Interventional Stroke Therapy: The Potential Benefit of Direct Intra-Arterial Infusion

John J. Connors, III, MD

Neuroscience Institute and Stroke Center, St. Joseph's Hospital, Tampa, FL

The goal of acute stroke therapy is preservation of the ischemic penumbra, the geographic area of relatively less ischemia surrounding the profoundly ischemic center. Emergent intravenous revascularization is currently the only U.S. Food and Drug Administration–approved therapy, but intra-arterial revascularization has also been shown to improve outcome significantly. Intravenous therapy has significant limitations: the time window for therapy is short, the large dose of fibrinolytic agent required may increase the risk of hemorrhagic complications, and questions have been raised regarding efficacy in patients with large vessel occlusions. Intra-arterial delivery of the lytic agent can address these issues, and direct intracranial intra-arterial fibrinolysis has been shown to be effective. Thrombolytic agents differ in stability, half-life, and fibrin selectivity, but effective therapies for acute stroke therapy must provide one common denominator: restoration of flow. It now appears certain that direct intra-arterial delivery of fibrinolytic agent improves the efficacy of lysis of bulk thrombus. The Interventional Stroke Therapy Outcomes Registry is acquiring data on all forms of interventional stroke therapy from around the nation as well as outside the United States to identify best practices in the treatment of acute stroke.
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There are over 700,000 new strokes diagnosed in the United States every year. Stroke is the leading consumer of health care dollars and the third leading cause of adult deaths. In the past, stroke treatment focused on supportive care, avoiding complications, rehabilitation, and elimination of treatable causes of recurrent stroke. In recent years, advances in medicine have led to a change in this focus.

The goal of acute stroke therapy is preservation of the acutely ischemic tissue, most typically referred to as the ischemic penumbra (the geographic area of relatively less ischemia surrounding the profoundly ischemic center).[1,2] At present, emergent intravenous revascularization is the only U.S. Food and Drug Administration (FDA)–approved therapy,[3] although intra-arterial revascularization has also been shown to improve outcome significantly.[4] Alternative pharmacological therapies aimed at protection against cellular death from ischemia have been tested in over 50 trials and have been uniformly unsuccessful. Other modalities show promise (hypothermia, hyperbaric therapy, etc).[5,6] Unfortunately, no pharmacologic neuroprotectant has been proven to be successful in humans yet. At present, the only forms of therapy that have shown efficacy for treatment of acute stroke are variations on a theme: flow enhancement.

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The Role of Intravenous Thrombolytic Therapy

Several multicenter randomized trials evaluating systemic (intravenous) administration of thrombolytic agents have been conducted.[3,7–11] Only the National Institute of Neurological Disorders and Stroke (NINDS) Tissue Plasminogen Activator Stroke Trial has demonstrated an acceptably low rate of intracranial hemorrhage and significant efficacy at 3 months.[3] Patients who presented within 3 hours of symptom onset and met the entrance criteria were given a weight-based bolus of recombinant tissue plasminogen activator (rt-PA) or placebo, followed by a 1-hour infusion. There was at least a 30% relative increase in patients with good outcomes in the rt-PA group compared with the placebo group across several indices. Symptomatic intracranial hemorrhage was more common in the rt-PA group (6.4% vs 0.6%; $P < .001$), but the overall mortality was comparable. As a result of the findings of this study, rt-PA received FDA approval for intravenous administration within 3 hours of onset of stroke symptoms.

In confirmation of statistical fallibility, a retrospective analysis confirmed suspicions concerning the reported outcomes of the NINDS trial. Although the results actually reported[3] indicated no differential in efficacy related to "time-to-treatment," the NINDS trial data had a statistically skewed cohort. Further analysis revealed that efficacy fell off sharply with time.[12] If treatment was performed within the first 90 minutes, the chance of favorable outcome was improved 2.8 times compared with controls. If treatment was performed from 91 to 180 minutes after symptom onset, however, the chance of favorable outcome was improved only 1.5 times.

