.

The rt-PA trials prohibited the use of antithrombotic or antiplatelet drugs during the first 24 hours. Although a minority of patients took ASA before their stroke in the rt-PA group of the NINDS trials, it did not increase the risk of subsequent ICH. Thus, there is no indication for IV heparin administration in the setting of thrombolysis for AIS, and it actually might be harmful.

Big Strokes Tend to Bleed

Patients with large neurologic deficits, large areas of cerebral ischemia, or areas of severe ischemia are more likely to suffer an ICH after thrombolytic therapy and reperfusion. In MAST-E, in which 30% of the patients suffered severe MCA stroke, the rate of parenchymal hematomas was 22% and the hemorrhagic conversion rate was 54% after SK. The placebo group suffered a much lower rate of parenchymal hematoma formation (2.6%) but still had a high rate of hemorrhagic transformation (41%). In the NINDS trials, those suffering a symptomatic ICH had a high mean NIHSS score of 20. Overall those with the most severe strokes (NIHSS score greater than 20) had a 17% rate of ICH.[34] The ECASS studies excluded patients with very severe strokes (hemiplegia, impaired consciousness, forced eye deviation) because of the perceived increased risk of ICH.

In cases of severe ischemia (caused by volume of infarct or duration of infarct), with a high likelihood of hemorrhagic transformation, thrombolysis might convert hemorrhagic infarctions into parenchymal hematomas. In ECASS 1, the total number of hemorrhagic events was not significantly different between the groups (43% with rt-PA and 37% with placebo). There was a higher rate of parenchymal hematomas with rt-PA (20%) compared with placebo (6.5%) and a lower rate of hemorrhagic transformation with rt-PA (23% versus 30%). Because ECASS excluded patients with very severe syndromes, this might imply that the duration of symptoms allowed

for greater ischemic damage and, consequently, a higher susceptibility to ICH.

Antithrombotic agents were avoided in ECASS and NINDS trials for the first 24 hours, but were allowed in all SK trials that might have increased their risk of ICH, especially in view of late treatment and large strokes.

Big Strokes Are Bad

Despite the inherent risks of thrombolysis for AIS, not treating can be equally deleterious. Patients judge a life of severe disability (inability to care for any of one's basic needs with full dependency) as an outcome equally adverse as death.[35] Therefore, it is important to understand the impact of not treating potential candidates, especially if their stroke is very severe. These randomized trials provided optimal standardized management and gave us insight into the natural history of stroke from the hyperacute phase through 3 to 6 months.

In MAST-I, the rate of death or severe disability at 6 months was 62% with SK alone, 63% with SK plus ASA, 61% with ASA alone, and 68% with placebo despite the increased early mortality and high ICH rate in the treatment group. Ultimately the placebo group had a higher rate of poor outcomes because of the natural history of large strokes. In MAST-E, the placebo group had a 38.3% mortality rate and a rate of combined mortality or severe disability of 81.8% at 6 months.

Is it futile to treat patients with severe strokes because they are likely to have a poor outcome or suffer an ICH? In a subanalysis of the NINDS trials[34] looking at those with the most severe strokes (NIHSS score greater than 20), 76% of the placebo group were severely disabled or dead at 3 months, whereas 69% of the rt-PA group were severely disabled or dead at 3 months. Those with severe strokes were still more likely to have a favorable outcome with treatment than without treatment (OR = 4.3, 95% CI = 1.6-1.9) despite the risk of ICH. Of this subset, 10% of the rt-PA group and 4% of the placebo group returned to normal function. Patients that do not receive thrombolysis are not exempt from complications; for example, in ECASS 2, cerebral edema was the most common cause of death in the placebo group.

Conversely, patients with smaller strokes tend to have better outcomes and a lower risk of ICH. This can be seen in ECASS 2, in which patients with lower median baseline NIHSS scores were enrolled (11 in both groups) as compared with NINDS (14 versus 15) and ECASS 1 (13 versus 12). The mortality rates at 90 days were concomitantly lower in ECASS 2 (rt-PA 10.5% versus placebo 10.7%) as compared with ECASS 1 (rt-PA 22.4% versus placebo 15.8%) and the NINDS trial (rt-PA 17% versus placebo 21%). In the NINDS trial, those with NIH-SS scores of less than 10 had a symptomatic ICH rate of 3%.

