Thrombolytic therapy for ischemic stroke—A review. Part I—Intravenous thrombolysis

Peter D. Schellinger, MD; Jochen B. Fiebach, MD; Alexander Mohr, MD; Peter A. Ringleb, MD; Olav Jansen, MD; Werner Hacke, MD, PhD

Objective: Thrombolytic therapy for acute ischemic stroke was implemented into clinical routine 4 yrs ago. Unfortunately, at present <2% of eligible patients receive thrombolytic therapy. We present an overview of all hitherto completed trials of intravenous thrombolytic therapy for carotid artery stroke including recommendations for therapy and diagnostic procedures and their impact on patient selection and meta-analyses.

Data Sources: We performed an extensive literature search not only to identify the larger and well-known randomized trials but also to identify smaller pilot studies and case series. Trials included in this review, among others, are the National Institute of Neurologic Disorders and Stroke (NINDS) study, European Cooperative Acute Stroke Study I and II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A and B and two large meta-analyses, including the Cochrane Library report.

Conclusion: Intravenous thrombolytic therapy with recombinant tissue plasminogen activator has demonstrated a significant benefit and has proven to be safe for patients who can be treated within 3–6 hrs after symptom onset. This benefit is at the cost of an increased rate of symptomatic intracranial hemorrhage without a significant effect on overall mortality. In general, the benefit of thrombolysis decreases and the risks increase with progressing time after symptom onset. Presently, thrombolytic therapy is still underutilized because of problems with clinical and time criteria, and lack of public and professional education to regard stroke as a treatable emergency. If applied more widely, thrombolytic therapy may result in profound cost savings in health care and reduction of long-term disability of stroke patients. (Crit Care Med 2001; 29:1812–1818)

Key Words: thrombolysis; ischemic stroke; review; intra-arterial lysis; intravenous lysis; vertebrobasilar stroke; diagnostic imaging; diffusion magnetic resonance imaging; perfusion magnetic resonance imaging; computed tomography

Stroke is the third most common cause of death in the industrialized nations, after myocardial infarction and cancer, and the single most common reason for permanent disability (1). Up to 85% of all strokes are of ischemic origin and most are the result of blockage of a cerebral artery by a blood clot (2). After introduction of thrombolytic therapy for the treatment of acute myocardial infarction in the early 1990s (3), major trials for the evaluation of this new therapeutic approach to ischemic stroke were initiated. Occlusion of a brain vessel leads to a critical reduction in cerebral perfusion and, within minutes, to ischemic infarction with a central infarct core of irreversibly damaged brain tissue and a more or less large area of hypoperfused but still vital brain tissue (the ischemic penumbra), which can be salvaged by rapid restoration of blood flow (4, 5). Therefore, the underlying rationale for the introduction and application of thrombolytic agents is the lysis of an obliterating thrombus and subsequent reestablishment of cerebral blood flow by cerebral vascular recanalization (6).

INITIAL PATIENT ASSESSMENT

In addition to standard care in acutely ill patients, such as stabilization of vital parameters and application of venous lines, an accurate assessment of the patient's neurologic status is essential (5). With the use of standard stroke scales such as the National Institutes of Health Stroke Scale (NIHSS) or the Scandinavian Stroke Scale (SSS) (7, 8), stroke severity can be rapidly graded, with the goal of excluding small as well as too severe infarctions from a potentially hazardous therapy. Furthermore, information about the time point of stroke onset is crucial as the therapeutic time window is small. Besides the usual contraindications for thrombolytic therapy in general, intracranial hemorrhage (ICH) and severe microangiopathy must be excluded by imaging procedures such as computed tomography (CT) or magnetic resonance imaging (MRI) (7, 9). Proof of an occluded vessel by Doppler ultrasound, CT, MRI, or digital subtraction angiography should be established, at least when thrombolysis is performed >3 hrs after symptom onset; however, it is not required yet for the indication of thrombolytic therapy. Overall, the proverb “time is brain” holds true; therefore, a rapid work-up of the patient who is a potential candidate for thrombolytic therapy is mandatory.

