Intravenous Thrombolysis for Acute Ischemic Stroke

Thomas A. Tomsick, MD

Intravenous recombinant tissue-type plasminogen activator (rtPA, alteplase) is the only drug currently approved for the treatment of acute ischemic stroke. It should be administered within 3 hours of stroke. There is additional evidence, however, that administration at later times, by means of other methods, is effective. Herein, is a broad review of the knowledge gained and insights created from studies in which thrombolytic treatment was used in patients with stroke.

ACUTE ischemic stroke is a heterogeneous disease process; prediction of course, recovery, disability, or death is difficult (1). The course of ischemic stroke may resemble a drama, frequently a tragedy, wherein the *discordia personæ*—the nature and origin of the arterial occlusive lesion, duration of ischemia, magnitude of neurologic deficit, time to therapy, time to recanalization, available collateral blood flow, cellular and genetic bases for metabolic alterations in the ischemic end-organ, and other patient-specific comorbid factors—all interact to determine the clinical and imaging outcome. Intravenously (IV) administered alteplase—a single-chain recombinant tissue-type plasminogen activator (rtPA)—is the only drug currently approved specifically designed to recanalize the acute arterial occlusive lesion in ischemic stroke.

This chapter is written with an interventional perspective on IV thrombolytic therapy with rtPA, and I focus on knowledge gained from both pilot trials and clinical studies. It focuses on therapeutic implications regarding recanalization by means of intraarterial (IA) interventions and, it is hoped, constructs a backdrop against which future interventional recanalization and neuroprotective therapies can be viewed.

**THE ARTERIAL OCCLUSIVE LESION**

Acute ischemic stroke is typically due to an acute thromboembolic arterial occlusive lesion. The location of the arterial occlusive lesion in acute ischemic stroke is relatively heterogeneous but somewhat predictable based on published observations (Table 1) (2–5). Most studies listed in Table 1 include patients with at least mild to moderate deficits, or “911” strokes. It is likely patients with smaller clinical deficits might have fewer demonstrable, or perhaps more distal, intracranial arterial occlusions.

The data used by Wolpert et al (2) were obtained from angiograms obtained in the Burroughs-Wellcome tPA Acute Stroke Study Group’s pilot trial of IV dual-chain rtPA (duteplase) for arteriographically demonstrated arterial occlusive lesions (6).

In the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) study (7), more than 10,000 patients suspected of having middle cerebral artery (MCA) occlusion were screened to find 480 treatment candidates who underwent angiography within an average of 5 to 6 hours of stroke onset.

The Interventional Management of Stroke (IMS) study investigators (5) obtained angiograms in selected patients with a National Institutes of Health Stroke Scale (NIHSS) score of at least 10 after the IV administration of reduced-dose rtPA, although some may have experienced recanalization after thrombolytic drug infusion. (The NIHSS is a clinical examination scale comprised of the sum of 42 score choices from 14 physical examination parameters, with 0 representing a near-normal examination and representing 42 maximal disability.) When examined with cervicocerebral angiography within hours of acute stroke onset, approximately 20%-25% of patients will have an M1 trunk occlusion, 15% will have an M2 division.
occlusion, 10% will have a distal intracranial cerebral artery (ICA) or carotid “T” occlusion, 15%–20% will have a proximal ICA occlusion or severe stenosis (typically with distal thromboembolism), and 5%–10% may have a vertebrobasilar occlusion.

Arterial occlusion is a dynamic process, and recanalization may allow occluding thrombi to completely or partially lyse, pass more distally with time, or fragment into one or more branches before imaging detection. In the PROACT II trial, 20% of cervicocephalic angiograms did not demonstrate an arterial occlusive lesion. Furthermore, their control group showed that 18% of M1–M2 occlusions recanalize at least partially within 2 hours on the angiographic table during the IV administration of heparin, up to 6 hours after onset. Transcranial Doppler analyses have shown that recanalization occurs in approximately 15% of untreated patients within 6 hours of acute stroke (8). Other previous observations suggested a similar rate of spontaneous recanalization in acute stroke (9). However, the absence of arteriographic occlusion does not exclude preexisting occlusion or perforating artery occlusion. The Emergency Management of Stroke (EMS) and IMS studies demonstrated that the follow-up images of virtually all patients in whom angiography had failed to show an arterial occlusive lesion (even after IV rtPA administration) demonstrated infarcts, most of which were small and deep in perforating artery distributions (10,11).

