I

In 1994, a special writing group of the Stroke Council of the AHA published guidelines for the management of patients with acute ischemic stroke. The guidelines, based on the best available evidence, focused primarily on the prevention and treatment of the complications of acute stroke such as cerebral edema and increased intracranial pressure, aspiration pneumonia, urinary tract infections, deep vein thrombosis and pulmonary embolism, decubiti, and seizures. The authors further concluded that “until more data are available, the use of heparin remains a matter of preference for the treating physician” and “that thrombolytic therapy is not currently recommended for the treatment of patients with acute ischemic stroke.” No supportive recommendations were given for any neuroprotective strategy, nor therapies given to stimulate neurological recovery.

In the 8 years since these guidelines were published, a large number of randomized studies of treatment strategies for acute stroke have been completed. These trials have included thrombolytic agents given intravenously, intra-arterially, or both, antithrombotic and antiplatelet therapies, neuroprotective agents, pharmacological and mechanical therapies to stimulate neurological recovery, and the use of stroke units. In addition, many pilot studies of new therapies for acute stroke have been reported and are entering Phase II and Phase III studies.

The current state of knowledge regarding the treatment of acute ischemic stroke that are based on these randomized studies can be summarized as follows. (1) Intravenous thrombolytic therapy, if administered within the first 3 hours after stroke, improves functional outcome after acute ischemic stroke. Even within the first 3 hours, the likelihood of an excellent outcome increases with earlier treatment. The effectiveness of thrombolytic therapy after 3 hours has yet to be conclusively demonstrated but studies are ongoing. (2) Intravascular intervention with medical therapies and mechanical devices is an active area of investigation. (3) Aspirin and other antiplatelet agents are the primary treatment for prevention of recurrent ischemic stroke in the acute care setting. Except for prevention of deep venous thrombosis, heparin and low-molecular weight heparin compounds have limited proven benefit in acute stroke. (4) Care units or multidisciplinary programs specifically designated for the care of acute stroke patients are associated with improved patient outcomes. (5) Effective neuroprotection for acute ischemic stroke remains a Holy Grail that has yet to be attained. However, several therapies, medical as well as surgical, are currently under study.

This article, as well as the companion article in a subsequent issue of Circulation, reviews the basis for these conclusions and the current recommendations for treatment of acute ischemic stroke. In the present article, we will review the use of thrombolytic agents and other recanalization strategies. In the subsequent article, we will discuss neuroprotective strategies such as hypothermia, the use of stroke units, general management of the acute stroke patient, and antithrombotic therapy.

Unique Challenges of Recanalization in Acute Ischemic Stroke

Successful techniques for treatment of acute myocardial infarction provide an excellent roadmap for physicians seeking better treatment of acute ischemic stroke. Very early recanalization of occluded arteries is the critical step for treatment of both diseases. Yet, although there are substantial parallels, major differences exist between acute myocardial infarction and acute ischemic stroke that make effective treatment of acute ischemic stroke particularly challenging.

Ischemia in myocardial infarction almost always results from acute platelet-rich thrombi that form on an atherosclerotic plaque. In contrast, many ischemic strokes are due to emboli from thrombi formed in a proximal extracranial artery or in the heart. These emboli likely vary substantially in composition and may consist of much older and harder clots that are less likely to respond to thrombolytic agents. Minimal data concerning clot composition in patients with embolic stroke are currently available.

Second, the volume of clot in some patients with ischemic stroke may be substantially greater that that seen in acute myocardial infarction. For example, the extracranial internal carotid artery is one common site of symptomatic arterial occlusion in patients with ischemic stroke and has a substantially larger diameter than the main coronary arteries. Clot
may occlude the internal carotid as well as the middle cerebral artery trunk and beyond. Such extensive clot is unlikely to be lysed by intravenous thrombolytic therapy alone during the first few critical hours after stroke onset in the large majority of cases.