THROMBOLYTIC AGENTS IN USE

In 1933, Tillet and Garner reported that streptococci released a substance that dissolved blood clots (10). Streptokinase has a molecular weight of 47,000 dalton; it is a single-chain protein with only minimal intrinsic enzymatic activity that combines with plasminogen and leads to its activation to plasmin. As streptokinase is not fibrin specific, high
concentrations may deplete coagulation factors V and VIII, plasminogen, α-II-antiplasmin, and fibrinogen, which characterizes the lytic state that impairs plasmatic coagulation and platelet aggregation, and, therefore, may result in hemostatic failure.

Urokinase has a molecular weight of 54,000 dalton; it is a double-chain, nonfibrin-specific serine protease that directly transforms plasminogen to plasmin (11). As urokinase, like streptokinase, activates bound as well as circulating plasminogen, it may cause depletion of the aforementioned coagulation factors and hemostatic failure. Pro-urokinase or saruteplase is the inactive single-chain precursor of urokinase. It has a low intrinsic activity but the efficacy is approximately 100-fold less than that of urokinase. Pro-urokinase has a significant fibrin specificity, which may be the result of a preferential conversion of pro-urokinase to urokinase at the fibrin surface (12).

Tissue plasminogen activator (rt-PA) is produced endogenously in physiologic concentrations, synthesized, and secreted by endothelial cells; is relatively fibrin specific (presence of fibrin enhances rt-PA effect by three orders of magnitude), leading to a minimal consumption of circulating coagulation factors; and appears as a single- or double-chain polypeptide with a molecular weight of 70,000 dalton (single-chain form) and a serum half-life of 4–6 mins if not bound to a fibrin-clot (13, 14). The clinically available form of rt-PA (recombinant rt-PA [rt-PA], alteplase) is produced by recombinant DNA techniques as its less commonly used double-chain form (duteplase). rt-PA is inactivated by plasminogen activator inhibitor type 1 (PAI-1), a 45,000-dalton protein found in endothelial cells and platelets, which rapidly inhibits circulatory rt-PA, but inhibits fibrin-bound rt-PA only slowly (15). In platelet-rich clots, there may be enough PAI-1 to result in a significant inhibition of rt-PA, which may explain their potential resistance to thrombolysis (16, 17).

**EARLY TRIALS OF INTRAVENOUS THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE**

The first anecdotal report of thrombolytic therapy for ischemic stroke dates back to the early 1960s (18). Three trials in the early 1980s investigated the effect of low-dose intravenous urokinase for the therapy of acute ischemic stroke (19–21). These trials are different from others for several reasons, such as a late time point of several days, and the lack of assessment of clinical outcome except death and ICH. In the early 1990s, three small trials of intravenous thrombolysis with rt-PA were carried out (22–24). These trials, although not large enough to prove the efficacy, demonstrated very well the feasibility of early thrombolytic therapy and also suggested a reasonable degree of safety and a potential benefit. All these trials were blinded or double-blinded, randomized, and placebo-controlled. Mori et al. (23) randomized 31 patients with acute carotid artery territory stroke to treatment with either 20 or 30 mega-international units (MIU) duteplase (equivalent to 40 or 60 mg rt-PA) or placebo given intravenously for 60 mins in a time window of 6 hrs after stroke onset. Baseline and postinfusion angiography demonstrated complete or partial reperfusion in 50% of patients treated with 30 MIU duteplase, 44% of those treated with 20 MIU duteplase, and 17% in the control group. Patients treated with 30 MIU duteplase showed earlier and better clinical improvement than those treated with placebo, there was one parenchymal hemorrhage in each of group. Yamaguchi et al. (24) randomized 98 patients into two treatment arms (20 MIU duteplase or placebo over 60 mins) within 6 hrs. According to immediate post-treatment angiography, recanalization rates were significantly better in the treatment group than in patients receiving placebo (21% vs. 4%). In the treatment group, 16% of the patients experienced a marked clinical improvement as opposed to 6% in the placebo group; the rates of ICH, however, were similar in the two groups. The smallest randomized trial reported was that of Haley et al. (22), who performed a pilot study with a time window to treatment of 3 hrs in preparation for the National Institute of Neurologic Disorders and Stroke (NINDS) rt-PA trial (7). Twenty patients received 0.85 mg rt-PA within 90 mins, another 7 patients within 91–180 mins after stroke onset. Six patients in the 90-mins group improved by four or more NIHSS points at 24 hrs compared with one patient in the placebo group ($p < .05$). There was no difference in the 91- to 180-min group, and one fatal ICH occurred in the placebo group. In the further course of this article, the following terms will be used: odds ratio (OR), 95% confidence interval (CI), relative risk (RR), events prevented per 1000 patients treated (EP), number needed to treat to prevent an event (NNT), and $p$ values. The 3- or 6-month outcome is frequently assessed with the modified Rankin scale (MRS) and dichotomized in favorable vs. unfavorable outcome (MRS 0–1 vs. 2–6) or independence vs. death (MRS 0–2 vs. 3–6). Zero points refer to absence of any residual symptoms and 6 points to death (25). Another outcome scale is the Barthel Index (BI), which measures daily activity by utilizing 10 items, such as urinary and fecal continence and ability to walk (complete dependence = 0 points, functional independence = 100 points, favorable outcome $\geq$95 points) (26).

