

Atherosclerotic Peripheral Vascular Disease Symposium II Stroke Intervention: State of the Art

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Stroke is the third leading cause of death and a leading cause of adult disability in the United States.¹ From a global perspective, stroke is also a leading cause of death and disability. The past 20 years have seen significant improvements in stroke prevention, yet each year, >700 000 people have a new or recurrent stroke.^{2,3} The medical and societal costs of stroke exceed \$62 billion in the United States alone.⁴ Any intervention that could reverse or limit the effects of a stroke would have dramatic medical, societal, and public health benefits.

This section will focus on treatment of acute ischemic stroke, which accounts for 80% to 85% of all strokes. Other recent publications have focused on therapies for intracerebral hemorrhage. Acute interventions to reduce the effects of an ischemic stroke can be organized into several main approaches: (1) reperfusion strategies (lytics, endovascular/mechanical); (2) neuroprotection; and (3) restoration, regeneration, and rehabilitation.

Reperfusion Strategies

Medical Therapies

Thrombolytic therapies for acute ischemic stroke have been used or under study for 30 to 40 years, yet only recently has an agent been approved by the US Food and Drug Administration (FDA) and included in the treatment guidelines. Intravenous recombinant tissue plasminogen activator (rtPA) is the only FDA-approved medical therapy proven to reduce the effects of an ischemic stroke.^{5,6} Its main mechanism of action is to lyse a clot that is occluding a cerebral vessel, thereby reperfusing distal ischemic brain tissue and preventing or limiting the area of cell death and tissue necrosis. The efficacy of intravenous rtPA was proven in the pivotal National Institute of Neurological Disorders and Stroke

(NINDS) rtPA study, which showed improved outcomes for patients treated within 3 hours of stroke onset.⁷ The NINDS tissue plasminogen activator (tPA) trial had an efficacy end point that was equivalent to the patient being normal or near normal 3 months after stroke onset. There was a 12% absolute increase in the number of patients with minimal or no disability in the group of patients treated with rtPA compared with the placebo group. Moreover, rtPA appeared to have efficacy for all types of ischemic strokes and across the range of stroke severities as measured by the National Institutes of Health stroke scale.⁸ The efficacy of intravenous rtPA compared with placebo within 3 hours was even greater for any improvement in neurological status across the full range of the modified Rankin scale.^{9,10} The benefits of tPA were persistent, as measured by 1-year outcomes.¹¹

Intracerebral hemorrhage is the principal risk of intravenous rtPA in stroke patients. These hemorrhages typically occur within the first 24 hours of tPA administration, and approximately half of these bleeds are fatal. The risk of a symptomatic intracerebral hemorrhage is ≈6% when intravenous rtPA is administered within 3 hours of stroke onset.¹² The risk of hemorrhage was increased in studies in which the rtPA administration protocol had been violated.¹³ Other risk factors for intracerebral hemorrhage include advanced age, large strokes, and significant early ischemic changes on the pretreatment head computed tomography scan. Systemic bleeding events from intravenous rtPA appear to be relatively uncommon. There is a small risk of angioedema after tPA treatment; this risk may be associated with the use of angiotensin-converting enzyme inhibitors.¹⁴

Although various aspects of the NINDS tPA study have been criticized, the overall efficacy and safety of this treatment have been confirmed in numerous large national regis-

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tries in the United States and Europe.^{15–20} The overall rate of neurological improvement in these studies is equal to or greater than that seen in the NINDS study. Furthermore, the rates of symptomatic intracerebral hemorrhage are 5% to 6%, which is similar to the NINDS study. Reanalyses of the NINDS tPA trial results have shown consistent efficacy even after correction for any baseline imbalances.^{9,21} An independent review of the NINDS tPA study methods, data, and results further confirmed the overall efficacy of this therapy.²²