In the NINDS study, despite a higher risk of ICH and death, patients with severe strokes still respond to treatment, showing a lower risk of severe disability and a greater chance to return to normal function. Thus, according to the treatment criteria from this study, there is no group that has been identified to date that should not be treated with intravenous rt-PA within 3 hours of symptom onset.[36] Rather, the risks and benefits of treatment compared with the risks and benefits of no treatment should be evaluated in view of the impact the stroke might have on the patient's quality of life.

Protocol Adherence Is Paramount

Protocol development is one of the most important tasks that must be completed before treating patients with thrombolysis for AIS. It can be very difficult to try to coordinate all of the necessary steps in patient management on a spur-of-the-moment basis when a patient presents for acute treatment. In the NINDS trial, in which patients were treated within 180 minutes of onset of symptoms, a great deal of attention was paid to systems development.[37] Participating institutions spent almost a year in preparation to ensure that the all of the components of care, from prehospital systems to acute stroke units, were working together. Flow-charting was used to identify and address bottlenecks in the care process.

In addition to patient care protocols, patient selection and treatment protocols must be in place. This allows for rapid evaluation in regard to inclusion and exclusion criteria, blood pressure management, and management of any complications. The NINDS rt-PA Stroke Study Group published their experience with protocol development and a systems approach to stroke care.[37]

Despite these efforts, post-hoc analysis showed that it takes more time to treat a patient when more time is available in the 3-hour window. For example, 30 minutes more were used before initiating treatment in patients treated within the 91- to 180-minute window than in the 0- to 90-minute window.[26] This is supported also by the experience in some of the phase IV studies.[38]

These protocols were a key part of the success of the NINDS trials and are now supported by the American Heart Association.[39] For example, strict blood pressure inclusion criteria (185/110), with standardized monitoring and treatment protocols for the first 24 hours, may have decreased the complication rate without harming patients from hypotension.[40] These types of systems interventions were not reported in the other trials.

Protocol Violations are Perilous

Violations of strict entry protocols can be very dangerous. The ECASS 1 study anticipated a 20% rate of protocol violations. Actually, 17% of patients (n = 109) violated the entry criteria and should not have been randomized. Most of them (n = 66) violated the prespecified CT scan criteria that excluded patients with early

ischemic changes in more than one third of the MCA distribution. The mortality among those that were treated and violated the protocol was 33% (40% if CT criteria were violated), much higher than the 14.6% in the treated target population (those without protocol violations).

The American Heart Association has made recommendations regardingpatient selection criteria.[39] Evidence from Phase IV studies[38,41] in centers that follow these guidelines supports the notion that complications are much higher in those patients that are treated outside of accepted protocols (See next article for details).

Placebo Often Works

Patients entered into the standardized environment of well-designed trials often have better outcomes even in the placebo group. This can make it difficult to show that a treatment is effective if the placebo group improves more than anticipated from historical evidence. In acute stroke trials, patients are often cared for in stroke units in which stroke vital signs such as blood pressure, pulse, temperature, glucose level, pulmonary status, cardinal neurologic signs, and so on, are monitored and patients are aggressively treated. Stoke units have been shown to decrease death and disability.[42]

In ECASS 2, 36.6% of the placebo group and 40.3% of the treatment group had a favorable outcome (mRS = 0 or 1) at 90 days. In the initial analysis, a 30% response was predicted in the placebo group to detect an absolute difference of 10% in the treatment group. From the results obtained, the investigators subsequently concluded they needed at least twice as many patients as were enrolled to show a significant difference in the predefined primary endpoint.

In Part 1 of the NINDS trial, an MNI (meaningful neurologic improvement) was defined as a 4-point improvement over baseline NIHSS score or a NIH-SS score of 0 or 1 at 24 hours. Thirty-nine percent of the placebo group and 47% of the rt-PA group had MNI. It was anticipated that only 20% of the placebo group would achieve this level.

