Acute Ischemic Stroke Management:
Medical Management

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ABSTRACT

The initial management of a patient with suspected stroke necessitates a rapid and focused evaluation. Establishing the time of symptom onset, performing a focused neurologic examination, and interpreting ancillary tests facilitates delivery of acute stroke therapies to eligible patients. This review emphasizes the fundamentals of urgent stroke evaluation and evidence-based acute ischemic stroke therapies. Results from randomized clinical trials of intravenous thrombolysis, glucose management, and blood pressure management in acute ischemic stroke patients will be highlighted. External ultrasound as an adjunct to intravenous thrombolysis and treatment of those patients that wake up with stroke symptoms will also be discussed.

KEYWORDS: Acute ischemic stroke, ischemic stroke management, tissue plasminogen activator

Acute ischemic stroke is a medical emergency. Patients with suspected stroke require urgent evaluation to identify those who may be eligible for time-sensitive therapies. Safe and effective treatment of acute ischemic stroke requires determination of the time of symptom onset, performance of a focused neurologic examination, and rapid interpretation of ancillary tests. This review will emphasize the fundamentals of urgent acute stroke evaluation and evidence-based ischemic stroke therapies. Results from randomized clinical trials of systemic thrombolysis, glucose management, and blood pressure management related to acute ischemic stroke will be reviewed. External ultrasound as an adjunct to intravenous (IV) thrombolysis and treatment of those patients that wake up with stroke symptoms will also be discussed.

BEDSIDE ASSESSMENT AND ANCILLARY TESTING

History and Examination

The history should focus on establishing the time of onset of symptoms and identifying potential exclusionary conditions for IV thrombolysis (Table 1). When available, an eyewitness can confirm the patient’s reported time of symptom onset or provide the time of onset when the patient cannot. In some circumstances, a precise time of symptom onset will prove impossible to determine and the line of questioning should then shift to identifying when the patient was last neurologically normal. For patients who awaken with symptoms, the time of onset becomes the time at which they went to sleep, assuming they were normal at that time. For patients with

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Intravenous Recombinant Tissue-Type Plasminogen Activator

<table>
<thead>
<tr>
<th>Exclusion Criteria for Intravenous Recombinant Tissue-Type Plasminogen Activator</th>
<th>&lt;3 Hours after Symptom Onset</th>
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<tbody>
<tr>
<td>CT or MRI evidence of intracranial hemorrhage</td>
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<tr>
<td>Rapidly resolving or minor and isolated deficit</td>
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<tr>
<td>Caution in severely affected, obtunded or comatose patients</td>
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<tr>
<td>Seizure with postictal deficits</td>
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<tr>
<td>Symptoms suggestive of subarachnoid hemorrhage</td>
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<tr>
<td>History of previous intracranial hemorrhage</td>
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<tr>
<td>Head trauma or prior stroke in previous 3 months</td>
<td></td>
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<tr>
<td>Myocardial infarction in previous 3 months</td>
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<tr>
<td>Gastrointestinal or urinary tract hemorrhage in previous 21 days</td>
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<tr>
<td>Major surgery in previous 14 days</td>
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<tr>
<td>Arterial puncture at a noncompressible site in previous 7 days</td>
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<tr>
<td>Blood pressure persistently elevated &gt;185 mm Hg systolic and &gt;105 mm Hg diastolic</td>
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<tr>
<td>Active bleeding or acute trauma (fracture) on examination</td>
<td></td>
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<tr>
<td>International normalized ratio &gt;1.7</td>
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<tr>
<td>aPTT within normal range if heparin received in previous 48 hours</td>
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<tr>
<td>Platelet count ≤100,000 mm3</td>
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<tr>
<td>Blood glucose ≤50 mg/dL</td>
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<tr>
<td>CT evidence of multilobar infarction (hypodensity 1/3 cerebral hemisphere)</td>
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CT or MRI, computed tomography; MRI, magnetic resonance imaging.

*Table adapted from Adams et al, 200710

Ancillary Testing

Laboratory and cardiac evaluation supplement the clinical impression derived from the bedside assessment. Some conditions that may present with stroke-like symptoms may be identified based on laboratory results (e.g., hypoglycemia). In addition, abnormal laboratory values may exclude patients from receiving thrombolytic therapy. Routine laboratory testing of blood glucose, electrolytes,
complete blood count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function is recommended. Testing for stool occult blood is not routinely recommended unless an indication exists (e.g., melena or hematochezia).