Transcranial Doppler studies have also provided insights into the duplex ultrasonographic (US) characteristics, location, and nature of baseline arterial occlusive lesions, and more data are forthcoming in this area (12–14). It has been suggested that external US at clinical diagnostic power may aid in thrombolysis (15). Although transcranial Doppler US can provide confirmation of major occlusion, its accuracy is operator-specific. Up to 10% of patients offer no imaging window due to thickened temporal bone attenuation. Computed tomographic (CT) angiography, magnetic resonance (MR) angiography, or digital subtraction arteriography may also suffice in demonstrating an arterial occlusive lesion.

**Table 1**  
Arterial Occlusive Lesions in Studies of Acute Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>ICA (%)</th>
<th>Distal ICA (%)</th>
<th>M1 (%)</th>
<th>M2 (%)</th>
<th>M3–4 (%)</th>
<th>Vertebrobasilar (%)</th>
<th>No Occlusions or Stenosis (%)</th>
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<tr>
<td>Wolpert (2)</td>
<td>139</td>
<td>17</td>
<td>1.5</td>
<td>25</td>
<td>12</td>
<td>12</td>
<td>1.5</td>
<td>19</td>
</tr>
<tr>
<td>Knepper (4)</td>
<td>97</td>
<td>20</td>
<td>8</td>
<td>16</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>NA</td>
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<tr>
<td>Furlan* (7)</td>
<td>476</td>
<td>20</td>
<td>20</td>
<td>23</td>
<td>14</td>
<td>8</td>
<td>NA*</td>
<td>19</td>
</tr>
<tr>
<td>IMS Investigators† (5)</td>
<td>77</td>
<td>37</td>
<td>9</td>
<td>20.5</td>
<td>15</td>
<td>11</td>
<td>2.5</td>
<td>5</td>
</tr>
</tbody>
</table>

Note.—NA = not applicable.
* Selection: Suspected MCA occlusion.
† After IV administration of 0.6 mg/kg rtPA.

**RECANALIZATION EFFICACY AFTER IV tPA THERAPY**

There is a wide discrepancy between recanalization rates reported in pilot studies in which angiography or delayed transcranial Doppler imaging were performed after IV rtPA treatment to determine recanalization efficacy. Mori et al (9) reported an on-the-table recanalization rate (though typically incomplete) of approximately 47% for 19 arteriographically demonstrated anterior circulation occlusions after a 1-hour infusion of 40 to 60 mg duteplase (a dual-chain rtPA) within 6 hours of stroke onset. In a larger study, the tPA Acute Stroke Study Group (ASSG) evaluated patients with cerebral angiography and treated those with arterial occlusive lesion within 8 hours of acute stroke by infusing variable doses of IV duteplase (without bolus) for 1 hour. Recanalization response was evaluated with a repeat angiogram after infusion. The recanalization rates, typically incomplete, are listed in **Table 2** (6). This study demonstrated that M1 occlusive lesions completely recanalize relatively infrequently with IV rtPA; they did not find a relationship between dose and recanalization rates.

von Kummer et al (16) reported that recanalization occurred in 11 of 53 patients immediately after either IV (100 mg rtPA over 90 min, n = 46) or IA (n = 7) rtPA administration. Eighteen patients demonstrated recanalization at transcranial Doppler US 24 hours after rtPA administration. They subsequently reported 24 additional patients, 15 who received IV rtPA and nine who received IA rtPA, with 11 recanalizations. Of interest, seven of the 55 patients in whom recanalization did not initially occur showed recanalization at transcranial Doppler US performed 24 hours after rtPA administration; three patients experienced reocclusion after initial recanalization (17).

The recanalization response of MCA occlusion to IV rtPA (alteplase) in the dose-escalation National Institute of Neurologic Disorders (NINDS)
pilot trial was likewise incomplete. No differences in clinical efficacy (as a marker of recanalization) between smaller versus maximal doses of rtPA were determined, although the study was not designed to determine an optimal dose (18,19). Fourteen of the 18 patients in the NINDS Pilot trial with MCA occlusion, as manifested by the hyperdense MCA sign, had cerebral angiograms within 2 days of stroke, and all still exhibited MCA occlusion, which is indicative of relatively poor recanalization (or recanalization with rethrombosis), of large-vessel occlusions after IV tPA at the doses used. Of the 19 patients with an NIHSS score of less than 10, patients typically had normal follow-up angiograms or distal recanalizing emboli (20). The implications of the ability of tPA to open smaller, peripheral vessels and lead to generally good outcomes while failing to open larger vessels, which is typically associated with less complete recoveries, is quite clear. However, caution is required when interpreting the data, when dose-escalation and early angiography may not reflect the effects of an optimum dose given in a reasonable time to show effect.

