Management of Ischemic Stroke: Current Concepts and Treatment Options

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Stroke is the third leading cause of death after cancer and heart disease in the United States, with approximately 160,000 stroke deaths occurring each year.[1] Of the approximately 750,000 strokes that occur annually, over 80% are ischemic. Recurrent stroke remains the leading cause of serious long-term disability.[1,2] The introduction of the thrombolytic recombinant tissue plasminogen activator (rt-PA) in 1995 provided an opportunity for more effective treatment of acute ischemic stroke and improved patient outcomes.[3] Nevertheless, no more than approximately 5% of acute ischemic stroke patients receive thrombolytic therapy, mostly because few patients present to the emergency department within the 3-hour therapeutic window following stroke onset. Newer treatment options such as intra-arterial thrombolysis, which delivers rt-PA directly to the thrombus, and mechanical clot retrieval devices represent an opportunity to expand the therapeutic window up to 8 hours.[4,5] However, the majority of acute stroke patients currently rely on in-hospital medical management of their stroke.

Stroke management involves both primary and secondary prevention strategies as well as appropriate evaluation and treatment of patients with acute stroke. Identification of stroke risk factors and treatment of hypertension, diabetes, elevated cholesterol, carotid artery disease, atrial fibrillation, and tobacco use significantly reduces the occurrence of stroke.[6,7] In addition, correct identification of stroke mechanism (eg, thrombotic versus embolic) leads to appropriate use of antithrombotic or antiplatelet agents. This review discusses stroke risk factors and mechanisms, the evaluation of patients with acute stroke, and therapies and neurointerventional approaches for the treatment of ischemic stroke.

TAKE HOME POINTS

- Stroke is the third leading cause of death in the United States and a leading cause of disability worldwide.
- Identification of specific risk factors and mechanism of stroke through neuroimaging and ultrasonography techniques is essential for preventing and treating stroke.
- Treating ischemic stroke with intravenous recombinant tissue plasminogen activator within 3 hours of stroke onset can substantially improve outcome after stroke.
- Secondary stroke prevention involves treating risk factors such as hypertension, diabetes, smoking, dyslipidemia, and atrial fibrillation.
- Newer neurointerventional therapies, such as intra-arterial thrombolysis and mechanical clot retrieval, can extend the therapeutic window to treat thrombosis within intracranial vessels and potentially can limit the effects of stroke.

PATHOPHYSIOLOGY

Brain ischemia occurs when blood flow to part of the brain is interrupted. Survival of brain tissue depends on the length of time the brain is deprived of oxygen and nutrients. Infarction occurs when areas of the brain suffer irreversible changes because of prolonged interruption of blood flow. The extent of infarction depends on the size and location of the occluded artery as well as the adequacy of collateral flow to that area. Ischemia in the affected region leads to the failure of ATP-dependent ion transport, resulting in the accumulation of sodium and water in the cellular elements, an effect referred to as cytotoxic edema. Cells in the center of infarcted tissue, or core, die. There is a zone of hypoperfused tissue around the core of infarction, the ischemic penumbra, representing

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Table 1. Signs and Symptoms Based on Location of Stroke

Middle cerebral artery (MCA)
Contralateral weakness (greater in the face and arm than the leg)
Contralateral sensory changes
Homonymous hemianopsia (loss of half of visual field)
Language disturbance
Aphasia (left MCA)
Dysarthria (right MCA)
Difficulty reading, writing, calculating (left MCA)
Extinction/hemineglect, spatial disorientation (right MCA)
Vertebral-basilar system
Vertigo
Ataxia (gait unsteadiness)
Contralateral weakness
Diplopia
Dysconjugate gaze
Dysphagia

brain tissue that is potentially salvageable if reperfusion occurs within a short period of time.