Despite the efficacy of intravenous rTPA as an acute stroke therapy and the lack of widely available alternative therapies, it remains grossly underutilized. Large studies and registries in the United States and elsewhere have found that only 2% to 4% of patients with ischemic stroke are treated with intravenous rTPA.^{6,15} Although some cities and regions have reported higher rates (10% to 20%), the national rate of use remains <5% in most studies. One issue is the narrow 3-hour time frame. Many stroke patients do not present within 3 hours for a variety of reasons. In fact, the time window for presentation for use of rTPA is actually only 2 hours, because it typically takes an additional hour to do an examination, blood work, and a head computed tomography scan before tPA is administered. Some trials have studied intravenous rTPA in the 3- to 6-hour time frame. Such studies (Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischaemic Stroke [ATLANTIS] and European Cooperative Acute Stroke Study [ECASS] I and II) have failed to show efficacy beyond \approx 4.5 hours but have shown an increased risk of death and bleeding complications.¹⁶ The recently published ECASS III trial showed evidence of efficacy for intravenous tPA when used in patients 3 to 4.5 hours after stroke onset, with absolute improvement at 3 months of 7% as defined by a Rankin score of 0–1. The rate of symptomatic intracerebral hemorrhage was reported to be 2.4% using the ECASS III definition; this increased to 7.9% using the original NINDS definition.

Transcranial ultrasound may be able to enhance clot lysis when used as an adjunct to intravenous rTPA therapy. Studies have shown increased reperfusion and improved outcomes when ultrasound is used with intravenous rTPA.^{23,24} Also, the introduction of bubbles into the circulation may enhance the ability of transcranial ultrasound energy to lyse clots.²⁵ These areas of therapeutics are undergoing further study.

New technologies such as telemedicine and air ambulances have the potential to extend and expand the use of acute therapies, such as intravenous rTPA, to a wider rural population that may be somewhat remote from large acute-care hospitals.^{26–28} In addition, hospital systems of care have the potential to develop networks that can provide the resources to extend acute care to many facilities that lack some of the elements of a stroke center.^{28–32}

The development and certification of “stroke centers” may enhance the safe use of rTPA and improve outcomes through a variety of processes: (1) standardized treatment protocols and infrastructure, (2) stroke teams and stroke units, (3) concentration of experience in stroke care, (4) tracking of disease performance measures, and (5) improvements in outcomes through quality-improvement processes.^{33,34} The various components of a stroke center may also improve outcomes and reduce complications beyond the use of tPA.

For example, a stroke unit within a stroke center is one component that has been shown to reduce the risk of death and improve functional outcomes.³⁵ A neuroscience intensive care unit and care by a neurointensivist within a comprehensive stroke center is another element that can reduce length of stay and improve outcomes for critically ill patients with strokes.³⁴ The Joint Commission on Accreditation of Healthcare Organizations has certified \approx 500 hospitals as primary stroke centers (see www.jointcommission.org). Various state-based health organizations have also certified \approx 300 hospitals as primary stroke centers. The increased use of intravenous rTPA has been shown to correlate with the establishment of a primary stroke center.^{36–38}

Stroke centers are an important component of a stroke systems approach to acute care. Such a system could be organized on a regional basis, with stroke centers and their personnel serving as a resource for other facilities.^{31,32} Emergency medical services systems and related services such as telemedicine and air ambulances are other elements of such an acute-care system.²⁹ The overlay of preexisting hospital networks organized by various health corporations could be one option to form the basic organizational pattern for an urban, regional, or rural stroke system. Although the vast majority of acute stroke patients do not receive tPA or other acute reperfusion therapies, many would still benefit from the components of a stroke center, including stroke units, care protocols, treatments to prevent acute complications, early initiation of secondary prevention measures, and initiation of rehabilitation assessment and therapies.^{33,34,39}

The failure to use intravenous rTPA in appropriate stroke patients may have legal implications. A number of legal cases focus on the failure to administer rTPA in patients who appear to fit the typical treatment protocol; in other cases, the treating physicians did not follow the guidelines for use of intravenous tPA in acute ischemic stroke.^{40,41} The newly published treatment guidelines for acute ischemic stroke emphasize the importance of using intravenous tPA and adhering to the treatment protocols.³⁹

Endovascular/Mechanical Intervention

Endovascular intervention to reduce the consequence of stroke has been another area of investigation. Major strategies include catheter-based intra-arterial delivery of thrombolytic drugs and antithrombotic medications, mechanical clot removal, and stenting of intracranial arteries. Recombinant prourokinase was a promising agent studied in the PROlyse in Acute Cerebral Thromboembolism (PROACT) trials.⁴² These studies found improved recanalization (66% versus 18%) and clinical outcomes (40% versus 15%) with intra-arterial recombinant prourokinase versus placebo in patients treated within 6 hours of stroke onset. The rate of symptomatic intracerebral hemorrhage with prourokinase treatment was 10%. Another confirmatory study was not performed; therefore, prourokinase is not available for use and is not FDA approved.