In both of these trials, the placebo group performed better than anticipated. This might have been caused by either the goals being too easy to reach or the effect of standardized and systematic care (with specific attention to detail) used in each trial.

Outcome Measures Can Determine Trial Outcomes

Determining whether a trial is positive or negative rests with its ability to show improvement by its predefined primary outcome measures. All other outcomes are considered secondary, post-hoc, or exploratory. Unlike trials of thrombolysis in myocardial infarction, the determination of the primary outcome measure is difficult for acute stroke trials as stroke is more disabling than lethal, and there is no gold standard to measure disability. In acute myocardial infarction, the leading cause of death in industrialized societies, the primary outcome of trials is often mortality, an objective endpoint. The ECASS trials are both negative according to their primary outcome measures. Yet, secondary analysis, analysis of target populations, and post-hoc analysis with different endpoints show benefit from rt-PA therapy in certain populations. Choice of different primary outcome measures might have resulted in positive trials. Similarly, in the NINDS trials, the primary outcome of Part 1 was negative. Had the investigators chosen a 6-point or greater change instead of a 4-point change in the NIHSS score as the definition of major neurologic improvement in Part 1, the primary endpoint would have been positive.[43]

For the evaluation of long-term function in Part 2 of the NINDS trial, the investigators chose to use four outcome measures (mRS, BI, GOS, and NIHSS). To reconcile all 4, especially if some had indicated opposite results, the global statistic was applied.[44] The use of this novel approach in clinical trials allows a combined evaluation of multiple endpoints into a single odds ratio with more power than any of the component outcomes. In the NINDS trial, all four outcome measures indicated a consistent and persuasive difference from placebo and the global outcome statistic showed an odds ratio of 2.0 (95% CI, 1.3-3.1) in favor of treatment.

Early Ischemic Changes on CT Scan Might Not Be Early (Or, It's Later Than You Think)

The ECASS studies attempted to exclude patients with major early infarct signs (diffuse swelling, hypodensity, or sulcal effacement) involving more than a third of the MCA territory on the initial CT scan. This was done because these patients were thought to be at high risk for subsequent ICH and death.[45] The actual ICH rate among those patients treated with rt-PA in the 6-hour window who had major early infarct signs on initial CT scan was not higher (19.4% versus 19.8%), but the mortality rate was higher (32% versus 16%).

The NINDS investigators did not exclude patients with major early infarct signs and only excluded patients with evidence of ICH on the initial CT scan. Yet, the symptomatic ICH rate was 6.4%, much lower than in the ECASS trial. Mass effect or obvious hypodensity was noted on initial CT in 5% (n = 16) of the NINDS rt PA–treated patients[34] and four died within 10 days. The volume of these findings was not quantitated as in ECASS. This subgroup did have an increased risk of ICH, but it did not outweigh the benefit of treatment; therefore, the risk of finding early CT changes seems time-dependent.

As signs of ischemia on CT scan are time dependent, the question arises as to the importance of the early

infarct signs when applying data from a 6-hour protocol to patients being treated in a 3-hour protocol. The current American Heart Association guidelines suggest that patients with major early infarct signs should be excluded from therapy within 3 hours, although data from the NINDS trials does not support this recommendation. For patients in the 3-hour window, detecting these findings might mean that the duration of ischemia is much longer than originally thought and further investigation of the time of symptom onset is warranted.

Advances in CT technology over the past decade complicate this issue further. The new generation of CT scanners can provide greater detail though their significance in helping to decide on rt-PA treatment remains uncertain. Many of the early infarct signs that we are detecting with today's scanners might not have been seen on the scanners used in these trials 7 to 10 years ago.

Conclusion

From the evidence gathered, it is clear that the time window to intervene most successfully in acute ischemic stroke treatment is less than 3 hours. Also, it has become obvious that attention to stroke vital signs has to be paid in the context of a predetermined protocol. Treating patients with a multidisciplinary approach is needed to achieve optimal results.

Other disease processes also call for rapid intervention and a multidisciplinary approach. We have the golden hour in trauma, the first 4 hours in acute myocardial infarction, and the early intervention in sepsis, as models for stroke care. An integrated approach will require full cooperation of emergency medical services, emergency medicine, and the neurosciences, along with the creation of protocols and pathways to help apply the lessons we have learned from these trials to stroke's 60 minutes to treatment.