MECHANISMS OF STROKE

The most common causes of ischemic stroke are atherosclerosis of large arteries (20%), small-vessel or lacunar disease (25%), and embolic phenomenon (25%); the cause of cerebral infarction cannot be determined in approximately 30% of strokes (ie, cryptogenic stroke). Atherosclerosis of extracranial (eg, carotid artery) or intracranial (eg, middle cerebral artery [MCA]) vessels with progressive narrowing compromises cerebral perfusion or results in artery-to-artery embolus from coexisting thrombus. The development of microatheroma or lipohyalinosis in small penetrating arteries in the brain, often due to long-standing hypertension or diabetes, is the most frequent cause of small-vessel disease, or subcortical lacunar infarcts. Ascending aortic arch atherosclerosis can be a source of embolic strokes. Atrial fibrillation is the most common cause of cardiogenic emboli; other cardioembolic sources include prosthetic mechanical valves, recent myocardial infarction with left ventricular thrombus, atrial myxoma, infective endocarditis, dilated cardiomyopathies, and marantic endocarditis.[8] In young patients with cryptogenic stroke, patent foramen ovale (PFO) is overrepresented as a potential source of right-to-left shunting and paradoxical embolous.[9,10]

CLINICAL FEATURES

The clinical features of stroke vary depending on the location and extent of the arterial territory affected (**Table 1**). Most MCA strokes produce contralateral weakness, sensory changes, and visual field deficits (homonymous hemianopsia). Language disturbances such as aphasia as well as difficulty in reading, writing, or calculating can occur, particularly with left hemispheric lesions; with right hemispheric lesions, extinction to left-sided stimuli (hemineglect), slurred speech (dysarthria), or spatial disorientation may be seen. Rare isolated anterior cerebral artery strokes cause contralateral leg weakness. Lesions affecting the posterior circulation (vertebral-basilar system) cause weakness, dysarthria, vertigo, nausea, ataxic gait and clumsiness, double vision, dysconjugate gaze, and difficulty swallowing. The symptoms of transient ischemic attack (TIA) are identical to those of stroke but last for a shorter duration (minutes).

APPROACH TO EVALUATION

Evaluation of the stroke patient includes initial clinical assessment, laboratory testing, neuroimaging, and ultrasonographic testing.

Stroke Assessment Scales

Assessment of stroke severity based on a complete neurologic examination is a strong indicator of prognosis. Several reliable, well-validated stroke scoring systems have been developed, each with strengths and limitations.[11–13] The National Institutes of Health Stroke Scale (NIHSS) is widely used for clinical assessment of the stroke patient (available at www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf). Possible scores range from 0 to 42, with severe disability indicated by a score greater than 20. The initial NIHSS score provides important prognostic information. Approximately 60% to 70% of acute ischemic stroke patients with a baseline NIHSS score below 10 will have a favorable outcome after 1 year compared with only 4% to 16% of those with a score greater than 20.[12–14] The NIHSS score can also identify patients at greatest risk for intracranial hemorrhage (NIHSS > 20) following thrombolytic treatment.[8] Other stroke scales such as the Barthel Index and modified Rankin Scale are useful in assessing the functional state of the stroke patient.

Laboratory Testing

Tests that should be performed in the evaluation of the acute stroke patient include measurement of blood glucose and electrolyte levels, complete blood and platelet count, determination of prothrombin time and activated partial thromboplastin time, and renal and hepatic function testing. These blood tests