**RANDOMIZED TRIALS OF INTRAVENOUS THROMBOLYSIS**

The **Streptokinase Trials.** One pilot study and three large trials investigated the efficacy of streptokinase for acute ischemic stroke. Morris et al. (27) evaluated 20 patients (10 streptokinase, 10 placebo) within 5.2 hrs (placebo) and 5.8 hrs (streptokinase). There were three deaths in each treatment group, with a higher incidence of hemorrhage in the streptokinase group (n = 3 vs. n = 1 patients).

The Multicenter Acute Stroke Trial–Italy (MAST-I) was a nonplacebo-controlled, randomized trial of streptokinase, which investigated whether, separately or together, streptokinase and aspirin have clinical benefits in acute ischemic stroke when given within 6 hrs after symptom onset (28). A total of 622 patients received either a 1-hr intravenous infusion of 1.5 MIU streptokinase (157 patients), 300 mg/day aspirin for 10 days (153 patients), both active treatments (156 patients), or neither (156 patients); intravenous or oral anticoagulation and other antiplatelet agents were to be avoided, and subcutaneous heparin was allowed. MAST-I aimed for 500 patients in each subgroup but had to be stopped because of excessive early hazard in the groups allocated to streptokinase treatment (29). Streptokinase (alone or with aspirin) was associated with high rates of death at 10 days (OR 2.7, 95% CI 1.7–4.3, $p < .001$). Streptokinase (alone or with aspirin) and aspirin (alone or with streptokinase) re-
duced, albeit not significantly, the incidence of combined 6-month mortality and severe disability: OR for streptokinase 0.9 (95% CI 0.7–1.3) and OR for aspirin 0.9 (95% CI 0.6–1.3). There was a substantial disagreement among the investigators with regard to interpretation of the results of MAST-I. The biostatisticians separately reported a different interpretation, mainly indicating that the excess risk of fatal and disabling hemorrhage is understated and that a potential trend toward benefit of stroke therapy with streptokinase is overestimated (30). The primary safety outcome was similar in the two groups (124 patients in the streptokinase group/126 in the placebo group with Rankin ≥3) at 6 months. The primary safety outcomes were death at 10 days and ICH. Because of an increase in mortality in the treated group, the trial was stopped after 310 of the planned 600 patients had been recruited. The incidence of the primary efficacy outcome was similar in the two groups (124 patients in the streptokinase group/126 in the placebo group with Rankin ≥3); however, the early mortality was significantly higher in the streptokinase group (day 10: 34.0% vs. 18.2%, p = .002; 6 months: 46.8% vs. 38.3% of patients, p = .06), which was mainly because of fatal ICH. One has to consider, although, that MAST-E allowed early anticoagulation, which was given to 31% of the streptokinase but only 12% of the placebo-treated patients within 12 hrs (p = .04), and this may have contributed to the high rate of ICH in the streptokinase group.