Cardiac abnormalities are common in patients with stroke, myocardial infarction, and atrial fibrillation and are common causes of cardioembolism. In addition, stroke symptoms, such as aphasia, may modify the clinical presentation of acute coronary syndrome. Serum troponin and a 12-lead electrocardiogram are recommended for all stroke patients. The utility of routine chest radiography as part of the acute stroke evaluation is limited and is currently not routinely recommended.

Other tests can be performed depending on the clinical setting but are not routinely warranted in every acute stroke patient. There is no role for routine cerebrospinal fluid (CSF) examination, unless warranted by the presence of sudden, severe headache concerning for subarachnoid hemorrhage. Urine toxicology screen, blood alcohol level, arterial blood gas, or testing for β – HCG may be indicated depending on the clinical setting, such as stroke with altered sensorium or stroke in a woman of childbearing age.

**Neuroimaging**

Brain imaging is mandatory prior to administration of thrombolytic therapy as it is the only reliable means to differentiate between ischemic and hemorrhagic stroke. Noncontrast head computed tomography (CT) is the imaging modality most readily available in most stroke centers. CT is sensitive to intracranial hemorrhage and may be rapidly performed as part of the acute stroke evaluation. CT is also inexpensive and less susceptible than magnetic resonance imaging (MRI) to artifact introduced by patient movement. In the acute setting, early ischemic changes may be apparent on CT. Examples of early ischemic changes include loss of differentiation of the gray–white matter interface, particularly in the region of the insular cortex or the lentiform nucleus. Sulcal effacement, representing focal tissue edema, may be appreciated in areas of relative hypoperfusion and may be another early indicator of ischemia. Whether these changes are present in the minutes to hours after symptom onset is probably related to the severity and extent of ischemia, collateral circulation, and presence of large vessel occlusion. Detection of early ischemic changes is variable and is likely related to reader experience. One study identified early ischemic changes in 75% of patients presenting within 3 hours of symptom onset and an even higher prevalence was observed within 6 hours in patients with hemispheric strokes. The presence of early ischemic changes involving greater than one-third of the middle cerebral artery (MCA) territory was used as an exclusion criterion in some early clinical trials of thrombolitics in an effort to minimize the risk of hemorrhagic complications. The presence of early ischemic changes, however, was not independently associated with adverse outcome after rtPA treatment in the National Institute of Neurological Disorders and Stroke (NINDS) Trial, and therefore should not be used as the singular reason to preclude thrombolytic therapy in otherwise eligible patients.

The appearance of ischemic changes on CT evolves with the duration of focal ischemia. Within 12 to 24 hours, an indistinct area of low density becomes apparent in the affected vascular distribution. After 24 hours, the ischemic region becomes increasingly hypodense and better circumscribed. Mass effect develops and results in sulcal asymmetry or ventricular distortion. The presence of a clearly delineated area of hypodensity with associated mass effect should therefore prompt reassessment of the time of symptom onset in patients thought to be eligible for thrombolytic therapy, as distinct hypodensity is inconsistent with focal cerebral ischemia of less than 3 hours. Other processes that can result in a distinct hypodensity include primary or metastatic ischemic stroke. Other processes that can result in a distinct hypodensity include primary or metastatic ischemic stroke. Other processes that can result in a distinct hypodensity include primary or metastatic ischemic stroke. Other processes that can result in a distinct hypodensity include primary or metastatic ischemic stroke. Other processes that can result in a distinct hypodensity include primary or metastatic ischemic stroke.