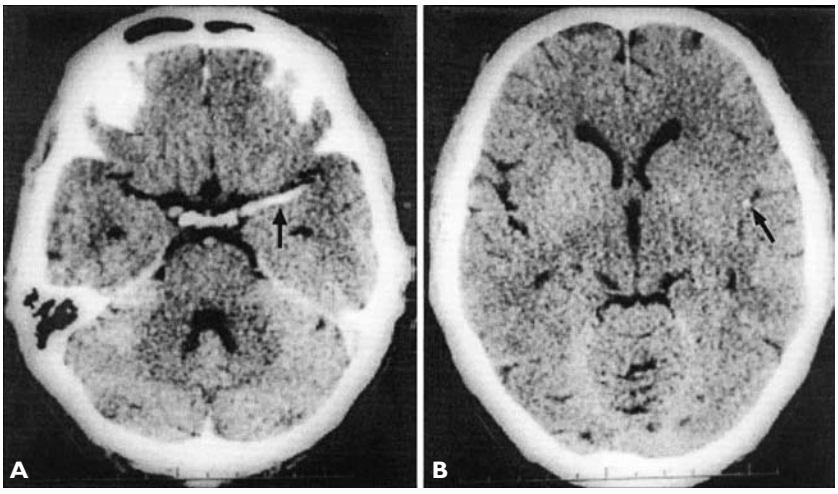


Figure 1. Noncontrast computed tomography scan demonstrating intraluminal thrombus with (**A**) hyperdense middle cerebral artery (MCA) sign (*arrow*) and (**B**) sylvian fissure MCA "dot" sign (*arrow*).

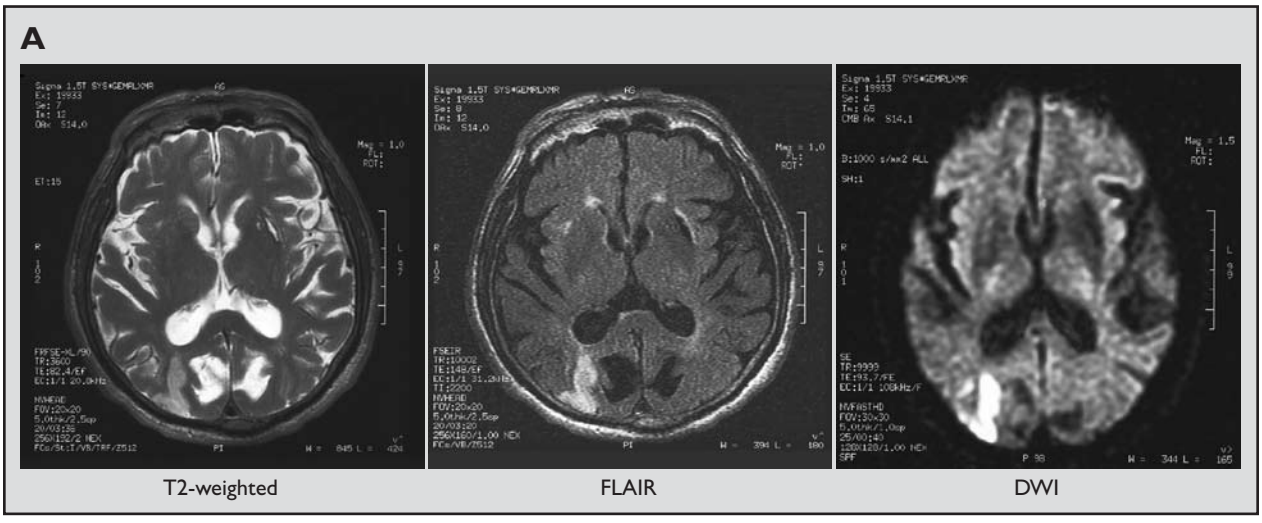
can identify conditions that mimic stroke (eg, hypoglycemia, hyponatremia) or cause stroke and may influence decision making around thrombolytic therapy (eg, thrombocytopenia).

Neuroimaging

Noncontrast computed tomography. Emergent, noncontrast computed tomography (CT) scan of the brain is the neuroimaging study most commonly used in the initial assessment of stroke patients. Although CT scan can accurately identify most cases of intracerebral hemorrhage, it is relatively insensitive in detecting acute ischemic stroke, particularly in the posterior fossa.[2] However, CT scan remains the imaging workhorse for evaluation of suspected stroke because it can be used to select patients for thrombolysis. A noncontrast CT scan can identify the following early signs of acute ischemic stroke: (1) thrombosis within the MCA (hyperdense MCA sign [**Figure 1**]); (2) clots in distal sylvian MCA branches (hyperdense sylvian dot sign [Figure 1]); (3) loss of gray-white junction differentiation; (4) loss of cortical ribbon (area between the frontal and temporal lobes); and (5) sulcal effacement. Early findings on head CT after stroke can help predict bleeding risk associated with thrombolysis. The presence of early hypodensity (within several hours) in an area larger than one third of the MCA territory is associated with an eight-fold increased risk of hemorrhagic conversion of ischemic stroke if rtPA is administered.[3,15,16] Scoring systems based on the initial CT scan may improve identification of early ischemic infarct and provide additional prognostic information.[2,17]