The Australian Streptokinase (ASK) trial, a randomized, double-blind, placebo-controlled trial with a 3-month follow-up, had a time window of 4 hrs for patient recruitment (32). The ASK aimed to determine whether the administration of 1.5 MIU streptokinase within 4 hrs of the onset of acute ischemic stroke would reduce morbidity and mortality at 3 months (BI ≤60). In addition, a prospective comparison of the patients randomized within 3 hrs and those randomized within 3–4 hrs was performed. A total of 340 patients were recruited before the safety committee advised trial suspension because of significantly (p = .04) poorer outcomes in patients (n = 270) treated between 3 and 4 hrs after symptom onset (<3 hrs: RR, 0.66; 95% CI, 0.28–1.58; 3–4 hrs: RR, 1.22; 95% CI, 0.80–1.86) and because of the low recruitment rate in the <3 hrs group (70 patients). Streptokinase resulted in too many deaths in the group treated after 3 hrs (RR, 1.98; 95% CI, 1.18–3.35), but not among those treated within 3 hrs (RR, 1.11; 95% CI, 0.38–3.21). There was a nonsignificant overall trend toward unfavorable outcomes for streptokinase vs. placebo (48.3% vs. 44.6%; RR, 1.08; 95% CI, 0.74–1.58) and a high rate of ICH in the drug-treated group (13.2% vs. 3%; p < .01).

In summary, all of the trials using streptokinase for acute ischemic stroke were prematurely stopped because of a high rate of early death, mostly resulting from ICH, and because of a lack of benefit at outcome in a meta-analysis as well (33). In the streptokinase trials together there were 92 (95% CI 65–120) additional fatal ICH per 1000 treated patients (OR 6.03, 95% CI 3.47–10.47) (34). The higher bleeding rate may be the result of pharmacologic properties of streptokinase other than, for instance, rt-PA, additional anticoagulation (MAST-E), a rather small fraction of patients treated within 3 hrs, and a rather high dose of 1.5 MIU, which is identical to the dose used in myocardial infarction (MI), whereas the rt-PA studies (see below) chose approximately two thirds the dose used in MI. Other side effects of streptokinase are a decrease in systolic blood pressure of >20 mmHg in 33% (only 6% in the placebo group) as well as anaphylaxis in 2.2% of the patients. Therefore, intravenous administration of streptokinase, outside the setting of a clinical investigation, is dangerous and not indicated for the management of patients with ischemic stroke.

The rt-PA Trials. In 1995, the results of the European Cooperative Acute Stroke Study (ECASS I) and NINDS trials of intravenous rt-PA for acute ischemic stroke were published (7, 9, 35) and followed by ECASS II in 1998 (35) and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) in 1999 (36). These four trials randomized a total of 2,657 patients to treatment with placebo (n = 1,316 patients) or intravenous rt-PA (n = 1,341 patients) within 0–3 hrs (NINDS), 3–5 hrs (ATLANTIS), or 0–6 hrs (ECASS I and II) after symptom onset. All four studies required a baseline CT scan to exclude ICH, and, except for the NINDS study, all others also established CT exclusion criteria such as major early signs of infarction. All trials used the 0.9 mg/kg body weight dose up to a maximum of 90 mg rt-PA, except ECASS I, in which 1.1 mg/kg up to a maximum dose of 100 mg was given. Ten percent of the total dose was given as a bolus; the rest was infused over 1 hr in all four trials.