There are significant limitations to intravenous therapy. The time window for therapy is short, and the large dose of fibrinolytic agent required may increase the risk of hemorrhagic complications. In addition, retrospective analysis of data from the NINDS trial has raised questions regarding the efficacy of this treatment in patients with large vessel occlusions.[12–14] Specifically, patients with dense middle cerebral artery (MCA) sign on computed tomography (CT) scan, indicative of thrombus within this vessel, have been shown to have extremely poor response to intravenous lytic therapy (1 out of 18 demonstrating positive outcome). The recently reported Emergency Management of Stroke (EMS) Bridging Trial demonstrated that the majority of patients with high National Institutes of Health Stroke Scale (NIHSS, see below) scores (> 10) have large vessel occlusions.[15] Previous studies have shown that intravenous rt-PA alone does not open major arterial occlusions during the first few hours,[16,17] thus necessitating intra-arterial therapy. These issues are specifically addressed by intra-arterial delivery of the lytic agent.

Intra-Arterial Thrombolysis

The determination of the optimal fibrinolytic agent for stroke use has been problematic. Streptokinase was evaluated in several early trials but its use was associated with an unacceptably high rate of intracranial hemorrhage. The NINDS trial used alteplase and achieved remarkable results, particularly considering the fact that there existed neither an acute stroke awareness nor a system in place even to treat strokes. This was a landmark study, giving initial proof that recanalization can and does give positive results.

Much of the early experience in intra-arterial thrombolysis was gained using urokinase. Urokinase is an enzyme produced by the kidney; its molecular weight ranges from 34,000–54,000 daltons. It exists in plasma in its single-chain proenzyme form (prourokinase). The serum half-life of urokinase is approximately 15 minutes; it has low affinity for fibrin. Although no randomized trial has proved the usefulness of

urokinase for acute stroke therapy, its use has been felt to be associated with an acceptable safety and efficacy profile.[18] Experience in treatment of peripheral arterial occlusion has demonstrated that the major drawbacks to the use of urokinase are its acquisition cost and the need for prolonged infusions.

Direct intracranial intra-arterial fibrinolysis has been shown to be effective.[19–24] The various thrombolytic drugs currently reported include rt-PA, urokinase, single-chain urokinase plasminogen activator, recombinant prourokinase (r-proUK), streptokinase, acylated plasminogen streptokinase activator complex, reteplase, and tenecteplase.[25–32] These thrombolytic agents differ in stability, half-life, and fibrin selectivity. Urokinase and streptokinase are non-fibrin-selective, whereas rt-PA and r-proUK are fibrin-selective and are active only at the site of thrombosis.[33–36] The arginine buffer that is mixed with the rt-PA preparation can potentially block the binding site for fibrin and theoretically decrease the efficacy of intra-arterial (IA) rt-PA as compared to intravenous (IV) rt-PA,[26,34–40] whereas r-proUK is not taken up by platelets, is promoted by a different fibrin fragment from rt-PA, and in coronary patients has a low rate of reocclusion.[35–37,40] However, r-proUK is a single chain form of urokinase and does require heparin for maximal thrombolytic effect.[4,37,41] Newer agents such as reteplase and tenecteplase are even more fibrin-specific.

The Prolyse for Acute Cerebral Thromboembolism (PROACT) I and II studies compared r-proUK plus IV heparin to intra-arterial placebo plus IV heparin.[4,41] The PROACT trials employed recombinant r-pro-UK and again gave proof that recanalization does result in positive outcomes. Indeed, current evidence indicates that therapies that are effective for acute stroke therapy must provide one common denominator: restoration of flow. The results of PROACT, however, were not sufficiently positive to receive FDA approval at that time. The lack of sufficiently powerful positive results was not due to lack of positive effect, however, but due to numbers and thus "power" in analysis. PROACT II demonstrated an improvement from a 25% favorable outcome with placebo treatment to a 40% favorable outcome with r-proUK infusion. This is an absolute improvement of 15% but a relative improvement of 60%. This was done without the benefit of clot manipulation and with therapy starting up to 6 hours after onset of deficit. In addition, the most ideal patients, the ones with the earliest presentation, may have been inadvertently excluded due to the recently approved therapy of intravenous rt-PA.

PROACT II demonstrated an improvement from a 25% favorable outcome with placebo treatment to a 40% favorable outcome with r-proUK infusion.

A third randomized trial was the EMS Bridging Trial.[15] This phase I pilot trial randomized patients to treatment with either reduced-dose IV rt-PA followed by arteriography and intra-arterial infusion of up to 22 mg of rt-PA if an appropriate arterial occlusive lesion was discovered (IV/IA), or placebo followed by intra-arterial lysis (IA). In one third of cases, arteriography did not confirm the presence of clot. Overall, of 15 patients with M1 or M2 occlusions, 66% good outcomes were achieved, with a mean time to intra-arterial treatment of 4.2 hours. The IV/IA group had better recanalization than the IA group, but there was no difference in outcomes between the two treatment groups.