Published post-NINDS recanalization efficacy is fragmentary, but a number of centers have reported recanalization rates of up to 70% with use of transcranial Doppler US (21–23). The discrepancy between angiograms obtained on the table after 1 hour of rtPA infusion and transcranial US data obtained 2 to 3 hours after infusion generally points to a continued benefit of rtPA beyond its 5-minute expected half-life, possibly due to activity-mediated improved hemodynamics, continued activity due to clot binding, and activity or upregulation of intrinsic thrombolytic systems. In fact, the recanalization data from transcranial Doppler US performed at 6 hours closely parallels recanalization effects that have been reported with IA thrombolytic therapy (24).

In the EMS trial, 35 patients were randomized to reduced-dose IV rtPA (0.6 mg/kg rtPA, 10% as bolus, the remainder over 30 min) or IV placebo. Arteriography was performed and, if an arterial occlusive lesion was present, IA rtPA was administered (25). Of interest, the absence of an arterial occlusion was less common in the IV rtPA group, although the NIHSS score (which may in part reflect reduced thrombus burden) was lower in the placebo group than in the active drug group.

After the EMS trial, a consecutive series of 62 patients with an NIHSS score of at least 10 were treated in Cincinnati, OH, by using a similar protocol but increasing the initial drug bolus to 15% of the total dose, followed by IV infusion for 30 minutes (26). Twelve (19%) patients exhibited no occlusion, distal emboli, or stenosis, which suggests that recanalization had probably occurred either spontaneously or secondary to reduced-dose therapy.

In the IMS trial, a multicenter trial in which 80 patients (NIHSS score ≥ 10, age < 81 y) were entered in open-label study of reduced-dose IV rtPA (0.6 mg/kg, 15% as a bolus, with the remainder administered over 30 min) followed by arteriography and IA rtPA if an arterial-occlusive lesion was found, 13 of seven (17%) patients exhibited no, distal, or recanalizing emboli at arteriography. This finding also suggests that reduced-dose IV rtPA effectively enables recanalization in some patients (albeit a minority) within the delay period to angiography (mean time to IV rtPA, 140 min; mean time to IA rtPA, 210 min).

Despite the failure the EMS, IMS, and Cincinnati trials to demonstrate a major arterial occlusive lesion in 37 patients, independent outcomes (modified Rankin 0–2) were achieved in only 66% of patients. This would seem to represent the practical limitation of timely recanalization therapies in achieving good outcomes in larger strokes. A time-outcome graph that the recanalization thrombolytic therapies suggests limited benefit, unless they are applied in the most timely of manners. Figure 1 includes data from IA trials and combined IV-IA trials and analyses. The percentage of Rankin 0 to 2 outcomes are charted versus the mean time to IA treatment for cases in which arterial occlusive lesions were encountered.

Although recanalization is the basis for optimal outcomes, adequate collateral flow is important as well (18,27). Data from diffusion-weighted MR imaging and CT perfusion studies (28,29) have shown that larger, progressive infarcts are expected in patients with poor collateral vessels in whom recanalization does not occur. Failure of recanalization does not exclude good outcomes, however, in the presence of adequate collateral vessels. Thus, stroke therapy must be directed to-

![Figure 1](https://example.com/figure1.png)

Figure 1. Percentage Rankin 0–2 outcomes versus mean time to treatment from three IA intention-to-treat studies. Data were obtained for patients with M1 or M2 occlusion and patients who have no major arterial occlusive lesion following IV administration of 0.6 mg/kg rtPA. From the right: control group from the PROACT II study (25%); prourokinase group from the PROACT II study (40%); Cincinnati trial (50%); IMS group (56%); and partial-dose, IV-only groups from the EMS, Cincinnati, and IMS studies combined (66%).
ward both more timely and more effective recanalization.