Intra-arterial rTPA and urokinase have been used for many years in selected stroke patients.⁴³ Some studies have assessed the efficacy of intravenous rTPA administered before intra-arterial rTPA therapy.^{44,45} Many of these studies have been relatively small or unblinded. Although these trials

showed a trend for improved recanalization rates, there appeared to be more intracranial bleeding, and the actual overall clinical benefit remains unclear.^{44–46} Intra-arterial rtPA and urokinase are not approved by the FDA for the treatment of acute ischemic stroke, but many vascular neurology and endovascular experts have adopted protocols for using such treatments in specific cases.^{47–49}

Mechanical clot removal is another endovascular intervention that is commonly considered for treatment of acute stroke and is undergoing investigation. The Mechanical Embolus Removal in Cerebral Ischemia (MERCi) clot removal system is approved by the FDA for the removal of intracranial clots causing strokes.⁵⁰ Other devices, such as snares, are also used in these settings.^{51–53} Success rates for recanalization with MERCi are typically in the 50% range.⁵⁴ Although recanalization is associated with improved outcomes, this is not always the case. Use of the MERCi clot retrieval system was associated with a 6% to 8% rate of symptomatic intracerebral hemorrhage.^{50,54} Despite its FDA approval, treatment with the MERCi clot removal system is not recommended strongly in new American Heart Association guidelines because it has not been compared rigorously with best medical therapy in a similar group of patients.³⁹ The stenting of intracranial atherosclerotic lesions is another technique that has been used for acute stroke management.^{55,56} The WINGSPAN Stent System (Boston Scientific Corporation, Natick, Mass), is approved by the FDA for this purpose, but its use is more for secondary stroke prevention, not acute reperfusion.^{57,58}

The proper selection of patients who should undergo lytic or endovascular therapy is an evolving area. Many centers use imaging technologies (eg, magnetic resonance perfusion, computed tomographic perfusion) to select patients with salvageable brain tissue. Some use magnetic resonance perfusion–diffusion mismatch as a way to identify patients with a presumed “ischemic penumbra,” who may be particularly amenable to reperfusion and improved outcome.^{59–61} For example, the Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study identified patterns of magnetic resonance imaging diffusion and perfusion that were associated with poor outcomes and a high risk of intracerebral hemorrhage after reperfusion therapy^{62,63}; however, many of these approaches are unproven by large, randomized studies.

Recent studies that combined intravenous thrombolysis with the presence of the ischemic penumbra were the Desmoteplase in Acute Ischemic Stroke (DIAS) 1 and 2 trials. A magnetic resonance imaging perfusion–diffusion mismatch (ie, the presence of a presumed penumbra) was used to select patients to receive desmoteplase, a lytic agent, up to 9 hours after stroke onset.⁶⁴ This treatment appeared to be efficacious in the DIAS-1 study⁶⁵; however, the recently completed, modestly sized, phase III, randomized and blinded DIAS-2 trial found no evidence of efficacy for desmoteplase therapy and found higher rates of intracerebral hemorrhage with treatment than with placebo (4.5% versus 0%).⁶⁶ It is unclear whether these results were due to failure of desmoteplase to recanalize the occluded vessel(s), poor patient selection by use of a penumbral approach, a time window that was too long, or some combination of these and perhaps other factors. Nevertheless, these negative results do call into question the utility of the presence of a penumbra as a means to select

patients for recanalization therapy. Other groups continue to work on validating this paradigm for the selection of patients for acute therapy.