It remains to be proven in a randomized controlled study whether one thrombolytic agent is superior to another in terms of safety and efficacy in interarterial thrombolysis for acute ischemic stroke. Therefore, the results of PROACT I and II may not be applicable when agents other than r-proUK are used for intra-arterial thrombolysis. However, it appears certain that direct intra-arterial delivery of fibrinolytic agent improves the efficacy of lysis of bulk thrombus.

Strategic Considerations Based on Location of Occlusion

Anterior Circulation Occlusions

Mechanism of occlusion. Anterior circulation acute ischemic insult is typically caused by embolus. Cardiac sources are believed to account for a significant portion of large vessel anterior circulation emboli; the remainder comes from the aorta and cervical vessels (commonly the carotid bifurcation). As many as 5%–10% of acute ischemic strokes are caused by intrinsic atherosclerotic stenoses of major intracranial vessels.[42] Large emboli to the MCA are most often cardiogenic in origin.

The significance of pial collaterals and the lenticulostriate arteries. Collateral or retrograde filling of the ischemic MCA region is provided by anastomoses between pial (superficial) branches of the MCA and those of the anterior and posterior cerebral arteries. The efficacy of this collateral flow depends not only on the total volume of supply to the anterior and posterior cerebral arteries but on the number and size of the pial-to-pial anastomotic branches. The

more robust the pial collaterals are, the more time is available for rescue and the better may be the response.

In the typical MCA occlusion, most collateral supply to the ischemic territory is from branches of the anterior cerebral artery, whose main supply is from the ipsilateral internal carotid artery. The anterior cerebral artery also receives a variable supply from the opposite anterior cerebral artery via the anterior communicating artery, but the amount of this supply is typically far less than that supplied by the ipsilateral internal carotid artery. The posterior portion of the MCA territory can be supplied by anastomoses with the posterior cerebral artery, which receives its supply from the vertebrobasilar system.

The status of the tiny lenticulostriate arteries is functionally important. These are true "end arteries" with essentially no collateral supply. The medial group arises from the A1 segment of the anterior cerebral artery; the lateral group typically arises from M1 but can arise as far distal as the MCA bifurcation or M2 branches. The lateral lenticulostriate arteries can arise individually or as one or more common trunks. Occlusion of the main trunk of the MCA therefore may produce direct occlusion of these vessels with resultant profound and rapid ischemia within their territory, limiting the time available for revascularization and decreasing the likelihood of a good functional result.[13] Occlusion distal (or even proximal) to the origin of these vessels may or may not produce similar profound ischemia, depending on the adequacy of collateral supply to their origins.

The lenticulostriate arteries supply the basal ganglia, radiating fibers from the cortex, and the deep white matter of the frontal and parietal lobes, including the internal and external capsules. Specifically, the internal capsule is a small deep cerebral structure that carries the motor and sensory fibers from the cortex. Thus the loss of this structure has profound results independent of the viability of the cerebral cortex.

Posterior Circulation Occlusions

Mechanism of occlusion. The posterior circulation does not have the prominent source of emboli that the anterior circulation has (the carotid bifurcation). Atherosclerotic debris can originate from the vertebral artery origin or proximal brachiocephalic vessels, but the heart is probably the largest source of large emboli. In addition, possibly more often than with the anterior circulation, occlusion may be due to intrinsic thrombus formation and subsequent occlusion associated with an underlying stenosis. Vertebral origin stenoses may be symptomatic more on the basis of hemodynamic insufficiency than because of emboli.

Prognosis of posterior circulation infarcts. The prognoses for posterior circulation occlusions are diverse.[43–45] The extent and mechanism of occlusion appear to be the primary predictive factor, with the presence or absence of subsequent reperfusion determining the outcome. If there is only a small embolus to any limited *intracerebellar* territory, the prognosis is fairly good. Acute symptomatic occlusion of the basilar artery or both vertebral arteries, however, carries a nearly certain death sentence unless the vessel can be reopened.

An underlying stenosis of the basilar artery is not uncommonly the cause of acute basilar occlusion. This frequently necessitates angioplasty after fibrinolysis to achieve success.