**SYSTEMIC THROMBOLYSIS FOR ACUTE ISCHEMIC STROKE**

**The First 3 Hours**

Intravenous recombinant tissue-type plasminogen activator (IV-rtPA) is the only Food and Drug Administration (FDA)–approved treatment for acute ischemic stroke. Approval was based on the results of the NINDS rtPA stroke study, which randomized 624 patients with acute ischemic stroke within 3 hours of symptom onset to treatment with either placebo or IV-rtPA (0.9 mg/kg, maximum dose 90 mg). Favorable outcomes at 3 months were achieved in the 31% to 50% of patients treated with rtPA compared with 20% to 38% of patients in the placebo arm. This difference was statistically and clinically significant. Patients treated within 90 minutes of onset achieved better outcomes than those who were treated between 90 and 180 minutes, although there was still benefit. The benefit persisted when outcomes were reassessed at 12 months. The major risk of treatment was symptomatic intracranial hemorrhage, which occurred in 6.4% of patients in the treatment group within 36 hours compared with 0.6% of patients in the placebo group. There was no significant difference in 3-month
mortality, which occurred in 17% of patients in the treatment group compared with 21% in the placebo group. The safety and efficacy of rtPA in routine clinical use has been subsequently confirmed in a large cohort of patients.21

Based on these data, IV-rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for carefully selected acute ischemic stroke patients. Intravenous recombinant tissue plasminogen activator is infused over 60 minutes with 10% of the dose given as an initial bolus over 1 minute. The exclusionary criteria for treatment with rtPA within 3 hours of symptom onset are modeled on the original eligibility criteria used in the NINDS study protocol (Table 1).10 Initiating treatment with rtPA prior to obtaining results of coagulation studies may be safe and feasible.22 In patients otherwise eligible for thrombolytic therapy, the American Heart Association/American Stroke Association (AHA/ASA) guidelines support the decision to initiate treatment prior to results of platelet or coagulation studies unless a bleeding disorder or thrombocytopenia is suspected. Seizures are a relative contraindication for rtPA treatment. Seizures are estimated to occur in up to 6% of patients at the time of ischemic stroke onset.23 Case series suggest that thrombolysis can be administered to patients with seizures at the time of presentation when advanced neuroimaging techniques such as CT perfusion or diffusion/perfusion-weighted MRI suggest that neurological deficits are due to cerebral ischemia rather than a postictal state.23,24

Written informed consent is not mandatory prior to administration of rtPA for acute ischemic stroke.10 However, treating physicians are obligated to inform the patient and/or family members regarding the rationale, risks, benefits, and alternatives to treatment with rtPA.25 Placement of invasive devices such as nasogastric tubes, indwelling bladder catheters, and intraarterial catheters should be delayed when possible in patients receiving rtPA. Antiplatelet and anticoagulant medications should not be administered until 24 hours have elapsed after treatment, and a follow-up CT scan at 24 hours is often obtained to evaluate for hemorrhage prior to introduction of an antithrombotic agent for secondary prevention.

When treatment with rtPA is initiated, frequent neurological assessments and blood pressure measurements should be performed every 15 minutes during the rtPA infusion, every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment. This level of monitoring is best achieved in an intensive care unit or stroke unit with nurses specifically trained and experienced in standard neurologic assessment tools, such as the NIHSS and the Glasgow Coma Scale. Severe headache, acute hypertension, emergence of worsening or a new neurologic deficit, nausea or vomiting, or depressed level of consciousness should raise the clinical suspicion for intracranial hemorrhage. If the rtPA infusion is ongoing when these signs or symptoms emerge, the infusion should be stopped immediately followed by emergent noncontrast head CT to evaluate for symptomatic intracranial hemorrhage.

Most symptomatic intracerebral hemorrhages occur within 24 to 36 hours after initiation of treatment.26 Hemorrhagic transformation occurs when there is extravasation of blood into the brain parenchyma after ischemic alteration of the blood–brain barrier. Several clinical, biological, and imaging predictors of intracerebral hemorrhage have been studied. Advanced age,27 baseline stroke severity as measured by the NIHSS,28 hypertension,29 and hyperglycemia30 have been identified as important clinical factors. Studies of an association between intracerebral hemorrhage and serum levels of biomarkers such as matrix metalloproteinase-9, cellular fibronectin, and plasminogen activator inhibitor-1 have yielded conflicting or inconclusive results. Routine measurement of these markers has not been incorporated into clinical practice.26 Further study is needed to clarify the predictive value of baseline neuroimaging parameters, such as diffusion-weighted imaging infarct volume and semiquantitative measurements of cerebral perfusion.