Third, extracranial arteries to the brain can be quite tortuous, particularly in the elderly, and the intracranial carotid arteries traverse through bony canals. These factors can make intraarterial delivery of mechanical devices to remove clot, and even maneuvering of guide catheters, difficult and time-consuming. Finally, the large majority of ischemic strokes occur in patients over the age of 65.3,4 Very elderly patients have higher risks of intracerebral hemorrhage after reperfusion with recanalization therapies.5 However, all age groups, including the elderly, are more likely to have an excellent outcome with intravenous tissue-plasminogen activator (t-PA) begun within 3 hours of onset.6

### Recanalization Strategies: Intravenous Therapy

#### NINDS-Funded Studies of Intravenous t-PA for Acute Stroke

In 1996, the Food and Drug Administration (FDA) approved the use of recombinant tissue-plasminogen activator (t-PA), a thrombolytic agent, for selected patients with ischemic stroke if begun within 3 hours of onset. This approval was based primarily on 2 studies funded by the National Institute of Neurologic Diseases and Stroke (NINDS) that were reported as the NINDS t-PA Stroke Trial.6–12 Patients in these 2 studies had to have t-PA administered within 3 hours of stroke onset and nearly half of patients had t-PA started within 90 minutes of onset.

The dose of t-PA used in these studies was 0.9 mg/kg administered intravenously over 1 hour, with 10% of the total dose given as a bolus. The maximum dose was 90 mg. This dose was determined by an NINDS-funded pilot dose escalation study in which 4 of the 5 symptomatic intracerebral hemorrhages occurred at a dose of 0.95 mg/kg or higher, one at dose of 0.89 mg/kg, and none at lower dose tiers \(P<0.02\).13 It should be noted that no difference in favorable outcome was detected between lower and higher dose tiers in this small nonrandomized pilot study.

In the subsequent randomized NINDS t-PA Stroke Trial, patients treated with t-PA were more likely to have an excellent functional outcome at three months as determined by 1 of 4 neurological or functional rating scales (absolute difference of 11% to 13%). A subsequent report from the NINDS t-PA Stroke Trial showed that the benefit seen for t-PA–treated patients was maintained at 1 year.12 t-PA was also cost-effective overall because patients treated with t-PA were likely to be discharged earlier and to home and were less likely to require nursing home care or extensive rehabilitation.11

The major risk of t-PA is bleeding into the damaged brain. Symptomatic intracerebral hemorrhage within 36 hours after the onset of stroke occurred in 6.4% of patients given t-PA in the NINDS t-PA Stroke Trial and 0.6% of the placebo group \(P<0.001\), but there was no significant difference in overall 90-day mortality between t-PA (17%) and placebo groups (21%, \(P=0.30\)).10 Patients with very severe neurological deficit and with acute hypodensity or mass effect on the baseline CT were more likely to have a symptomatic ICH.10 However, patients with severe neurological deficit or CT findings of hypodensity or mass effect who received t-PA were more likely than placebo-treated patients to have a favorable 3-month outcome and were equally likely to be dead or severely disabled. The authors concluded that despite a higher rate of intracerebral hemorrhage, patients with very severe neurological deficit strokes or hypodensity or mass effect on the baseline CT are reasonable candidates for t-PA if administered within 3 hours of stroke onset.10

A subsequent report from the NINDS t-PA Stroke Trial indicated that the beneficial effect of t-PA is time-dependent, even within the first 3 hours of onset.14 In addition, t-PA appears to be effective for all ischemic stroke subtypes and patient subgroups in those patients who met all of the inclusion and exclusion criteria of the trial.6

#### Other Randomized Trials of Intravenous t-PA

There have been 3 other major randomized trials of intravenous t-PA for acute ischemic stroke. Two randomized trials evaluated the safety and efficacy of t-PA in stroke patients treated within 0 to 6 hours (European Cooperative Acute Stroke Study (ECASS) I and ECASS II).15,16 The Atlantic Trials (Part A, 0 to 6 hours time window; Part B, 0 to 5 hour time window) focused primarily on patients treated within 3 to 5 hours of stroke onset.17 Except for the ECASS Study using a slightly higher dose of 1.1 mg/kg, the studies had similar designs and endpoints as the NINDS t-PA Stroke Trial but differed primarily in the time from stroke onset to start of t-PA (Table 1).