In the basilar artery, distal occlusion is better than proximal occlusion, possibly because of multiple factors:

1. If the occlusion is distal, the main trunk of the basilar artery is still perfused.
2. If the occlusion is distal, the posterior inferior cerebellar artery (PICA) and anterior inferior cerebellar artery (AICA) can supply practically the entire cerebellum and brainstem. There is a reciprocal relationship between the AICA and PICA regarding supply to the brainstem. As long as one is open, there is usually enough flow to supply this structure, but if both are eliminated, there is a high likelihood of ischemia of the brainstem. The posterior portions of the PICA collateralize with the superior cerebellar artery around the periphery of the cerebellar hemisphere. This helps to supply the distal basilar artery past an occlusion but usually does not help the midbrain and pons, which may be ischemic from occlusion of the AICA (from a proximal basilar occlusion).
3. A distal occlusion is more likely due to an embolus, implying a potential lack of intrinsic vascular disease in the vertebrobasilar arterial system.

The final factor has direct implications pertaining to therapy as well. Occlusions secondary to underlying plaque in the basilar artery are resistant to simple reperfusion with fibrinolytics and may require angioplasty as well to reestablish perfusion. However, angioplasty in this diseased artery is difficult and carries significant risk. Pontine perforators may also be involved in the vasculopathy, with resultant borderline perfusion of the brainstem and pons.

The length of the occluded seg-

Table 1
Inclusion and Exclusion Criteria for Intracranial Fibrinolytic Therapy: Clinical (Absolute or Relative)

Inclusion Criteria	
1.	No prior neurologic event that would obscure the interpretation of the signal neurologic deficits.
2.	Onset of new neurologic signs of a stroke within 6 hours of the time to initiation of fibrinolytic therapy, but preferably sooner.
3.	Clinical signs consistent with the diagnosis of ischemic stroke, including impairment of language, motor function, cognition, gaze, and/or vision, or neglect. Ischemic stroke is defined as an event characterized by the sudden onset of focal neurologic deficit presumed to be due to cerebral ischemia following exclusion of intracranial hemorrhage by baseline computed tomography (CT) scan.
4.	The signal stroke must be: • acute, and • the most recent significant, acute worsening of serial neurologic events, or • related to a radiographic procedure.
5.	Minimum score of 4 according to the National Institutes of Health Stroke Scale (NIHSS) except for isolated aphasia or isolated hemianopia.
Exclusion Criteria	
1.	Coma.
2.	Neurologic signs that are rapidly improving by the time of randomization.
3.	Major stroke symptoms (> 30 on the NIHSS).
4.	History of stroke within the previous 6 weeks.
5.	Seizure at the onset of stroke.
6.	Clinical presentation suggestive of subarachnoid hemorrhage, even if the initial CT scan is normal.
7.	Previous known intracranial hemorrhage at any time, neoplasm, and/or subarachnoid hemorrhage; patients with a known arteriovenous malformation or aneurysm with any evidence of associated hemorrhage.
8.	Presumed septic emboli.
9.	Presumed pericarditis related to recent acute myocardial infarction.
10.	Suspected lacunar stroke.
11.	Recent (within 30 days) surgery, biopsy of a parenchymal organ, or lumbar puncture.
12.	Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.
13.	Recent (within 90 days) head trauma.
14.	Known active inflammatory bowel disease, ulcerative colitis, or diverticular disease.
15.	Any active or recent (within 30 days) hemorrhage.
16.	Known hereditary or acquired hemorrhagic diathesis, eg, activated partial thromboplastin time or prothrombin time greater than normal; unsupported coagulation factor deficiency.
17.	Baseline laboratory values that reveal platelets < 100,000/μL, hematocrit or packed cell volume < 25 volume %, or international normalized ratio > 1.7.
18.	Pregnancy, lactation, or parturition within the previous 30 days.
19.	Known serious sensitivity to contrast agents (eg, iodothalamate).
20.	Other serious, advanced, or terminal illness.
21.	Any condition in which angiography is contraindicated.
22.	Any other condition that the treating physician feels would pose a significant hazard to the patient if fibrinolytic therapy were initiated (eg, amyloid angiopathy).
23.	Uncontrollable hypertension.

ment of the basilar artery is an independent predictor of outcome, presumably because there is a greater chance of pontine perforators surviving if the amount of basilar artery that is occluded is minimal. As opposed to MCA occlusion, the downstream structures (occipital lobe, distal pons, basilar apex) are not necessarily in immediate jeopardy because of potential collateral supply from the posterior communicating arteries, pial collaterals from the MCA to the posterior cerebral artery, and flow around the occlusion from the PICA to the superior cerebellar artery by cerebellar pial collaterals. The status of the posterior communicating arteries and other collaterals impacts greatly on the eventual clinical outcome. The presence of these arteries is an asset that the anterior circulation (MCA) does not have.