Acute stroke remains a clinical diagnosis. The rapid clinical assessment and interpretation of neuro-

<table>
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<tr>
<th>Table 3</th>
<th>Characteristics of Common Stroke Mimics</th>
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<tr>
<td><strong>Diagnosis</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>Seizure (postictal)</td>
<td>Focal deficits likely caused by seizure-induced neuronal dysfunction (reversible); may occur with simple partial or generalized seizures; clinical seizure often unwitnessed or unrecognized; spontaneous resolution over hours (may last up to 48 hours).</td>
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<tr>
<td>Hypoglycemia</td>
<td>Aphasia or hemiplegia may be present; variable drowsiness or obtundation; blood glucose usually &lt;45 mg/dL; resolution of symptoms (immediate—hours) with IV glucose.</td>
</tr>
<tr>
<td>Metabolic encephalopathy</td>
<td>Etiologies include hyperosmolar hyperglycemia, hyponatremia, hepatic encephalopathy; may be associated with altered level of consciousness, poor attention, disorientation (e.g., delirium), and asterixis.</td>
</tr>
<tr>
<td>Conversion reaction</td>
<td>Diagnosis of exclusion; conversion disorder most common psychiatric diagnosis; comorbid psychiatric problems common; paresis, paralysis, and movement disorders common.</td>
</tr>
<tr>
<td>Reactivation of prior deficits</td>
<td>Imaging evidence or history of remote stroke is often apparent. Previous deficit may have resolved completely.</td>
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</table>
imaging studies necessary to provide thrombolytic therapy within a short time window has raised concern about administering rtPA to patients with nonstroke diagnoses.31 Between 3% and 7% of patients who receive systemic thrombolysis for acute stroke are ultimately found to have a stroke mimic.32,33 Commonly encountered stroke mimics include postictal deficits (Todd paralysis), hypoglycemia, migraine with aura, hypertensive encephalopathy, reactivation of prior deficits, and conversion reactions. Many stroke mimics have unique characteristics that may aid in their differentiation from acute ischemic stroke (Table 3). In a consecutive series of 69 patients who received IV–rtPA and were ultimately diagnosed with a stroke mimic, there were no instances of symptomatic or systemic hemorrhage despite a range of nonstroke diagnoses.34 These data suggest that rtPA can be safely administered to patients with nonstroke diagnoses. Therefore, delaying initiation of therapy to obtain additional diagnostic testing when alternate etiologies are being considered may not be warranted.

Other intravenously administered thrombolytic agents have been studied as possible alternatives to rtPA. These agents include streptokinase, urokinase, reteplase, desmoteplase, and tenecteplase. None are currently recommended for the treatment of acute ischemic stroke in routine clinical practice. Early clinical trials of streptokinase were terminated due to unacceptably high rates of hemorrhage.35 Tenecteplase is a modified version of rtPA with greater fibrin specificity and a longer half-life that allows bolus administration. Early experience with tenecteplase was promising as a stroke therapy with potentially greater safety than rtPA.36 In the phase IIB study, 112 patients were randomized to one of three doses of tenecteplase (0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg) or standard rtPA (0.9 mg/kg) in patients with acute stroke within 3 hours of onset.37 In an adaptive, dose-selection study design the 0.4 mg/kg dose was discarded after enrollment of 73 patients. The selection procedure was unable to distinguish between the 0.1 mg/kg and 0.25 mg/kg doses at the time the trial was stopped prematurely for slow enrollment. No statistically significant different 90-day clinical outcomes were apparent between the remaining tenecteplase group and rtPA. No conclusions could be drawn from the data regarding the potential safety and efficacy of tenecteplase; however, the trial demonstrated the potential efficiency of a novel design in selecting a potential dose of a future thrombolytic agent.

Between 3 to 4.5 Hours
The Third European Cooperative Acute Stroke Study (ECASS III) was designed to test the hypothesis that IV–rtPA would be effective when administered between 3 and 4.5 hours after onset of symptoms in patients with acute ischemic stroke. The study was conceived after a pooled analysis of previous major IV–rtPA trials had suggested a beneficial effect, albeit smaller, when IV–rtPA is given more than 3 hours after symptom onset.38 Patients were randomized to receive either standard dose rtPA (n = 418) or placebo (n = 403). Disability at 90 days was assessed by the modified Rankin scale and dichotomized as a favorable outcome (score of 0 or 1) or an unfavorable clinical outcome (score of 2 to 6). Intracranial hemorrhage associated with clinical deterioration (≥4 point increase in NIHSS score) or death was considered symptomatic in ECASS III.