None of these 3 other t-PA studies were positive as defined by a statistically significant difference between t-PA and placebo with regards to the a priori primary clinical endpoint, although the direction of benefit was in favor of t-PA. Several predefined secondary analyses and post hoc analyses, including those using the defined primary endpoint from the NINDS t-PA Stroke Trial, did indicate a positive benefit for patients treated with t-PA in the two European Studies.18–20 The risk of symptomatic ICH in the 3 trials was similar to, but nonsignificantly higher, than that reported for the NINDS t-PA Stroke Trial.

#### Community Use of Intravenous t-PA for Acute Stroke

Since the approval of t-PA for ischemic stroke by the FDA in 1996, community use of t-PA has resulted in a similar percentage of successful outcomes and a similar rate of symptomatic ICH when the NINDS treatment protocol has been followed.21–23 Deviations from the NINDS treatment protocol have been associated with higher rates of symptomatic ICH.21,22,24 Currently only 1% to 2% of all ischemic stroke patients are estimated to be treated with intravenous t-PA within 3 hours of onset.23,25 At selected centers, this may approach 5% or greater.23,26 The major reason for failure to treat is that the majority of patients arrive beyond the 3-hour window.7,25,26
Studies of Intravenous Streptokinase for Acute Stroke

Three randomized trials of intravenous streptokinase for acute ischemic stroke have been reported. Two studies, the MAST-I and the MAST-E, treated patients within 6 hours and the Australian Streptokinase Trial treated patients within 4 hours.27–29 The dose of streptokinase was 1.5 million units, the full cardiac dose. No dose-escalation pilot safety studies preceded the Phase III trials. All studies were stopped prematurely because of excess mortality and intracranial hemorrhage. The Australian Streptokinase Trial did find a trend toward benefit in patients treated within 3 hours of onset.30

Why are both intravenous streptokinase and t-PA effective treatments for acute myocardial infarction whereas only intravenous t-PA has been proven effective for acute ischemic stroke? The answer probably relates more to study design than activity of the medications. First, the major difference in the NINDS t-PA Stroke Trial, as compared with all other randomized trials of intravenous streptokinase and t-PA, is the time from stroke onset to treatment. Nearly half of patients treated in the NINDS t-PA Stroke Trial were treated within 90 minutes and all within 3 hours. Relatively few patients in the other t-PA studies, and particularly the streptokinase trials, were treated within 3 hours of onset. The trend toward benefit in patients treated with streptokinase within 3 hours in the Australian Streptokinase Trial is consistent with the importance of the time to treatment.

Secondly, the full cardiac dose of streptokinase was used in the streptokinase stroke trials. In contrast, the NINDS t-PA Stroke Trial used about 2/3 of the total dose of t-PA used for the streptokinase trials. In contrast, the NINDS t-PA Stroke Trial used about 2/3 of the total dose of t-PA used for the streptokinase trials. Lower-dose protocols for intravenous t-PA have been used in some communities with similar reported rates of effectiveness as in the NINDS-funded Phase I pilot study (Clark Haley, MD, oral communication, 2001). Retepase has also been used in small series of patients with acute stroke but has yet to be evaluated in a controlled trial.30 One pilot study of ReoPro, a GIIb/IIIa receptor antagonist has been completed and a subsequent randomized Phase II Study is ongoing.31 Small series of patients with a combination of GIIb/IIIa receptor antagonists and t-PA or reteplase have been reported in the context of intraarterial therapies.32–34

One of the newest observations is that the response to intravenous t-PA may depend on the genotype of the patient.35 In the NINDS t-PA Stroke Study, persons with an Apo E2 phenotype were much more likely to have an excellent response to t-PA than persons with Apo E4 or Apo E3 genotype, although these patient groups also had a beneficial response. This finding needs confirmation.