Considerations Regarding Patient Selection and Evaluation

Criteria for Intra-Arterial Fibrinolytic Therapy

Tables 1–4 list inclusion and exclusion criteria for intracranial fibrinolytic therapy. These criteria are based on those established for the PROACT trial but are applicable to intracranial fibrinolysis for de novo acute ischemic stroke in general.

A noncontrast CT scan should be performed on all patients suspected of having suffered an ischemic event.

After it has been determined that a patient meets all of the clinical and CT scan inclusion criteria and none of the exclusion criteria, and after the procedure has been explained to the patient or the patient's legal representative, he or she will be asked to sign a consent form prior to cerebral angiography.

Table 2
Inclusion and Exclusion Criteria for Intracranial Fibrinolytic Therapy: Cerebral CT Scan

Inclusion Criteria
1. Normal study or early findings that do not meet CT scan exclusion criteria.
Exclusion Criteria
1. Early CT scan changes: • High-density lesion consistent with hemorrhage of any degree. • Evidence of significant mass effect with midline shift due to a large infarct. • Acute hypodense parenchymal lesion or effacement of cerebral sulci in more than 1/3 of the MCA territory.
2. Other CT scan findings: • Evidence of an intracranial tumor (except small coincidental meningioma). • Subarachnoid hemorrhage.

CT, computed tomography; MCA, middle cerebral artery.

The National Institues of Health Stroke Scale

NIHSS scale has implications regarding prognosis and is used to guide therapy.[46] A patient with a score of less than 4 is generally not treated endovascularly. Patients with scores from 4 to 10 may have small vessel rather than large vessel disease and may respond well to intravenous therapy only. Scores greater than 20 have been shown in several prior studies to correlate with a poorer outcome despite therapy but can yield the most dramatic recovery when treated by intra-arterial therapy.

Performance of Intra-Arterial Thrombolysis

Angiography

In patients with appropriate clinical and CT criteria, a complete cerebral arteriogram (both carotids and one or both vertebral arteries, and possible arch study) should be performed to evaluate the site of vessel occlusion, extent of thrombus, number of territories involved, and collateral circulation. Cerebral angiography should be repeated at defined time points (eg, every 15 minutes following initiation of thrombolysis unless complete recanalization occurs sooner). The angiogram should be performed using the same catheter position, contrast injection volume and rate, and angiographic views each time to assess adequately the results of therapy.

Technique of Intra-Arterial Thrombolysis

After the diagnostic angiogram, a neuro guide catheter is placed in the parent artery of the target lesion. Following confirmation of the intracranial occlusion site and documentation of the Thrombosis in Cerebral Infarction (TICI) flow, the microcatheter is guided to the site of vessel occlusion. Variations in therapeutic technique include traversing the occlusion and lacing the clot with drug, imbedding the microcatheter in the occlusion, or simple proximal infusion. Institution of therapy may be with or without initial bolus.

Many variations in catheter design and delivery technique have been described. Two types of microcatheters are being used most often for local cerebral thrombolysis, depending upon the extent of clot formation. For the majority of intra-arterial cases, a single end hole microcatheter is used, whereas for longer segments of clot formation, multiple side hole infusion microcatheters may be used. Superselective angiography through the microcatheter may be performed at regular intervals to assess for degree of clot lysis and to adjust the dosage and volume of the thrombolytic agent. An angiogram may be performed at specified time periods during the procedure; if there is partial clot dissolution, the microcatheter may be advanced into the remaining thrombus, where additional thrombolysis is performed.

As the thrombus is dissolved, the microcatheter is advanced into more distal branches of the intracra-

Table 3
Inclusion and Exclusion Criteria for Intracranial Fibrinolytic Therapy: Angiographic

Inclusion Criteria
1. Only patients with complete occlusion or minimal residual perfusion of the apparent symptom-related vessel are candidates for therapy.
Exclusion Criteria
1. Inability to safely catheterize the vessel harboring the occlusion or, in the case of a branch occlusion, the main trunk of the vessel.
2. Any nonatherosclerotic arteriopathy (eg, vasculitis).