CT angiography and perfusion. CT angiography (CTA) performed after rapid bolus administration of intravenous contrast provides accurate and detailed images of extracranial and intracranial vessels, allowing for the identification of atherosclerotic plaque, thrombosis, or occlusion. CT perfusion (CTP), obtained at the same time as CTA, can supply vital information regarding regional cerebral blood flow, blood volume, and mean transit times. Both CTA and CTP can provide important information in the acute stroke patient regarding the extent of ischemic penumbra and presence and location of occlusion or stenosis as well as help identify which patients will benefit from thrombolytic therapy.[18]

Magnetic resonance imaging and angiography. Standard magnetic resonance (MR) imaging sequences (eg, T1-weighted, T2-weighted images, and fluid attenuation inversion recovery [FLAIR]) are relatively insensitive in detecting early ischemic changes in patients with stroke. More recently, MR diffusion-weighted imaging (DWI) has been used to detect infarcted brain tissue within minutes of stroke.[2,19,20] MR DWI imaging detects decreased water diffusion within ischemic brain tissue, resulting in a bright signal on scan (**Figure 2**). An MR perfusion-weighted image (PWI) obtained through rapid administration of gadolinium contrast defines brain tissue at risk that is potentially salvageable. Ischemic penumbra can be defined as the difference between an MR DWI lesion (infarcted tissue) and the area at risk delineated by MR PWI (hypoperfused area), or the "diffusion-perfusion mismatch." A core lesion identified on DWI surrounded by much larger area, defined by PWI, may indicate the need for immediate thrombolysis to establish reperfusion. Initial lesion volumes identified on DWI correlate well with the final size of infarct seen on follow-up imaging and stroke severity assessed by clinical stroke and outcomes scales.[2,20,21] A limitation of MR imaging is its relative insensitivity in identifying acute intracranial hemorrhage because blood appears isointense to surrounding brain tissue in the early stages of hemorrhage.