In summary, intravenous t-PA is effective if administered to appropriate patients within 3 hours of onset and its effectiveness increases even within the first 3 hours when given as soon as possible. t-PA is reasonably safe if used in a carefully defined manner, including close attention to blood pressure, careful monitoring of the patient, no use of heparin and aspirin during first 24 hours, and appropriate selection of patients.36 It is still unclear whether a lower dose of t-PA administered within 3 hours could be as effective but safer than the current approved intravenous dose of 0.9 mg/kg over 1 hour. Lower-dose protocols for intravenous t-PA have been used in some communities with similar reported rates of effectiveness as in the NINDS t-PA Stroke Study.37

The effectiveness and safety of intravenous t-PA beyond 3 hours has yet to be conclusively demonstrated. One attractive development is the potential use of imaging, such as diffusion/perfusion MRI to determine if salvageable brain remains and if t-PA should be given in patients who are beyond the 3-hour time window.38–41 The drawback to MR imaging is the additional time that is required before the start of recanalization therapy. Advanced MR and CT imaging to select patients for recanalization therapy is an area of intense study.

Streptokinase cannot be recommended as a viable therapy for acute ischemic stroke. Other newer thrombolytic agents,
platelet-receptor blocking agents, and combinations of the two therapies are in the beginning phases of testing.

Recanalization Strategies: Intraarterial Therapy

Intravenous t-PA is an effective treatment for acute ischemic stroke, but its limitations are also clear. For example, intravenous t-PA administered within 8 hours from symptom onset, reopens partially only 30% to 40% of occluded major intracranial trunk arteries within the first 1 to 2 hours after initiation of treatment as determined by cerebral angiography.44–46 The majority of recanalization in these studies was only partial.

In the NINDS t-PA Stroke Trial, patients with a high NIHSS Score (severe stroke) did better overall with intravenous t-PA than with those patients who were treated with placebo.6,7 Although these patients with high NIHSS scores did better with t-PA, the overall prognosis of these patients after therapy in the NINDS t-PA Trial was poor.6,7 For example, only 29% of patients with an NIHSSS ≥10 (moderate to severe neurological deficit) at the start of intravenous t-PA treatment had an NIHSS of 0 or 1 (essentially normal neurological examination) at 3 months as compared with 17% of placebo-treated patients. In addition, patients with a high NIHSSS (ie, a large ischemic stroke) are highly likely to have an occlusion of a major intracranial and/or major extracranial artery.47,48 The likely explanation for poor outcome in patients with a moderate to severe neurological deficit at baseline, despite rapid administration of intravenous t-PA, is that most large arteries are not recanallized by intravenous t-PA in the time window necessary to prevent brain infarction.

Because of the low rates of early recanalization with intravenous t-PA, several groups of investigators have investigated the use of intraarterial thrombolytic agents, including urokinase, t-PA, and prourokinase, almost always with the additional use of intravenous heparin (Figure 1). The only 2 published randomized studies of intraarterial thrombolytic therapy are the PROACT I and II studies,59,60 which compared prourokinase plus intravenous heparin to intraarterial placebo plus intravenous heparin. PROACT I demonstrated a recanalization rate of 58% (partial or complete) after 2 hours of infusion of prourokinase plus heparin in 26 patients compared with 14% after an infusion of a placebo plus heparin in 14 patients.49 The rate of symptomatic intracerebral hemorrhage in the group that was treated with 6 mg of prourokinase plus, a 100 u/kg bolus of heparin followed by 1000 U of heparin/hour for four hours, was 27%. For this reason, the heparin dose was decreased to a 2000 U bolus followed by a 500 U/hour infusion of heparin for 4 hours. The rate of symptomatic ICH in the patients treated with 6 mg of prourokinase and lower dose heparin was 7%. Although the recanalization rate in the prourokinase-treated group was significantly greater than in placebo-treated patients, neurological outcome was not significantly different between the small number of prourokinase and placebo-treated patients.

The PROACT II Study was published in December 1999.50 One hundred eighty patients with M-1 or M-2 occlusions by angiography were randomized within 6 hours of symptom onset to receive 9 mg of prourokinase plus low-dose heparin (n = 121) versus placebo plus low-dose heparin (n = 59). Of patients in the prourokinase group, 40% had a Rankin of 0 to 2 (mild or no significant disability) at 3 months compared with 25% of control patients (P = 0.04). Only 19% of patients who received prourokinase had complete reperfusion of the arterial occlusions after 2 hours of therapy as compared with 2% of placebo patients. But, 66% of patients who received prourokinase did have complete or partial reperfusion.