NINDS. The NINDS trial randomized 624 patients (312 each placebo and intravenous rt-PA) within a time window of 3 hrs after stroke symptom onset (7). Half of the patients were treated within 0–90 mins, the other half within 91–180 mins. The trial had two parts. Part 1 (in which 301 patients were enrolled) tested whether rt-PA demonstrated a clinical effect, as indicated by an improvement of 4 points over baseline values in the NIHSS score or the resolution of the neurologic deficit within 24 hrs of the onset of stroke (primary end point). Part 2 (in which 333 patients were enrolled) used a global test statistic to assess clinical outcome at 3 months, according to scores on the BI, MRS, Glasgow Outcome Scale (GOS), and NIHSS, evaluating each single score and all four as a combined end point. A good outcome was defined as a NIHSS score of ≤1, GOS = 1, BI ≥95, and MRS ≤1. The median baseline NIHSS score was 14 (rt-PA group) vs. 15 (placebo group). There was no significant difference between the drug treatment and placebo group in the percentages of patients with neurologic improvement at 24 hrs (rt-PA 47% vs. placebo 57%; RR, 1.2; p = .21), although a post hoc analysis comparing the median NIHSS scores at 24 hrs showed a median of 8 in the rt-PA-treated group vs. 12 in the placebo group (p < .02). Furthermore, a benefit was observed for the rt-PA group at 3 months for all four outcome measures. In part 2, the long-term clinical benefit of rt-PA predicted by the results of part 1 was confirmed in all single scores as well as in the global test: BI (50% vs. 38%; OR 1.6 (1.1–2.5), p = .026); MRS (39% vs. 26%; OR 1.7 (1.1–2.5), p = .019); GOS (44% vs. 32%; OR 1.6 (1.1–2.5), p = .025); NIHSS (31% vs. 20%; OR 1.7 (1.0–2.8), p = .033); and combined end point (OR 1.7 (1.2–2.6), p = .008). For every 100 patients treated
with rt-PA, an additional 11–13 will have a favorable outcome as compared with 100 not treated with rt-PA. The combined analysis of all 624 patients of parts 1 and 2 together yielded results that were nearly identical to those of part 2 alone; interestingly, however, outcome did not vary by stroke subtype at baseline, meaning that patients with small vessel disease benefited as well as patients with, for instance, cardioembolic stroke. Symptomatic ICH within 36 hrs after the onset of stroke occurred in 6.4% of patients given rt-PA but only in 0.6% of patients given placebo (p < .001). Nevertheless, severe disability and death were higher in the nontreated group (mortality at 3 months: rt-PA 17% vs. placebo 21%; p = .30).

After publication of the NINDS trial in 1996, rt-PA received Food and Drug Administration approval for the treatment of acute ischemic stroke in a time window of 3 hrs.

**ECASS I.** ECASS I, a prospective, multicenter, randomized, double-blind, placebo-controlled trial, recruited 620 patients for treatment either with 1.1 mg/kg rt-PA or placebo within 6 hrs after stroke symptom onset (9). Anticoagulants, neuroprotectants, and rheologic therapy were prohibited during the first 24 hrs. Patients with a severe deficit (hemiplegia, forced head and eye movement, impairment of consciousness), with only mild or improving stroke symptoms, or CT signs of early infarction exceeding 33% of the middle cerebral artery (MCA) territory were excluded. Primary endpoint included a difference of 15 points in the BI and 1 point in the MRS at 90 days in favor of rt-PA. Secondary endpoint included combined BI and MRS, SSS at 90 days, and 30-day mortality. Tertiary endpoint included early neurologic recovery (SSS) and duration of inhospital stay. In anticipation of a substantial number of protocol violations resulting from the first time early CT signs of infarction were being used as an inclusion criterion, the investigators prospectively specified a target population (TP) analysis in addition to the primary intention to treat (ITT) analysis, which was performed at the end of the trial. The median NIHSS score at baseline was 13 (rt-PA patients) and 12 (placebo group), respectively. ECASS I was the first trial of thrombolysis to use CT exclusion criteria (37–40). Despite these predefined parameters, there were 109 protocol violations in ECASS I (17.4%), 66 (11%) of which were CT protocol violations and 52 (8.4%) of these resulting from failure to detect of early infarct signs. There was no difference in the primary end points in the ITT analysis, whereas the TP analysis revealed a significant difference in the MRS (but not BI) in favor of rt-PA-treated patients (p = .035). Of the secondary end points, the combined BI and MRS showed a difference in favor of rt-PA–treated patients (p < .001). Neurologic recovery at 90 days was significantly better for rt-PA–treated patients in the TP (p = .03). There was a nonsignificant trend toward a higher mortality rate at 30 days (p = .08) and a significant increase in parenchymal ICH (19.8% vs. 6.5%, p < .001). There was a significant inverse relationship between protocol violation in rt-PA patients and 7-day-survival. A post hoc analysis of the ECASS I 3-hr cohort (n = 87 patients) did not reveal a significant difference between rt-PA and placebo group outcomes (41).