Reocclusion after recanalization may also lead to poor outcomes. Clinical deterioration occurred in approximately 13% of patients treated with IV rtPA in the NINDS trial, which is similar to that in patients receiving placebo (30). Early reocclusion occurred more commonly with the hyperdense MCA sign, early CT hypodensity, higher serum glucose levels, and the absence of previous aspirin therapy. Early reocclusion was documented in 34% of a subsequent group of patients and accounted for two-thirds of the deterioration that occurred following initial improvement (31).

RELATIONSHIP BETWEEN THE NEUROLOGIC DEFICIT AND ARTERIAL OCCLUSIVE LESION

Considerable opinion exists that the extent of cerebral ischemia, or even the presence of an arterial occlusive lesion, cannot be assessed with neurologic examination alone. Other information indicates that the volume of decreased cerebral perfusion, or ischemic volume at risk, does relate to the neurologic deficit (as measured with the NIHSS) (32). The NIHSS score is a surrogate of hypoperfused brain, either already damaged or still at risk. Collateral flow modulates the value of the NIHSS (33).

The absence of deficit, however, does not mean that a major arterial occlusive lesion (eg, asymptomatic ICA occlusion) is absent and the presence of a deficit does not ensure discovery of an arterial occlusive lesion. The presence of an acute neurologic deficit, however, does show correlation, although imperfectly, with the level and magnitude of intracranial arterial occlusive lesion and cerebral blood flow. Determination of the NIHSS score is the most rapidly and easily available correlate of ischemic risk and a predictor of outcome and patient disposition (1). Any other attempt to gain further information about the arterial occlusive lesion and volume of brain at risk is gained at the cost of time spent acquiring that information. Any proposed diagnostic and treatment paradigm must take these factors into consideration.

It is notable that the pilot trial for the NINDS tPA study first correlated the magnitude of neurologic deficit associated with M1 or M2 occlusion (21). In patients with prima facie evidence of MCA occlusion in the form of the hyperdense MCA sign, the NIHSS score was at least 10 in all 18 patients with hyperdense arteries. Left-sided infarcts tend to have a higher NIHSS score because of language function exaggerating the clinical findings for an equal volume of infarction (34). Supporting that observation, 87% of M1 or M2 occlusions in the PROACT II trial had an NIHSS score of more than 10. In the EMS trial, five of 11 of patients (45%) with an NIHSS score of less than 10 did not demonstrate an arterial occlusive lesion; all of the patients with an NIHSS score of more than 14 demonstrated an arterial occlusive lesion. Nakajima et al (35) recently reported that 96.9% of patients with an NIHSS score of at least 10 had occlusions, whereas only 63.6% of patients with an NIHSS score of 9 or lower had occlusion.

Although these relationships do not show perfect correlation, it is clear that the NIHSS score quickly reveals a great deal about the presence of an arterial occlusive lesion and the need for recanalization therapy. The chance that a potentially treatable thrombus is present in patients with an NIHSS score of at least 10 is high. This finding is almost universal in patients with an NIHSS score of more than 14, unless dynamic (or therapeutic) recanalization has occurred.

CLINICAL EFFICACY OF IV rtPA ADMINISTRATION

In 1995, rtPA (activase) was approved by the U.S. Food and Drug Administration on the basis of results of the two-part NINDS stroke trial, in which 628 patients were randomized to IV rtPA or placebo within 3 hours of stroke onset. Half of the patients were treated within 90 minutes of onset according to study design. The dose of IV rtPA (0.9 mg/kg, 10% as a bolus, the remainder over 60 min; maximum dose, 90 mg) theoretically creates a systemic blood level that approximates optimum in vitro rtPA recanalization levels, at approximately 1.5 to 2 μg/mL after the bolus and during infusion (36).

Compared with patients given placebo, treated patients were at least 30% more likely to have minimal or no disability at 3 months (37). No pre-treatment information had a substantial effect on response. Although diabetes, age, hypertension, and early CT findings did affect outcome, they did not preclude a favorable response to IV rtPA (38). Post-randomization anti-hypertensive therapy was associated with less favorable outcomes for treated patients (39). A positive trend toward reduction in infarct volume in treated patients (15 mL vs. 24 mL) was also achieved (40). The use of rtPA is also likely to be cost-effective, with a shorter length of stay and more frequent discharge to home (41).