The symptomatic rate of ICH in the prourokinase group was 10.9% as compared with 3.1% in the heparin-only group.51 Only elevated baseline serum glucose was significantly associated with symptomatic ICH. Patients with a baseline serum glucose of ≥200 mg/dL experienced a 36% risk of symptomatic ICH as compared with 9% in patients with serum glucose of ≤200 mg/dL (P = 0.02). Possible biological explanations for the relationship between elevated glucose and ICH, such as elevated levels of lactic acid due to anaerobic glycolysis, remain speculative.

Although the absolute benefit for patients treated with prourokinase was at least moderate in effect, the FDA requested an additional confirmatory study. The small number of control patients in the PROACT II Study makes it difficult to adjust for differences in baseline variables between the 2 groups that may affect the interpretation of the study results.

Intraarterial administration of thrombolytic agents appears to have higher rates of recanalization than intravenous t-PA, and the rate of intracerebral hemorrhage is similar to that seen in the NINDS t-PA Stroke Trial. However, the intraarterial approach also has limitations. The most important limitation of intraarterial therapy has been the time from onset of symptoms to initiation of therapy and the time to recanalization once therapy has begun. For example, in the PROACT II study, the median time from onset of symptoms to initiation of intraarterial treatment was >5 hours and only 4 patients had prourokinase started within 3 hours (Tony Furlan, MD, P.I. PROACT II Study, oral communication, 2002). In addition, the median time for recanalization after start of thrombolytic therapy in intraarterial studies is about 2 hours. Several published reports of intraarterial thrombolytic therapy indicate that treatment begun within 3 to 4 hours of symptom onset is associated with higher rates of recanalization and better outcome.52,53

Figure 1. Supraselective intraarterial tissue plasminogen activator (t-PA) was started 6 hours after onset of acute aphasia and right hemiplegia and rheumatic heart disease. Angiogram in A demonstrates complete occlusion of the left middle cerebral artery near its origin. B, Complete recanalization after 15 mg of t-PA administered intra-arterially over 90 minutes. Reprinted with permission from Brott T, Broderick J, Kothari R. Thrombolysis in ischemic stroke: A review of recent clinical trials. Curr Opin Neurol. 1994;7:25–35. Copyright 1994 Lippincott Williams & Wilkins.
Other Experimental Intraarterial Strategies

Other intravascular interventional approaches are under study. These have included lower-dose intravenous t-PA begun within 3 hours of onset followed by intraarterial t-PA and mechanical disruption (The EMS Study),47,48 angioplasty with intraarterial thrombolytic agents,30 devices that deliver laser energy, ultrasound devices,54 the Neurojet (a modified version of the Angiojet catheter currently approved for removal of clot in the coronary circulation and in the pulmonary veins),55 and angioplasty.34,56 Administration of small doses of thrombolytic agents or platelet receptor antagonists with these mechanical devices has also been reported in a small number of cases.30,34

Whatever combination of agents or methods is tested, the primary goal remains to shorten the time from onset of symptoms to recanalization of the artery. Recent reports using transcranial doppler and MR angiography have demonstrated that these techniques can be used to monitor the time to recanalization after treatment with intravenous t-PA and have shown that earlier recanalization is associated with a greater likelihood of a good outcome (Figure 2).42,57,58 Stroke physicians will likely follow the steps of cardiologists who have used a multipronged approach to reopen occluded coronary arteries that involves drugs and mechanical devices, and that depends on the availability of technology and expertise at a given hospital.

Current Guidelines for Use of t-PA in Clinical Practice

Currently, the only FDA-approved indication for thrombolytic therapy is intravenous rt-PA given to appropriately selected patients with ischemic stroke within 3 hours of onset. A list of eligibility criteria in patient selection is summarized in Table 2.36,59 One of the remaining questions in the use of t-PA is whether patients with early ischemic changes on the baseline CT are eligible for t-PA during the first 3 hours after onset. Early ischemic changes on the baseline CT were not an exclusion for treatment with t-PA in the NINDS t-PA Stroke Trial. A recent publication from the NINDS t-PA Stroke Study Trial in JAMA December, 2001, reported a detailed reevaluation of all baseline CT scans for early ischemic changes.60 That study showed that early ischemic changes on the baseline CT scan are prevalent within the first 3 hours of stroke onset and correlate with severity. However, these early changes were not independently associated with an increased risk of adverse outcome after t-PA treatment. Patients treated with t-PA did better, whether or not they had these early ischemic changes.