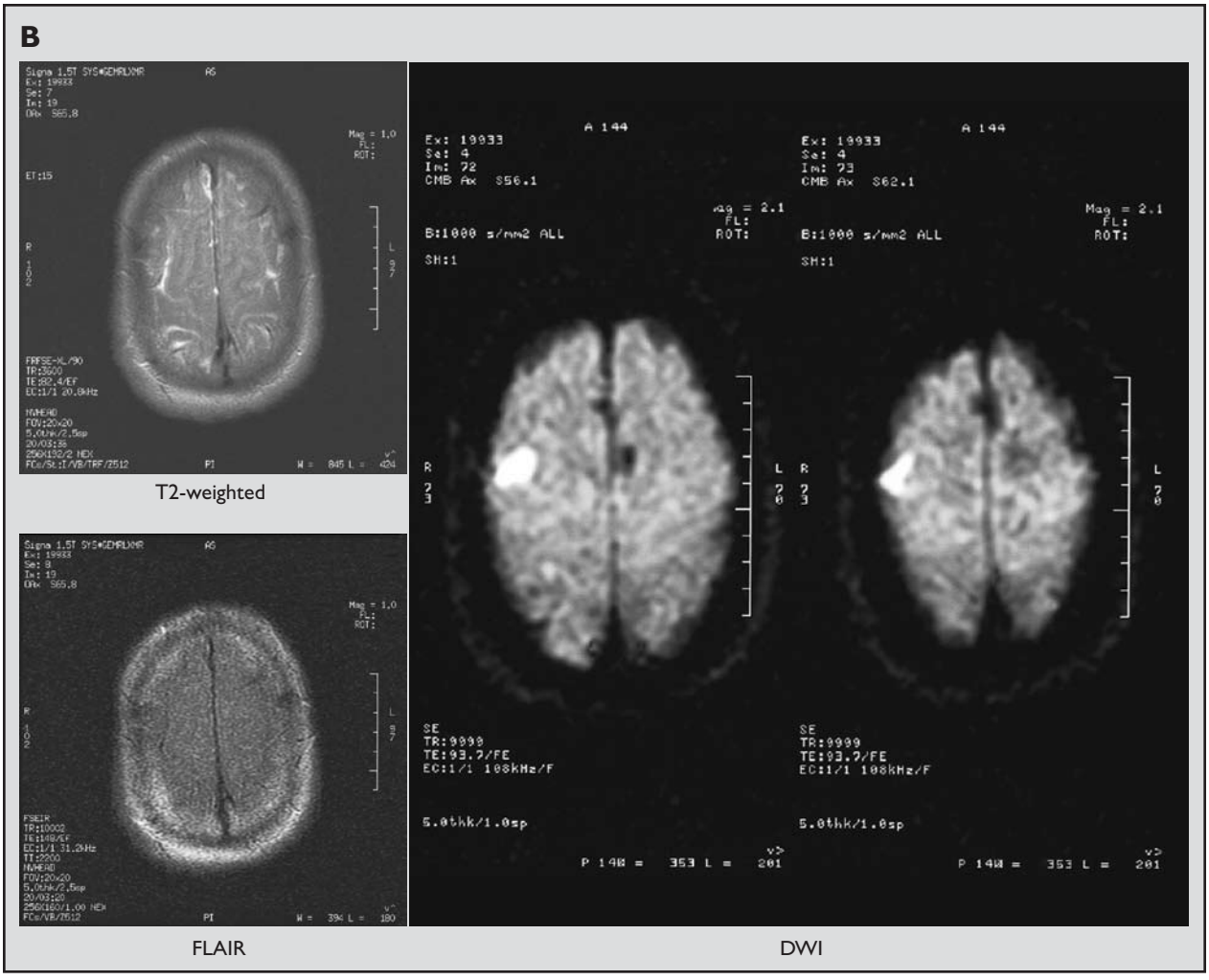


Figure 2. Acute ischemic stroke demonstrated on magnetic resonance imaging sequences with T2-weighted, fluid attenuation inversion recovery (FLAIR), and diffusion-weighted imaging (DWI). (**A**) Matching areas of stroke seen on T2-weighted, FLAIR, and DWI. (**B**) Increased sensitivity in detecting stroke on DWI not seen with T2-weighted or FLAIR imaging sequences.

An MR angiogram of the head and neck can examine both intra- and extracranial vessels and help determine the cause of stroke (eg, atherosclerosis, dissection).

Echocardiogram

A transthoracic echocardiogram (TTE) is useful in detecting a cardiac source of emboli, such as left ventricular dysfunction, hypokinetic or akinetic segments, or left ventricular thrombus. Transesophageal echocardiogram (TEE) may provide detailed information, particularly when examining for apical or left atrial appendage thrombus or atrial septal defects (eg, PFO) as the cause of ischemic stroke. TTE is widely used in the evaluation of stroke patients and some may benefit from a TEE.

Doppler Ultrasound

Carotid Doppler ultrasound is an easy to administer noninvasive tool that can be used to determine patency of extracranial vessels (eg, carotid and vertebral arteries). Ultrasound can also provide information about plaque morphology and composition. Transcranial Doppler (TCD) ultrasonography performed by positioning a probe over the temporal bone or suboccipital area can detect intracranial arterial stenosis or occlusion.[22] TCD can monitor recanalization of vessels over time after thrombolytic therapy and determine prognosis.[22,23] Recently, the Combined Lysis Of Thrombus in Brain ischemia using 2 MHz transcranial Ultrasound and Systemic T-PA (CLOTBUST) study[24] showed that continuous energy emitted from TCD improved recanalization rates and safely augmented the effectiveness of rt-PA following stroke.