It has been suggested that demonstration of an arterial occlusive lesion is requisite before administration of IV rtPA, with the fear that the drug might be administered where occlusion is not present, the diagnosis is in error, or occlusion no longer exists. The use of IV rtPA in the treatment of transient ischemic attacks that will improve, or errors in clinical diagnosis where no occlusion exists, have been uncommon. In the NINDS trial, only 2.6% of patients had no ischemic neurologic deficit at 24 hours (42). It is believed that most failures to show an arterial occlusive lesion are due to recanalization of previously occluded vessels or undemonstrable occlusion of perforating arteries. Lacunar syndromes, which are typically ascribed to perforating artery occlusions, have been demonstrated to benefit from IV rtPA. In addition, the absence of arteriographically demonstrable occlusion is not necessarily indicative of a good outcome.

Currently, there has been some skepticism regarding the reported NINDS results, and this has contributed to the treatment of less than 5% of eligible stroke patients (43). A number of objections to the data have been raised, including (a) the primary end point of part I of the study, to reduce the NIHSS score by at least 4 points within 24 hours in treated patients, was not met; (b) with only a 12% difference in excellent outcomes (NIHSS score of 0 or 1) between patients who received treatment and those who received placebo, one must treat eight patients to benefit one; (c) compared with the placebo group, more patients who received IV rtPA had an NIHSS
score of less than 5, and fewer had an NIHSS score of more than 20; (d) almost 40% of patients in the NINDS trial were entered in two cities (Cincinnati, OH, and San Diego, CA), which raises the objection that universal reproducibility may be difficult to achieve.

Although there was no significant difference in the 4-point improvement between treated and untreated patients, this was too low a hurdle to overcome. Many untreated patients achieved that end point. However, there were significant differences for all levels of improvement of more than 4 points (Fig 2) (44).

The concept that one must treat eight patients to have one return to baseline values fails to recognize lesser degrees of improvement in other treated patients. For example, only seven patients must be treated to achieve an independent Rankin 0 to 2 outcome. Treated patients also achieved better outcomes according to other NIHSS, Rankin, and Barthel index measures.

Although differences in the distribution of patients within various stroke scale groups may have been present, the rtPA group nevertheless did better across all stroke scale levels.

Even though the differences in excellent outcomes for an NIHSS score of less than 5 were not significant, if one removes those patients from analysis, a positive treatment result is still present (P. Lyden, personal communication, 2003). For an NIHSS score of more than 20, treated patients recovered 5 times more frequently, despite having higher mortality rates.

Questions of reproducibility are defused by post-NINDS data. In a phase IV study performed after the approval of alteplase, the Standard Treatment with Alteplase to Reverse Stroke (STARS) study (45) helped confirm the outcome results of the NINDS study. With use of follow-up data obtained at 30 days after treatment, the STARS investigators also confirmed that patients with a hyperdense MCA sign or effacement more than one-third MCA distribution had an 87% decrease in odds of recovery (Rankin 0–1). Other small population based–analyses of efficacy have been reported as well. Adherence to the strict NINDS treatment criteria is crucial for reproducing similar good outcomes.

Other trials in Europe and North America have also been performed. In the first European Cooperative Acute Stroke Study (ECASS I), 624 patients were randomized to receive either 1.1 mg/kg IV rtPA or placebo up to 6 hours after stroke onset. In the intention-to-treat group, no difference in primary end point outcomes (Barthel index and the modified Rankin score after 90 d) were achieved. However, CT exclusion criteria, which should have excluded patients with more than one-third MCA distribution hypodensity) were violated in 66 (10.6%) patients, 40 in the treated and 26 in the placebo group. Excessively poor outcomes and intracerebral hemorrhage (ICH) occurred in the CT violation group. In a posthoc analysis of the target population (excluding the CT exclusion violations from analysis), significant differences in modified Rankin (P = .035) and Scandinavian Stroke Scale score (P = .04) outcomes were determined. Furthermore, application of the same global end point analysis of the NINDS trial demonstrated a significant increase in the favorable outcome in the intention-to-treat group (46). Mortality rates were higher in the tPA group with both the intention-to-treat and target analyses. Stroke volumes were smaller in the treated group, and treated patients experienced more infarcts limited only to the basal ganglia and capsule, without cortical component, than did those who received placebo (47).