**ECASS II.** The results of ECASS I and NINDS led to the design of ECASS II, which was conducted from October 1996 to January 1998 in 108 centers in 16 countries in Europe, New Zealand, and Australia (35). A total of 800 patients (409 rt-PA, 391 placebo) were randomized to treatment with either 0.9 mg/kg rt-PA or placebo within 6 hrs (stratified into a 0- to 3-hr and a 3- to 6-hr group) after stroke symptom onset. The primary end point was the MRS at 90 days, dichotomized for favorable (score 0–1) and unfavorable (score 2–6) outcome. Analyses were by ITT and an 8% absolute difference was aimed for in the primary end point. Secondary endpoint were a combined BI and MRS at day 90 and the NIHSS at day 30. A post hoc analysis requested by the board of reviewers was performed for an alternative dichotomization into independent vs. death and dependent outcome (MRS 0–2 vs. 3–6). Baseline median NIHSS was 11 in both groups, which is 2–3 points less than in NINDS and ECASS I. The safety analysis showed a similar mortality in the two groups (10.5% vs. 10.7%). There was a substantially larger number of fatal ICH in the rt-PA group (11 vs. 2 patients) whereas more patients died as a result of space-occupying brain edema in the placebo group (8 vs. 17 patients). There was a four-fold increase in symptomatic parenchymal ICH (48 vs. 12 patients) in the rt-PA group, which was a far lower rate than in ECASS I. The primary end point was negative for rt-PA (MRS ≤1: 40.3% vs. 36.6%; Δ = 3.7%; p = .277). There was a trend for the combined BI/MRS end point (p = .098) and a significant difference in day 30 NIHSS (p = .035). With the alternative dichotomization, a significant advantage for patients treated with rt-PA (MRS 0–2: 54.3% vs. 46.0%; Δ = 8.3%; p = .024) was demonstrated. Like in ECASS I, the 3-hr cohort did not show any significant differences because of the small patient numbers (n = 80 patients/group). Symptomatic ICH occurred in 36 (8.8%) rt-PA patients and 13 (3.4%) placebo-treated patients. Interestingly, there was a high number of benign spontaneous disease courses in the placebo group (36.6%), which is larger than the favorable outcome rate in the ECASS I rt-PA group (35.9%). Furthermore, a comparison of the 3-hr cohorts of ECASS I and II and NINDS demonstrates a surprisingly high number of favorable outcomes among the placebo group patients in ECASS II (ECASS I rt-PA: 38.5%; NINDS rt-PA: 38.7%; ECASS II placebo: 37.7%). Whether this is the result of general improvements in the treatment of acute stroke patients, a less severe baseline deficit, or other factors is unclear. Although negative for the primary end point, ECASS II was a clinically highly relevant study and showed that treatment of ischemic stroke with rt-PA in a time window of less than 6 hrs may lead to an improved outcome if given to selected patients in experienced centers.

**ATLANTIS.** The ATLANTIS study began in 1991 and originally was designed to assess efficacy and safety of thrombolytic therapy with rt-PA within 0–6 hrs after stroke symptom onset (36). In 1993, the time window was changed, because of safety concerns, to 0–5 hrs and restarted as part B (ITT), only to be further modified in 1996 to a 3–5 hr window (TP) after rt-PA had been approved by the Food and Drug Administration. Part A enrolled 142 patients (22 <3 hrs, 46 >5 hrs) (42). The primary end point was an improvement of ±4 points on the NIHSS at 24 hrs and day 30; secondary end points included functional outcome (BI and MRS) at days 30 and 90. There was a significant improvement at 24 hrs in the rt-PA group (40% vs. 21%, p = .02); this effect, however, was reversed at day 30 (60% vs. 75%, p = .05). rt-PA significantly raised the rate of symptomatic ICH (11% vs. 0%, p < .01) and mortality at 90 days (23% vs. 7%, p < .01). The primary end point for part B was a NIHSS score of ±1 at 90 days; secondary end points were outcome at days 30 and 90 according to...
BI, MRS, and GOS. An ITT population of 613 acute ischemic stroke patients was enrolled, with 547 of these treated as assigned within 3–5 hrs of symptom onset (TP). There were no differences on any of the primary (34% vs. 32%, p = .65) or secondary functional outcome measures; however, there was a significant difference in the rate of major neurologic recovery (complete or ≥11 NIHSS points improvement: 44.9% vs. 36%, p = .03), which did not affect overall outcome. Treatment with rt-PA significantly increased the rate of symptomatic ICH (7.0% vs. 1.1%, p < .001). As in ECASS II (median baseline NIHSS: 11 points), the median baseline NIHSS score was substantially lower than in the NINDS trial (10 vs. 14 points), which (as in ECASS II) may have led to a better than expected outcome in the placebo group. In contrast to ECASS II, ATLANTIS was negative for the alternate outcome measure—dependence or death (MRS 3–6) (rt-PA 54% vs. placebo 56%, p = .75). The authors conclude that thrombolyis with rt-PA for acute ischemic stroke >3 hrs after symptom onset cannot be recommended.