MEDICAL THERAPY FOR STROKE PREVENTION

There are nonmodifiable and modifiable risk factors for stroke.[6] Nonmodifiable factors include age, gender, race, and heredity. Modifiable risk factors include hypertension, TIA/stroke, elevated cholesterol, diabetes, obesity, atrial fibrillation, alchohol use, and smoking. Controlling modifiable risk factors with medical treatment or reducing high-risk behaviors can significantly decrease the incidence of stroke (**Table 2**).[7] In addition, evaluation of carotid arteries or the myocardium with duplex Doppler ultrasound or echocardiogram, respectively, can identify potential sources for thromboembolic stroke.

Table 2. Stroke Risk Reduction with Treatment of Vascular Risk Factors

Factor	Risk Reduction with Treatment
Hypertension	30%–40%
Smoking	50% at 1 year; baseline after 5 years
Diabetes	44% reduction in hypertensive diabetics with tight blood pressure control
Hyperlipidemia	20%–30% with statin use in patients with known coronary artery disease
Atrial fibrillation (nonvalvular)	68% with warfarin therapy 21% with aspirin therapy

Adapted with permission from Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Circulation 2001;103:165.

Antiplatelet Therapy

For patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is the standard of care for secondary prevention. The Antiplatelet Trialists' Collaboration showed that antiplatelet agents reduced the secondary risk of stroke, myocardial infarction, and vascular death by approximately 27%.[25] Aspirin doses ranging from 30 to 1300 mg have been used,[26–29] but the dose currently recommended by the US Food and Drug Administration (FDA) for prevention of ischemic stroke is 50 to 325 mg/day. Other antiplatelet agents (eg, ticlopidine, clopidogrel, dipyridamole) in combination with low-dose aspirin are alternatives to aspirin. Ticlopidine is no longer used as it has been associated with the development of severe neutropenia (1%) and thrombotic thrombocytopenic purpura.[30]

Guidelines for prevention of stroke in patients with ischemic stroke or TIA have recently been published.[31] In comparison to aspirin alone, combination aspirin and extended-release dipyridamole or clopidogrel are safe. Based on direct-comparison trials, the combination of aspirin and extended-release dipyridamole is suggested instead of aspirin alone,[29] and clopidogrel may be used instead of aspirin for treatment of stroke.[31,32] However, the recently published Management of Atherothrombosis with Clopidogrel in High-risk patients with recent Transient Ischemic Attack or Ischemic Stroke (MATCH) trial showed no benefit of combination daily clopidogrel 75 mg and aspirin 75 mg versus clopidogrel 75 mg alone for prevention of myocardial infarction, stroke, or vascular death.[33] The risk of hemorrhage increased with the addition of aspirin to clopidogrel; thus combination therapy is not routinely recommended for ischemic stroke or TIA. Clopidogrel and aspirin may be acceptable for stroke patients who have undergone recent carotid artery stenting.[2]

The Warfarin-Aspirin Recurrent Stroke Study (WARSS)[34] evaluated switching patients with recurrent stroke who had been on aspirin, so-called "aspirin-failure" patients, to warfarin and found no benefit. Similarly, in the Warfarin-Aspirin Symptomatic Intracranial

Disease (WASID) study, warfarin (international normalized ratio, 2–3) was not superior to aspirin (1300 mg/day) for stroke prevention in patients with 50% to 99% stenosis of major intracranial vessels supplying the territory of stroke.[35] In this study, symptomatic intracranial stenosis conferred a significantly higher rate of recurrent stroke (up to 23%) than expected after first-ever stroke, and use of warfarin was associated with significantly increased major bleeding rates and higher death rates than aspirin. Several ongoing trials continue to examine the benefit of antiplatelet therapy in specific subsets of stroke patients (Prevention Regimen For Effectively avoiding Second Strokes or [PRoFESS] and the Secondary Prevention of Small Subcortical Strokes [SPS3] study).