In ECASS II (48), 800 patients were randomized to receive 0.9 mg/kg IV rtPA or placebo. Greater attention to the early CT exclusion criteria was applied. Randomized patients had lower mean NIHSS scores, which in itself may have limited the ability to demonstrate a positive treatment effect. No difference in the primary end point (modified Rankin score, 0.1) was found. Posthoc analysis of independent Rankin 0 to 2 outcomes, however, did demonstrate an absolute benefit of 8.3% in favor of alteplase treatment (P = .024, Fisher exact test).

In the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study (49), investigators analyzed patients treated with a similar dosing technique, focusing on the 3 to 5-hour window after the NINDS study data were reported. The primary efficacy results, which targeted NIHSS 0.1 outcomes, did not support the use of IV rtPA for stroke treatment beyond 3 hours (49). Of importance, however, the number

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**Figure 2.** Graph shows the percentage of treated patients (y axis) who improved by the number of NIHSS points indicated (x axis). P values for differences compared with the placebo group (not depicted) are in parentheses. For improvements of 4 points, there was no difference between treated and placebo groups (P = .21). Statistically significant differences occurred for all numbers higher than 4 (from P = .034 for 5 points to P = .001 for 14 points).
of patients whose NIHSS scores improved by more than 11 points was significantly greater in the treated group (P = .03) (49).

Preselection of the appropriate end point is crucial for achieving positive results in a study. Achieving an NIHSS score of 0 or 1 would indeed be a desirable end point. The practicality of achieving that goal in practice, however, may be reduced when time to treatment is important and the artificiality of study entry design (where 50% of patients must be treated in a specific ultra-early time window) is removed. Less than 25% of patients present less than 3 hours after stroke, and less than 50% of patients present within 6 hours. Other more practical outcomes, such as independence (Rankin 0–2) or absence of death or disability (Rankin 3–6), might be targeted. Data regarding ability to achieve independent or functional outcomes may be biased in trials where patients with lower NIHSS scores are entered, simply because untreated patients with low NIHSS scores more easily achieve good outcomes. Broderick et al (50) examined end points in an attempt to identify those that might be achieved with the fewest number of patients, based on retrospective NINDS data.

A recent meta-analysis of these major trials (51) identified a benefit to the use of IV rtPA in the 3 to 6-hour window, focusing on independence (modified Rankin 0–2) as a primary outcome. A positive effect of 37% relative odds reduction for treatment within 6 hours was identified, with a 45% reduction of unfavorable outcome within 6 hours. On the basis of this multistudy analysis, the number of patients needed to treat to prevent disability or death would be seven in the 0 to 3 hour window, 11 in less than 6 hours, and 25 within the 3 to 6-hour time window.

An additional meta-analysis of IV treatment studies has again demonstrated benefit to therapy, even at later time windows. In NINDS, ECASS I and II, and ATLANTIS, 2,775 patients were randomized within 6 hours, and 928 were treated within 3 hours. The median NIHSS score was 11. For patients treated within 90 minutes, the odds ratio for a favorable outcome, compared with the placebo group, was 2.8. For treatment between 90 and 180 minutes, the odds ratio was 1.5 (52).

### INTRACRANIAL HEMORRHAGE

Currently, less than 5% of eligible patients in North America receive IV rtPA for acute ischemic stroke (53). Enthusiasm for the use of IV rtPA has been tempered in part by concern for ICH (54). Spontaneous ICH following thrombolysis-related ICH was reported in 4% of patients in the dose-escalation NINDS pilot trial and was related to time to treatment; patients with ICH received rtPA later than those without ICH (6.1 ± 1.5 vs. 5.3 ± 1.7 h). Symptomatic ICH was reported in 4% of patients in the dose-escalation NINDS pilot trial and was related to dose, with no ICH at doses less than 0.9 mg/kg. This dose then became the dose chosen for the subsequent NINDS trial. Hemorrhages were also more common with an initial diastolic blood pressure greater than 100 mm Hg (56).