Meta-Analyses. A search of the literature revealed two large meta-analyses (34, 43, 44). The first meta-analysis by Hacke et al. (43) from 1999 covered the NINDS study and both ECASS trials, with a total of 2044 patients included (1,034 rt-PA patients vs. 1,010 placebo patients). The authors assessed the benefit of rt-PA and dichotomized the outcome into independent vs. dependent or dead (MRS 0–2 vs. 3–6) and favorable vs. unfavorable (MRS 0–1 vs. MRS 2–6). Risk in these three trials can be defined as ICH and mortality. Differences between the trials such as the dose of rt-PA (1.1 mg/kg in ECASS I vs. 0.9 mg/kg in NINDS and ECASS II) and the therapeutic time window (3 hrs in NINDS vs. 6 hrs in ECASS I and II) were taken into account. ICH occurred significantly more often in patients receiving rt-PA (144/1,034 vs. 43/1,010, OR 3.23, CI 2.39–4.37), and was slightly less increased in the 3 hr time window and at the lower dosage (41/393 vs. 15/389, OR 2.68, CI 1.56–4.62). There was no significant difference in mortality between rt-PA and placebo (OR 1.07, CI 0.84–1.36) but a slight trend toward a lower mortality in the 0.9 mg/kg and 3 hr group (OR 0.91, CI 0.63–1.32), rt-PA, on the other hand, led to a 37% reduction in death and dependence regardless of dose and time window (OR 0.63, CI 0.53–0.76). If treated with the lower dose and within 3 hrs the chance of an unfavorable outcome was reduced by 45% (OR 0.55, CI 0.41–0.72). For every 1,000 patients treated with either dose there are 90 fewer patients who are dead or disabled but 96 hemorrhages more than expected with placebo. Conversely, for 1,000 patients treated with 0.9 mg/kg and within 3 hrs, there are 65 additional ICH and 140 fewer patients dead or disabled. The NNT for all doses and time windows is 11; for the 3-hr and 0.9 mg/kg group it is 7. These numbers are far better than the NNT for thrombolysis in MI, which is 30–40 (43). See Figure 1 for an illustration of these meta-analyses.