References

1. Sussman BJ, Fitch TS: Thrombolysis with fibrinolysin in cerebral arterial occlusion. JAMA 167:1705-1709, 1958
2. Culbras A, Kase CS, Masdeu JC, et al: Practice guidelines for the use of imaging and transient ischemic attacks in acute stroke. Report of the Stroke Council, American Heart Association. Stroke 28:1480-1497, 1997
3. Wardlaw JM, Warlow CP: Thrombolysis in acute ischemic stroke: Does it work? Stroke 23:182-1839, 1992
4. Zeumer H, Freitag HJ, Knowpe V: Intravascular thrombolysis in central nervous system cerebrovascular disease. Neuroimag Clin North Am 2:349-369, 1992
5. Zeumer H, Freitag HJ, Zanella F, et al: Local intraarterial fibrinolytic therapy in patients with stroke: Urokinase versus recombinant tissue plasminogen activator (r-TPA). Neuroradiology 35:159-160, 1993
6. Mori E, Tabuchi M, Yoshida T, Yamadori A: Intracarotid urokinase with thromboembolic occlusion of the middle cerebral artery. Stroke 19:802-812, 1988
7. Del Zopo GJ, Ferbert A, Otis S, et al: Local intra-arterial fibrinolytic therapy in acute carotid territory stroke: A pilot study. Stroke 19:307-313, 1998
8. Fitt GJ, Farrar J, Baird AE, et al: Intra-arterial streptokinase in acute ischemic stroke. Med J Aust 159:331-334, 1999
9. Higashida RT, Halbach VV, Tsai FY, et al: International neurovascular techniques for cerebral revascularization in the treatment of stroke. Am J Roentgenol 163:793-800, 1994
10. Yamaguchi T, Hayakawa T, Kiuchi H: Japanese Thrombolysis Study Group: Intravenous tissue plasminogen activator ameliorates the outcome of hyperacute embolic stroke. Cerebrovasc Dis 3:269, 1993
11. Ohtomo E, Araki G, Matuda, et al: Clinical efficacy of urokinase in the treatment of cerebral thrombosis. Clin Eval 13:711-751, 1985
12. Von Kummer R, Hacke W: Safety and efficacy of intravenous tissue plasminogen activator and heparin in acute middle cerebral artery stroke. Stroke 23:646-652, 1992
13. Mori E, Yoneda Y, Tabuchi M, et al: Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 42:976-982, 1992
14. Yamaguchi T: Thrombolytic therapy in embolic and thrombotic cerebral infarction: A cooperative study in Hacke W, del Zoo M, Hirschberg M (eds): Thrombolytic therapy in acute ischemic stroke. Heidelberg, Springer-Verlag, 1991, pp 168-174
15. Haley EC, Brott TG, Sheppard GL, et al: For the T-PA Bridging Study Group. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. Stroke 24:1000-1004, 1993
16. Brott TG, Haley EC Jr, Levy DE, et al: Urgent therapy for stroke: Part 1. Pilot study of tissue plasminogen activator administered within 90 minutes. Stroke 23:632-640, 1992
17. Haley EC Jr, Levy DE, Brott TG, et al: Urgent therapy for stroke: Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. Stroke 23: 641-645, 1992
18. The Multicenter Acute Stroke Trial-Europe Study Group (MAST-E): Thrombolytic therapy with streptokinase in acute ischemic stroke. N Engl J Med 335:145-150, 1996
19. Multicentre Acute Stroke Trial-Italy (MAST-I) Group: Randomised controlled trial of streptokinase, aspirin and combination of both in treatment of acute ischaemic stroke. Lancet 346:1509-1514, 1995
20. Donnan GA, Davis SM, Chamber BR, et al, for the Australian Streptokinase (ASK) Trial Study Group: Streptokinase for acute ischemic stroke with relationship to time of adminstration. JAMA 276:961-966, 1996
21. 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 274:1017-1025, 1995
22. Hacke W, Kaste M, Fieschi C, et al: for the Second European-Australian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet 352:1245-1251, 1998
23. Clark WM, Wissman S, Albers G, for the ATLANTIS Study Investigators: Recombinant tissue-type plasmino-