In the NINDS trial, 6.4% of treated patients had symptomatic ICH, compared with 0.6% of patients treated with placebo (P < .001). Despite the 10-fold increased risk of hemorrhage in the treatment group, better outcomes and fewer deaths (17% vs. 21%, not statistically significant) were achieved in treated patients. Higher NIHSS scores and early edema at CT predisposed to ICH. Of patients with

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Treated Patients</th>
<th>Time to Treatment (h)</th>
<th>Median NIHSS Score in Treated Patients</th>
<th>Hypodensity Exclusion Criteria</th>
<th>Positive for Primary End Point</th>
<th>Rankin 0–2 Outcomes (%)</th>
<th>Percentage ICH (Symptomatic or Parenchymal Hemorrhage) in Treated Patients</th>
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<tr>
<td>NINDS</td>
<td>74</td>
<td>0–1.5</td>
<td>&lt;90</td>
<td>13</td>
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<td>Pilot I</td>
<td></td>
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<td>13</td>
<td>Yes</td>
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<td>11</td>
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<td>No</td>
<td>54* NA</td>
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<td>ASSG Pilot</td>
<td>104</td>
<td>0–8</td>
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<td>NA</td>
<td>No</td>
<td>NA</td>
<td>9.6 NA</td>
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Note.—NA = not available.

* P < .05.
Table 4  
Hemorrhage Classification in ECASS I

<table>
<thead>
<tr>
<th>Hemorrhage Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>Hemorrhagic infarct type 1</td>
<td>Small petechial hemorrhagic changes along the</td>
</tr>
<tr>
<td>(HI-1)</td>
<td>margins of infarct</td>
</tr>
<tr>
<td>Hemorrhagic infarct type 2</td>
<td>More confluent petechiae without space occupying</td>
</tr>
<tr>
<td>(HI-2)</td>
<td>mass effect</td>
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<tr>
<td>Parenchymal hemorrhage type 1</td>
<td>Confluent, homogeneous hematoma smaller than one-</td>
</tr>
<tr>
<td>(PH-1)</td>
<td>third of the infarct with little or no mass</td>
</tr>
<tr>
<td>with mass effect</td>
<td></td>
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<tr>
<td>Parenchymal hemorrhage type 2</td>
<td>Hematoma larger than one-third of the infarct</td>
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<tr>
<td>(PH-2)</td>
<td>with mass effect</td>
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Relationship of NIHSS Score to Outcome

In the NINDS pilot trial, clinical response, as measured by the NIHSS score at 3 months, was also relatively poor in the hyperdense MCA sign group, with only one of 18 patients returning to near-baseline status. Patients with an NIHSS score of less than 10 did much better clinically, with more than 50% returning to an NIHSS score of 0 or 1.

These observations regarding NIHSS score and outcome were subsequently confirmed with placebo comparison in the NINDS trial. Fifty-two percent of patients with an NIHSS score of less than 10 returned to near-normal values (NIHSS score of 0 or 1), compared with 37% in the placebo group. A benefit accrued across all levels of neurologic deficit, and the patients most severely affected (NIHSS score ≥ 20) benefited most statistically, being 5.3 times more likely to return to an NIHSS score of 0 or 1 than untreated patients with similar NIHSS scores. Unfortunately, only 8% of such patients (compared with 1.5% in the placebo group) did so (Table 3). Of note, this benefit is achieved with higher mortality, where, in the NINDS, 42% of patients younger than 81 years with an NIHSS score of more than 20 died, compared with 33% in the placebo group. In patients younger than 81 years with an NIHSS score of less than 10, mortality was reduced from 6% in the placebo group to 1% in the rtPA group in patients (Table 5).

Whereas IV therapy within 3 hours may offer the greatest benefit to patients with an NIHSS score of more than 20 (odds ratio of near-total recovery, approximately 5), it is gained at a higher mortality risk. In the NINDS, the likelihood of achieving a functional outcome (Rankin 0–2) in patients younger than 81 years was 13% (n = 67) in the placebo group and 19% (n = 48) in the IV rtPA group. In the Cincinnati IV-IA experience and in the IMS trial, where reduced-dose IV rtPA preceded IA rtPA for persistent occlusion, Rankin 0 to 2 outcomes were achieved in 63% (n = 19, P = .001) and 38% (n = 21, P = .08) of patients, respectively. This selective experience emphasizes that this therapy may be most advantageous in this group.

The STARS study demonstrated that patients with an NIHSS score of more than 10 had a 75% decreased chance of recovery; for every 5-point increase in baseline NIHSS score, patients had a 22% decrease in the odds of recovery.

The significance of the baseline NIHSS score was demonstrated in the PROACT II study as well. Treated patients with an NIHSS score of less than 10 did no better than control subjects in achieving independent outcome (Rankin 0–2).