Emergency ancillary care during and after administration of thrombolytic drug is based on careful patient monitoring in the emergency department or in an intensive care setting. The purpose of close monitoring is to prevent complications, observe for signs of neurological deterioration that would be indicative of an intracerebral hemorrhage, and detect any
TABLE 2. Suggested Guidelines for Use of t-PA in Patients With Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Eligibility for IV treatment with t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical diagnosis of ischemic stroke causing a measurable neurological deficit</td>
</tr>
<tr>
<td>Time of symptom onset well established to be less than 180 minutes before treatment would begin</td>
</tr>
</tbody>
</table>

**Patient selection: contraindications**

- Evidence of intracranial hemorrhage on pretreatment CT†
- Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT†
- Active internal bleeding†
- Platelet count less than 100,000 per μL (100 × 10^9 per L)†
- Patient has received heparin within 48 hours and has an elevated aPTT (greater than upper limit of normal for laboratory)†
- Current use of oral anticoagulants (eg, warfarin [Coumadin]) with an elevated INR of 1.5 or greater‡
- Within 3 months: any intracranial surgery, serious head trauma, or previous stroke‡
- On repeated measurements, systolic blood pressure is greater than 185 mm Hg or diastolic blood pressure is greater than 110 mm Hg at the time treatment begins or patient requires aggressive treatment to reduce blood pressure to within these limits‡
- History of intracranial hemorrhage‡
- Known arteriovenous malformation or aneurysm‡
- Patient was observed to have seizure at the same time the onset of stroke symptoms was observed†
- History of gastrointestinal or urinary tract hemorrhage within 21 days†
- Recent arterial puncture at a noncompressible site†
- Recent lumbar puncture†
- Abnormal blood glucose level (<50 or >400 mg/dL [<2.8 or >22.2 mmol/L]†
- Only minor or rapidly improving stroke symptoms†
- Postmyocardial infarction periocarditis†

- t-PA indicates tissue-plasminogen activator; IV, intravenous; CT, computed tomography; aPTT, activated partial thromboplastin time; and INR, international normalized ratio.
- *Contraindication. †Relative contraindications. ‡In patients without recent use of oral anticoagulants or heparin, treatment with t-PA can be initiated before availability of coagulation study results but should be discontinued if the INR is greater than 1.5 seconds or the partial thromboplastin lasting time is elevated by local laboratory standards.

Other episodes of hemorrhage. Thrombolytic treatment should not be used unless facilities or arrangements to manage complications are in place. Detailed guidelines concerning general medical care, blood pressure management, and treatment of hemorrhagic complications in stroke patients treated with thrombolytic therapy are detailed elsewhere.36,59—61

Acknowledgments

The protocol outlined in Table 2 is based on research supported by the National Institute of Neurological Disorders and Stroke (NINDS): N01-NS-02382, N01-NS-02374, N01-NS-02377, N01-NS-02391, N01-NS-02379, N01-NS-02373, N01-NS-02378, N01-NS-02376, and N01-NS-02380. Physicians should also refer to the manufacturer’s prescribing information for alteplase (Activase), Genentech Inc, South San Francisco, Calif, as well as important web sites containing stroke therapy protocols and consensus statements (Stroke-site.org, sponsored by the NINDS Stroke Division; Americanheart.org, sponsored by the American Stroke Association; Stroke.org, sponsored by National Stroke Association; and EUSISTROKE.COM, sponsored by the European Stroke Initiative, the common organ of the European Neurological Society (ENS), the European Federation of Neurological Societies (EFNS), and European Stroke Council (ESC)).

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Key Words: cerebral infarction stroke thrombolysis
Treatment of Acute Ischemic Stroke: Part I: Recanalization Strategies
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Circulation. 2002;106:1563-1569
doi: 10.1161/01.CIR.0000030406.47365.26
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/106/12/1563

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