Warldal et al. (34, 44) included in their Cochrane Library meta-analysis all randomized trials of thrombolysis regardless of time window, dosage, administration route, and substance. Seventeen trials with a total of 5,216 patients (2,889 of which were from rt-PA-trials) were included. The 17 trials were NINDS, ECASS I and II, ATLANTIS A and B (with preliminary data), Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II (with preliminary data), ASK, MAST-E, MAST-I, and the early trials by Abe, Atarashi, Haley, Mori, Morris, Ohtomo, and Yamaguchi (7, 9, 19–24, 27, 28, 31, 32, 35, 36, 42, 45, 46). The main objectives were to show that thrombolytic therapy reduces the risk of late death, increases the risk of early and fatal ICH, and that the benefit at outcome (reduction of death and dependence) offsets any early hazard. Symptomatic and fatal ICH were significantly more common as a result of thrombolytic therapy (symptomatic ICH: OR 3.53, CI 2.79–4.45, p < .00001; fatal ICH: OR 4.15, CI 2.96–5.84). This translates into 70 additional instances of symptomatic ICH for patients receiving thrombolysis and 29/1,000 (OR 3.2) additional instances of fatal ICH in rt-PA patients but 92/1000 (OR 6.03) additional ICH in those patients receiving streptokinase as opposed to placebo. Despite this, thrombolytic therapy, administered up to 6 hrs after ischemic stroke, significantly reduced death or dependence at the end of follow-up (55.2% vs. 59.7%, OR 0.83, CI 0.73–0.94, p = .0015), which is equivalent to 44 fewer patients being dead or dependent per 1,000 treated (CI 15–73). For patients treated with rt-PA only, the OR was 0.79 (CI 0.68–0.92, p = .001) or 57 deaths/dependence prevented per 1,000 patients treated (CI 20–93). An alternative end point analysis yields similar results for favorable vs. unfavorable outcome (OR 0.79 for all patients and 0.76 for rt-PA patients). When treatment was given within 3 hrs after stroke onset, there was an even better risk reduction for dependency or death (55.2% vs. 68.3%; OR 0.58, CI 0.46–0.74, p = .00001) or 126 fewer dead or dependent patients per 1,000 treated. The difference of benefit of rt-PA in the 0–3 hr window or 3–6 hr window was nonsignificant but showed a trend toward better improvement with early therapy (OR 0.7 vs. 0.76). The authors conclude that the significant increase in early death and fatal and nonfatal symptomatic ICH are offset by the significant reduction of disability in survivors. Therapy with rt-PA is associated with less risk and more benefit than with other substances.

CONCLUSION, RECOMMENDATIONS, AND FUTURE PROSPECTS FOR INTRAVENOUS THROMBOLYSIS

Overall, thrombolysis with 0.9 mg/kg rt-PA for acute ischemic stroke within 6 hrs leads to an overall clinically significant effect in favor of treated patients but is associated with an excess rate of symptomatic ICH, which does, however, not take effect on mortality. Intravenous rt-PA (0.9 mg/kg, maximum of 90 mg) is therefore the recommended treatment within 3 hrs after stroke symptom onset and has been approved with restrictions for stroke patients in Germany since August 2000. The mutual recognition procedure, however, did not result in a Europe-wide approval of rt-PA. At present, an arbitration procedure, where evidence and expert reports are reviewed with regard to a Europe-wide approval has been initiated. Restrictions for patients older than 75 yrs or with regular prestroke use of platelet inhibitors are not based on any data and thus not understood by these authors. Thrombolytic therapy should be performed in centers experienced with the procedure. The benefit from the use of intravenous rt-PA for acute ischemic stroke beyond 3 hrs from onset of symptoms is lower, but definitely present in selected patients. Also, the European Stroke Initiative (EUSI) recommendations state that thrombolytic therapy is the therapy of choice within 3 hrs and in selected patients up to 6 hrs after stroke onset (47). The adjunctive use (and also the optimal time point of use) of anti-
thrombotic agents is still controversial and at present no recommendation can be given with regard to concomitant administration of heparin or antiplatelet agents in the setting of thrombolytic therapy. Intravenous rt-PA is not recommended when the time of onset of stroke cannot be ascertained reliably; this includes patients in whom strokes are recognized upon awakening. Intravenous administration of streptokinase for acute ischemic stroke is dangerous and not indicated. Data on the efficacy of any other intravenously administered thrombolytic drugs are not available such that a recommendation could be provided. A stroke-MRI-based study on the efficacy of recombinant desmoteplase (DSPA, derived from saliva of the vampire bat Desmodus rotundus) for treatment of stroke in the 3–6 hr time window is underway (Desmoteplase in Acute ischemic Stroke, or DIAS). Finally, the benefits of arterial recanalization may be supplemented by neuronal protection (first protocol drafts underway), particularly when the two strategies are used simultaneously, and if they can be used very early following symptom onset. At present, thrombolytic therapy is still underutilized. Among the major problems are that relatively few candidates meet the clinical and time criteria. Educating the general public to regard stroke as a treatable emergency and training emergency caregivers in the use of thrombolysis may decrease these problems. Healthcare institutions should be made aware of the potential in long-term cost savings, once stroke management is optimized and thrombolysis is more widely available. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy but also about its potential benefit and, thus, the risk of not being treated.

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