The NIHSS score may also help predict complete recanalization with IV alteplase. A recent report found that the NIHSS score in patients who had complete recanalization was lower than that in patients who did not have complete recanalization (median NIHSS score, 14 vs. 18, respectively; P = .009) (61).

Relationship Between Time to Treatment and Outcome

The relationship between duration and depth of ischemia to outcome is well known. Jones et al (62), who used a monkey MCA occlusion model, determined that a reduction in cerebral blood flow of less than 18 mL per 100 g/minute led to ischemic signs, and lower levels of blood flow were tolerated for lesser periods of time. Zivin (63) determined that, after 6 hours, 100% of animals had suffered neuropathologic evidence of infarction, determining that 88 minutes represents the median lethal dose for neuropathologic injury. The key question that remains is this: Although some neuropathologic injury has occurred by this time, how much tissue and function is still salvageable? Human
data derived from perfusion-weighted MR imaging give conflicting information depending on how the penumbra between diffusion and perfusion abnormalities (the diffusion-perfusion mismatch) is measured. Whereas some suggest approximately 75% of patients have a mismatch with potential brain salvage (30,64–66), others suggest salvageable tissue is present in as low as one-third of patients (67). Neither of these concepts take into account that some injured brain, with diffusion restriction and perfusion reduction, is salvageable with recanalization (68).

A definite beneficial relationship between earlier time to treatment and good outcome was determined with retrospective analysis of the NINDS trial (69). Although patients treated within 90 minutes had larger neurologic deficits than did those treated between 90 and 180 minutes, those treated within 90 minutes had a higher odds ratio for favorable outcome (2.11; 95% confidence interval = 1.33, 3.35) than did those treated after 90 minutes (1.69; 95% confidence interval = 1.09, 2.62). Examination of the response and/or time-to-treatment curve even suggests that a 20-minute delay in treatment reduces the odds ratio of a favorable outcome by approximately 20% in the first 90 minutes, or about 1% per minute. Kanter et al (70) determined a similar relationship in patients treated with IV tPA in Cincinnati after the NINDS trial. It is axiomatic that earlier time to treatment translates to better outcomes.

In the IMS trial, patients did no better than the treatment group from NINDS with respect to functional outcomes, with only a 4% objective difference. The median time to treat in the NINDS, however, was 90 minutes, and the mean time to treatment was 120 minutes. The mean IV time to treat in the IMS trial was 140 minutes (P < .001). When the data were reanalyzed for outcomes in patients treated less than 120 minutes, compared to those treated more than 120 minutes, there was a 7% objective, 25% relative difference. It is hypothesized that a comparison study between full dose IV alteplase versus combined IV-IA therapy with comparable IV treatment times in the practical IV window (2–3 h), with particular emphasis on patients with higher NIHSS scores, would be positive.

### CONCLUSION

Overwhelming evidence points to the efficacy of IV rtPA in selected patients who present less than 3 hours after stroke, perhaps even to 5 to 6 hours after the onset for certain others. Recovery is most commonly achieved with treatment within 90 minutes after stroke, but functional independence may be achieved with treatment up to 5 to 6 hours. Adjunctive or even other sole intraarterial recanalization therapies may amplify this benefit.

All the above considerations of predictive variables—such as magnitude of neurologic deficit, time from onset, time to treatment, likely recanalization efficacy, and treatment risks—could be ignored in favor of an imaging technique that could help predict which patient has salvageable tissue or injured tissue that can be reversed or in which patient maximal damage has already been done. The management and disease process would be improved by having some method that could reasonably help predict the subsequent chain of events. It is intuitive that diffusion-weighted and perfusion MR imaging techniques and CT perfusion technology are promising in this regard, but no study has rigorously applied imaging techniques to a treatment group in a timely, prospective fashion to determine the ability of the technique to help predict who might still benefit or who should not be treated (30,70–82). In a recent report of IV alteplase administration, better outcomes were achieved in the 3 to 6-hour window by using diffusion-perfusion mismatch data than in the standard 0 to 3-hour time frame (83). We must integrate all the above information when applying clinical judgment as to whom to treat as expeditiously as possible, by whatever route, with or without advanced imaging delay, and each center must adapt its own unique capabilities and limitations to that task (84).

### References

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