gen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset. JAMA 282:2019-2026, 1999
24. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 333:1581-1587, 1995
25. Hacke W, Bluhmki E, Steiner T, et al: Dichotomized efficacy end points and global end-point analysis applied to the ECASS intention-to-treat data set: Post-hoc analysis of ECASS I. Stroke 29:2073-2075, 1998
26. Marler JR, Tilley BC, Lu M, et al: for the NINDS rt-PA Stroke Study Group. Early Stroke Treatment Associated with Better Outcome. Neurology 55:1649-1655, 2000
27. Zivin JA, Lyden PD, DeGirolami, et al: Tissue plasminogen activator. Reduction in neurologic damage after experimental embolic stroke. Arch Neurol 50:387-391, 1988
28. Zivin JA: Factors determining the therapeutic window for stroke. Neurology 50:599-603, 1998
29. Del Zopo GJ, Poeck K, Pessin MS, and the rt-PA Acute Stroke Study Group: Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. Ann Neurol 32:78-87, 1992
30. Gurwitz JH, Gore JM, Goldberg RJ, et al: Risk for intracranial hemorrhage after tissue plasminogen activator for acute myocardial infarction Participants in the National Registry of Myocardial Infarction 2. Ann Intern Med 129:597-600, 1998
31. Adams HP Jr, Brott TG, Crowell RM, et al: Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. Stroke 25:1901-1914, 1994
32. Coull BM, Williams LS, Goldstein LB, et al: Anticoagulant and antiplatelet agents in acute ischemic stroke: A report by the American Academy of Neurology/American Heart Association Joint Stroke Guidelines Committee. (in press)
33. del Zoppo GJ, Higashida RT, Furlan AJ, et al: PROACT: A phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke 29:4-11, 1998
34. The NINDS t-Pa Stroke Study Group: Intracerebral hemorrhage following intravenous t-PA therapy for ischemic stroke. Stroke 28:2109-118, 1997
35. Solomon NA, Glick HA, Russo CJ, et al: Patient preferences for stroke outcomes. Stroke 25:1721-1725, 1994
36. The NINDS t-PA Stroke Study Group: Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA stroke trial. Stroke 28:2119-2125, 1997
37. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group: A systems approach to immediate evaluation and management of hyperacute stroke: Experience at eight centers and implications for community practice and patient care. Stroke 28:1530-1540, 1997
38. Albers GW, the STARS Investigators: Prospective, monitored, multicenter, post-approval experience with intravenous t-PA for treatment of acute stroke: The standard treatment with activase to reverse stroke (STARS) study. JAMA 283:1145-1150, 2000
39. Adams HP, Brott TG, Furlan AJ, et al: Guidelines for thrombolytic therapy for acute stroke: A supplement to the guidelines for the management of patients with acute ischemic stroke. Circulation 94:1167-1174, 1996
40. Brott T, Lu M, Kothari R, et al: Hypertension and its Treatment in the NINDS rt-PA Stroke Trial. Stroke 29: 1504-1509, 1998
41. Katzan IL, Furlan AJ, Lloyd LE, et al: Use of tissue-type plasminogen activator for acute ischemic stroke. The Cleveland experience. JAMA 283:1151-1158, 2000
42. Stroke Unit Trialists' Collaboration: Collaborative systematic review of the randomized trials of organised inpatient (stroke unit) care after stroke. Br Med J 314: 1151-1159, 1997
43. Haley EC, Lewandowski C, Tilley B, et al: Myths Regarding the NINDS rt-PA Stroke Trial: Setting the Record Straight. Ann Emerg Med 30:676-682, 1997
44. Tilley BC, Marler J, Geller N, et al: Use of a Global Test for Multiple Outcomes in Stroke Trials with Application to the NINDS t-PA Stroke Trial. Stroke 27:2136-2141, 1996
45. Bazzao L, Fantozzi L, Bastianello S, et al: Early collateral blood supply and late parenchymal brain damage in patients with middle cerebral artery occlusion. Stroke 20:735-740, 1989