Neuroprotection

Advances in understanding the complex and multiple mechanisms of cerebral ischemic cell death via necrosis or apoptosis have led to neuroprotection strategies as an approach to reduce ischemic brain injury and improve outcomes.^{67–70} More than 1000 neuroprotective drugs or approaches have been studied in animal models of stroke, human trials, or both (Table).⁷¹ Many of these agents target 1 or more mediators of neuronal damage, including excitatory neurotransmitters and their receptors, free radicals, secondary mediators of neuronal damage, temperature, hyperoxygenation, inflammation, and other potential targets.^{72–75} Some recent and ongoing studies are focusing on the use of hyperoxygenation,⁷⁶ albumin,⁷⁷ and statins^{78–81} as potential new approaches to neuroprotection (see Restorative, Regenerative, and Rehabilitative Strategies). Recent data from patients with fatal ischemic strokes suggest that apoptosis is a dominant mechanism of neuronal cell death in the peri-infarct region (penumbra) and in areas of less severe ischemic damage.^{70,75,82,83} Hence, strategies that target antiapoptosis may be promising, although no agent has been shown to be effective in large clinical trials to date (Table).

Until recently, all randomized clinical trials of these neuroprotective agents were negative for the primary pre-specified end point, even though many of these agents appeared to be very effective in animal models of stroke. One exception was the Stroke Acute Ischemic NXY-059 Trial (SAINT) I, which appeared to show a modest effect on 3-month outcomes for the free radical scavenger NXY-059.⁸⁴ A larger follow-up phase 3 study was negative, and this agent is no longer being investigated.⁸⁵ Another recent exception was a report of a small, randomized trial of minocycline as a neuroprotective agent for acute ischemic stroke.⁸⁶ It showed impressive efficacy in terms of functional improvement at 3 and 12 months after stroke, but baseline imbalances may have exaggerated the treatment response. Replication with a large, double-blinded study design is needed. The ongoing Field Administration of Stroke Therapy—Magnesium (FAST-MAG) trial is using intravenous magnesium treatment begun in the ambulance once a potential stroke patient is identified.^{87,88} This approach will certainly minimize any time delays in therapy. The use of albumin as a neuroprotective agent is another treatment paradigm that appears promising on the basis of preliminary trials.^{77,89}

Many reasons have been postulated for the failure of prior trials to show efficacy of neuroprotection, including the treatment time window, eligibility criteria, patient selection, exclusion criteria, dosing of the drug, choice of outcome measures and the primary end point, and sample-size considerations (studies underpowered to detect modest benefits).^{68,90–92} In some cases, the overall approach, such as targeting free radicals, may not be potent enough to affect the overall damage caused by the initial ischemic damage. Delivery of the drug to the damaged brain region may also be problematic because of reduced blood flow caused by the ischemic stroke.

Table. Partial Listing of Some Neuroprotective and Restorative Agents for Stroke

Type of Agent	Mechanism of Action*	Clinical Status†
NMDA (<i>N</i> -methyl <i>D</i> -aspartate) receptor blockade	IENI	Failed clinical trials
AMPA (β -amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor blockade	IENI	Failed clinical trials
Glutamate antagonists	IENI	Failed clinical trials
Dopamine receptor modulators	IENI	Pending clinical trials
Sodium/potassium channel modulation	IENI	Failed clinical trials
Adenosine modulators	IENI	Pending clinical trials
Alcohol/caffeine	IENI/restoration	In clinical trials
Angiotensin receptor blockade	Unknown	In clinical trials
Colony-stimulating factors	Restoration	Pending clinical trials
Serotonin receptor modulators	IENI	Failed clinical trials
Calcium-channel blockage	IENI	Failed clinical trials
Magnesium	IENI	In clinical trials
Nitric oxide/nitric oxide synthase inhibition	IENI, vascular effects	Pending clinical trials
Free radical scavengers	Block secondary damage	Failed clinical trials
Antioxidants	Block secondary damage	Failed clinical trials
Hypothermia	Multiple	In clinical trials
Hemodilution	Improved cerebral flow	Failed clinical trials
Albumin	Bind mediators	In clinical trials
Statins	Multiple	In clinical trials
Antiinflammatory agents	Multiple	Failed clinical trials
PARP (poly-ADP-ribose polymerase) inhibitors	Apoptosis	Pending clinical trials
Calpain/caspase inhibition	Apoptosis	Pending clinical trials
Lithium	Apoptosis	Pending clinical trials
Vascular endothelial growth factor	Restoration	Failed clinical trials

IENI indicates inhibition of excitatory neuronal injury.