Compared with the NINDS rtPA trial, the design of ECASS III included notable differences in the exclusion criteria:
- Patients older than 80 years were not enrolled.
- Patients with severe stroke (NIHSS >25) were not enrolled.
- Patients with a history of diabetes and prior stroke were not enrolled.

Treatment with rtPA was significantly associated with a favorable outcome at 3 months (OR 1.34; 95% CI 1.02–1.76). Compared with placebo, the absolute increase in favorable outcome for the treatment group was 7.2% (52.4% vs. 45.2%, p = 0.04). The number needed to treat was 14. Symptomatic intracranial hemorrhage was significantly more frequent in the treatment group (2.4% vs. 0.2%, p = 0.008). Death was similar for both groups with a nonsignificant trend favoring the rtPA group (7.7% vs. 8.4%, p = 0.68). The authors concluded that rtPA given 3 to 4.5 hours after the onset of stroke symptoms was associated with a modest but significant improvement in clinical outcomes.

A recently published AHA/ASA advisory endorses administration of rtPA to eligible acute ischemic stroke patients that can be treated within the 3– to 4.5-hour time window.39 Based on the eligibility criteria used in ECASS III, additional exclusion criteria for treating patients in the extended time window include >80 years old, oral anticoagulant use (regardless of INR value), baseline NIHSS >25, or a history of stroke and diabetes. Ancillary care for those patients receiving rtPA at 3 to 4.5 hours should be similar to those included in the most recently published AHA/ASA guidelines.10 A final approval decision from the FDA or other regulatory agencies for rtPA in the 3- to 4.5-hour time window has not been rendered.

Wake-Up Stroke
Patients who retire to bed without stroke symptoms and then awaken with stroke symptoms are often denied potentially beneficial thrombolytic therapy because the time they were last seen normal often exceeds 3 to 4.5
hours. It is not known what the best course of therapy is for this group of patients. The University of Texas Health Sciences Center’s experience with wake-up stroke has been described. Thrombolytic therapy has been given on a compassionate basis to a subset of patients with wake-up stroke at the University of Texas. Barreto and colleagues reported their experience treating 46 patients with wake-up stroke with thrombolytics. These patients had a greater degree of neurologic impairment than patients with wake-up stroke who were not treated with thrombolytics (median NIHSS 16 vs. 10.5), and they had greater impairments compared with patients treated at the same center within 0 to 3 hours of onset of symptoms using IV-rtPA per standard of care (median NIHSS 16 vs. 11). Controlling for differences in baseline stroke severity, treated patients with wake-up stroke had significantly higher rates of excellent and favorable outcomes, but they also had significantly higher mortality (15 vs. 0%). These results, though intriguing, should be interpreted with caution. Treatment was not randomized, so there are likely imbalances in baseline characteristics not reflected in the NIHSS. The numbers of individuals in the treatment groups are small. The outcomes assessor was unblinded to treatment, and thus observer bias might explain the favorable functional outcomes. Observer bias is not a concern with regard to differential mortality rates.

**Sonothrombolysis**

External ultrasound may augment the fibrinolytic properties of IV-rtPA and has been shown to improve recanalization rates. Ultrasound-enhanced thrombolysis has been termed sonothrombolysis. A randomized clinical trial compared standard dose rtPA (0.9 mg/kg, max 90 mg) to rtPA plus continuous 2 MHz transcranial ultrasound directed at the occluded MCA through a trans-temporal approach. Complete recanalization was demonstrated with clinical recovery in 49% of patients receiving sonothrombolysis versus 30% in patients receiving IV-rtPA only. A meta-analysis of 6 randomized and 3 nonrandomized studies confirmed higher complete recanalization rates in patients receiving combined transcranial ultrasound and rtPA compared with patients receiving rtPA alone (37.2% vs. 17.2%). The systematic review found that sonothrombolysis was not associated with an increased risk of symptomatic intracranial hemorrhage. As with other ultrasound techniques, transcranial Doppler is operator-dependent and blood-flow velocities measured with this technique are not corrected for the angle of insonation. Additional studies incorporating complementary noninvasive vascular imaging modalities such as CT or MR angiography to confirm intracranial vascular occlusion and recanalization will be needed before ultrasound-enhanced thrombolysis can be recommended outside of clinical trials.