Table 4
Exclusion Criteria for Intracranial Fibrinolytic Therapy: Neurologic

Significant spontaneous neurologic recovery prior to administration of fibrinolytic agent (minor fluctuations are acceptable).

nial circulation, so that the majority of the thrombolytic agent enters the occluded vessel and is not washed preferentially into adjacent open blood vessels. The goal is to achieve rapid recanalization with as little thrombolytic agent as possible to limit the extent of brain infarction and to reduce the risk of hemorrhage. The effect of recanalization on angiographic perfusion should be reported using the TICI grading system. Subjects can be categorized as complete responders (TICI 3), partial responders (TICI < 3 but > 1 category improvement from baseline), and nonresponders (no improvement in TICI category).

When utilizing urokinase, an initial bolus is probably not necessary and an infusion of 250,000–1,000,000 U/hr is appropriate. More than this would probably not result in improvement in efficacy. Standard preparations are 500,000– 2,000,000 U in 100 cc normal saline infused at 50 cc/hour. It has been determined that low-dose heparin improves results but high-dose heparin is counterproductive in that this may increase hemorrhagic transformation. Therefore an initial bolus of 2000 U followed by an infusion of 500 U/hr only during the lytic infusion is recommended.

The Interventional Stroke Therapy Outcomes Registry

At present there is inadequate knowledge concerning the appropriate drug, dose, interventional method, patient population, or timing for emergency interventional stroke therapy, even though there is increasing acknowledgment of the profound patient benefits achievable with this method of therapy. This information is necessary to advance the science of acute stroke intervention as well as to influence health care policy. This creates a need to identify best practices in the treatment of acute stroke by collecting outcomes data from those physicians currently treating acute stroke utilizing interventional techniques. A patient registry capturing and documenting treatment modalities and outcomes has been established to collect this invaluable information regarding the treatment of acute stroke.

The Interventional Stroke Therapy Outcomes Registry (INSTOR) is acquiring data concerning all forms of interventional stroke therapy for the purpose of optimizing therapeutic outcomes for stroke victims. It is an open registry available for any interested participant to enroll in. INSTOR is a voluntary data collec-

Main Points

- The only forms of therapy that have shown efficacy for treatment of acute stroke involve flow enhancement.
- Intravenous thrombolysis has limitations and may not be efficacious in patients with large vessel occlusions.
- Direct intracranial intra-arterial fibrinolysis has been shown to be effective.
- Thrombolytic drugs currently reported include recombinant tissue plasminogen activator, urokinase, single-chain urokinase plasminogen activator, recombinant prourokinase, streptokinase, acylated plasminogen streptokinase activator complex, reteplase, and tenecteplase.
- Thrombolytic agents differ in stability, half-life, and fibrin selectivity; urokinase and streptokinase are non–fibrin-selective, whereas tissue plasminogen activator and recombinant prourokinase are fibrin-selective and are active only at the site of thrombosis.
- Heparin is required with recombinant pro-urokinase for maximal thrombolytic effect.
- Much of the early experience in intra-arterial thrombolysis was gained using urokinase.
- It remains to be proven in a randomized controlled study whether one thrombolytic agent is superior to another in terms of safety and efficacy in interarterial thrombolysis for acute ischemic stroke, but it appears certain that direct intra-arterial delivery of fibrinolytic agent improves the efficacy of lysis of bulk thrombus.
- Occlusions secondary to underlying plaque in the basilar artery are resistant to simple reperfusion with fibrinolytics and may require angioplasty as well to reestablish perfusion.

tion registry. Sites from around the nation as well as outside the United States are welcome and encouraged to submit their results to INSTOR. The Internet is being used for data acquisition using a medically secured storage facility through encrypted and password-protected access. The web site address is www.strokeregistry.org. The database is accumulating information on outcomes and complications as well as unforeseen results. In addition, combination pharmaceutical and/or mechanical/pharmaceutical therapies may ultimately result in the optimal method to treat acute stroke. Methods of stroke therapy include pharmaceutical agents, mechanical devices, and techniques. It is hoped that INSTOR will be the definitive evaluation for interventional stroke therapy, comprising all means to reverse optimally the acute insult. ■

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