*In some cases, a compound or class of compounds may have >1 mechanism of action.

†In many cases, a class of medication includes >1 agent; therefore, the clinical status may not summarize all results for all compounds in testing.

Restorative, Regenerative, and Rehabilitative Strategies

Restorative, regenerative, and rehabilitative strategies to reduce the degree of injury/disability include the use of growth factors (neuronal and glial) and agents that may enhance plasticity, including enhancement of synaptogenesis, angiogenesis, stem cell transplantation, amphetamines, transcranial magnetic stimulation, and constraint-induced movement therapy.^{93–95} Pilot studies and randomized clinical trials are exploring these promising avenues.⁹⁶ For example, a recent large, randomized trial showed that constraint-induced movement therapy can improve motor function of the affected extremity during daily activities in patients with chronic stroke.^{97,98}

Clinical trials are under way to address the treatment of systemic factors to further protect the brain and limit the final volume of infarct, as well as the degrees of neurological deficit and disability. For example, the efficacy of acute reductions in serum glucose with intravenous insulin to diminish brain injury has been studied, because elevated blood glucose is associated with poorer outcome, increased cerebral edema, and death.⁹⁹ A large clinical trial found that such a therapy reduced serum glucose levels, but there was no overall clinical benefit.¹⁰⁰ This study was limited by the fact that most of the serum glucose levels were not elevated significantly (mean levels of ≈ 150 mg/dL); therefore, the reductions of glucose in the treatment group were quite modest, in the range of 10 to 15 mg/dL. Such a change may not have been sufficient to result in overt clinical benefit.

Treatment of blood pressure in patients with stroke is controversial. It is important to determine whether raising or lowering blood pressure during acute stroke is beneficial. New guidelines recommend that antihypertensive therapy begin after the first 24 hours after a stroke if the patient is clinically stable and if the blood pressure is elevated above normal.³⁹ The degree of lowering is determined in part by how much the blood pressure is elevated. Few data from large, high-quality randomized trials are available to support such recommendations, however.

Other investigative therapies to reduce the consequences of stroke include the prevention of fever and hyperthermia with antipyretics, hypothermia, and statin therapy. Various studies have demonstrated the adverse consequences of elevated temperature in patients with a stroke, yet few have been able to show that treatment with agents such as acetaminophen can reduce neurological deficits.^{101,102} Hypothermia to temperatures in the range of 31°C to 32°C does appear to be an effective neuroprotective approach, particularly immediately after a cardiac arrest.^{103,104} Hypothermia in the setting of focal ischemic strokes is feasible, but the efficacy is less dramatic than with cardiac arrest, and complications related to paralysis and intubation are problematic.^{105–108} In addition, some cooled patients may show deterioration when they are rewarmed.^{107,109} This remains an area of active study.¹¹⁰

Summary

Treatment interventions for acute ischemic stroke are quite limited. Current therapies such as intravenous rtPA and endovascular interventions are beneficial for small groups of

stroke patients. Patient selection for these therapies often requires additional testing, and the techniques require specialized training and equipment. These factors limit the applicability and usefulness of acute stroke intervention in the general population. Although neuroprotective agents hold much promise, their efficacy in humans remains largely unproven. We need therapies that are safe and effective for larger populations of stroke patients. These therapies must have a broader time window, be easy to administer, and have an acceptable safety profile. The use of stroke centers is one approach to focus expertise, infrastructure, and patients in a single area to improve care and enhance the testing of new therapies. The treatment of systemic factors and complications may reduce overall morbidity, yet even these interventions remain unproven or controversial in some cases.

Disclosures

Potential conflicts of interest for members of the writing groups for all sections of these conference proceedings are provided in a disclosure table included with the Executive Summary, which is available online at <http://circ.ahajournals.org/cgi/reprint/118/25/2811>.

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