**GLUCOSE MANAGEMENT**

Approximately one-third of patients with acute ischemic stroke will have moderate elevations of blood sugar (>$140$ mg/dL) at the time of presentation. Clinical studies have demonstrated poorer outcomes after stroke in patients with hyperglycemia or diabetes, including patients treated with IV thrombolysis. The mechanisms underlying neurologic worsening associated with hyperglycemia are likely multifactorial, and include tissue acidosis, free radical formation, blood–brain barrier disruption, and augmentation of cerebral edema formation. Despite these consistent observations, a definitive study has yet to establish that tight control of glucose improves outcomes. Consensus exists regarding the need to treat hyperglycemia after stroke, and current guidelines recommend a goal glucose concentration of 140 to 180 mg/dL. This can be achieved with the administration of insulin with close monitoring and adjustment of insulin dosing to avoid hypoglycemia.

A recently completed multicenter 3-group pilot randomized clinical trial compared tight control (target plasma glucose concentration, 70–110 mg/dL), loose control (target, 70–200 mg/dL), and standard of care (70–300 mg/dL). The study was designed to assess the safety and feasibility of two insulin infusion protocol targets in patients with acute ischemic stroke. Seventy-four subjects (median NIHSS 8) were enrolled. The tight control group had a median glucose concentration of 111 mg/dL compared with 151 mg/dL in the loose control and standard of care groups. Only one individual in the trial had symptomatic hypoglycemia (in the loose control group). Exploratory analyses found no significant differences in functional or neurologic outcomes at 3 months, but the study was not powered for efficacy. These results have the potential to inform future phase III trials of glucose concentration control in acute ischemic stroke.

**BLOOD PRESSURE MANAGEMENT**

The optimal management of blood pressure after acute ischemic stroke has yet to be definitively established. Blood pressure is commonly elevated in patients with acute stroke and may be related to the stress of cerebral infarction, preexisting hypertension, or a response to increased intracranial pressure. Arterial blood pressure spontaneously declines in most patients with ischemic stroke within the first 24 hours of admission. When the blood pressure does not spontaneously decline, worse outcomes and increased edema formation have been observed.

The current guidelines for management of blood pressure during acute ischemic stroke recommend permissive hypertension for those patients who have not received IV-rtPA. The guidelines recommend withholding antihypertensive treatment unless the systolic blood pressure is greater than 220 mm Hg or the diastolic blood
pressures greater than 120 mm Hg. When the blood pressure exceeds this threshold and antihypertensive therapy is warranted, blood pressure should be cautiously reduced by no more than 15% over the initial 24-hour period.

Recommended antihypertensive therapy in acute ischemic stroke includes nicardipine, labetalol, esmolol, or enalaprilat. These medications have predictable and titratable effects, and are relatively short acting. These characteristics are desirable, as even brief periods of hypotension can lead to worsening neuronal injury. Medications such as nitroprusside should be avoided due to the potential for precipitous drops in blood pressure and the possibility of increasing intracranial pressure through venodilatation. For patients treated with rtPA, blood pressure measurements >180/105 necessitate urgent treatment to reduce the risk of symptomatic intracranial hemorrhage. This goal blood pressure should be maintained for at least the first 24 hours after rtPA treatment.

CONCLUSION

To date, intravenous recombinant tissue-type plasminogen activator remains the only FDA-approved treatment for acute ischemic stroke within 3 hours of onset. Emerging data suggests rtPA is safe and effective when administered between 3 to 4.5 hours in carefully selected patients, but regulatory bodies have not officially endorsed rtPA therapy in this time window. Adherence to the published eligibility criteria for rtPA remains crucial to maintaining a favorable risk-benefit ratio for systemic thrombolysis. Sonothrombolysis and therapeutic interventions for patients with wake-up stroke require further study. Results from well-designed, prospective studies of optimal blood pressure and glucose management in the poststroke setting are needed to guide future evidence-based recommendations.

REFERENCES