Anticoagulation

Oral anticoagulation is not superior to antiplatelet therapy for secondary stroke prevention except when there is an embolic source, such as underlying atrial fibrillation.[36] Whether antiplatelet therapy or anticoagulation should be used for medical management of complex atherosclerotic aortic plaques, a potential source of embolic stroke, remains controversial.[37] The incidence of PFO in young stroke patients approaches 40% to 50%, but optimal therapy in these patients remains uncertain. Options include antiplatelet therapy, anticoagulants, open surgical closure, or closure via endovascular technique.[38–40] Trials are underway to determine the best treatment (closure device placement versus best medical management) for patients with PFO and stroke.[40]

Treatment of Dyslipidemia

Several large clinical trials with statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) have reported an up to 30% reduction in the rate of stroke with the use of these agents.[41–43] Potential mechanisms of statins in stroke reduction and overall reduction of vascular events include their effects on endothelial function,[44,45] inflammatory response,[46] and plaque stability and thrombus formation.[47] Elevated total and low-density-lipoprotein (LDL) cholesterol levels may be associated with thickening of the intima-media layer of carotid arteries as determined by B-mode ultrasonography. Lipid-lowering therapy with statins may reduce progression of carotid intima-media thickening and possibly result in regression of plaque.[48,49] The recommended threshold for beginning statin therapy in stroke patients is an LDL cholesterol level greater than 100 mg/dL. Periodic liver function and muscle enzyme testing can be performed to monitor potential adverse effects of statins.

MEDICAL THERAPY FOR ACUTE STROKE

Thrombolytics

Prior to 1995, 9 randomized placebo-controlled trials reported use of intravenous (IV) rt-PA, streptokinase, or intra-arterial recombinant pro-urokinase (rproUK)[50–52] in ischemic stroke. The 1995 landmark trial by the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group demonstrated substantial benefit with use of IV rt-PA in patients with ischemic stroke of no more than 3 hours' duration.[3] Based on these results, the FDA approved the use of rt-PA for use in early ischemic stroke in 1996. Symptomatic intracerebral hemorrhage within 36 hours of onset of stroke occurred in 6.4% of the rt-PA group compared with 0.6% of the placebo group.[3] However, patients treated with rt-PA were at least 30% more likely to have minimal or no disability at 3 months compared to placebo patients. Interestingly, there were no significant differences in neurologic improvement at 24 hours between the rt-PA group and the placebo group. Despite well-defined inclusion and exclusion criteria for giving rt-PA in the acute stroke patient, arriving at the emergency department more than 3 hours after stroke onset is the main reason patients do not receive IV rt-PA. Other therapies, such as intra-arterial rt-PA and mechanical clot retrieval devices, have extended the therapeutic time window.[4,5]

Treatment of Hypertension

Elevated blood pressure is common in the early stages of acute stroke. Increased blood pressure may be a physiological response to the stroke itself or may be due to other unknown factors. Guidelines for an acceptable blood pressure range in acute stroke have been established based on the NINDS rt-PA Stroke Trial.[53] Treatment strategies for potential rt-PA candidates include maintaining systolic blood pressure (SBP) at or below 185 mm Hg or diastolic blood pressure at or below 110 mm Hg within the first 48 to 72 hours. Acceptable limits for blood pressure may be even higher (≤ 220/120 mm Hg) for patients who do not receive thrombolytics.[54] The rationale for "permissive hypertension" is to maintain adequate cerebral perfusion to the penumbral region. Recent studies support this practice, demonstrating best prognosis with a SBP of at least 150 mm Hg[55] or baseline SBP of 180 mm Hg and worse prognosis with early correction of hypertension.[56] Gentle blood pressure lowering can be achieved with IV labetalol, a combination α_1-adrenergic and nonselective β-adrenergic receptor blocker given in 10 mg IV pushes up to 200 mg, or with enalapril, an angiotensin-converting enzyme inhibitor

(ACEI) given in 1.25 mg IV pushes every 6 hours. Long-term therapy with ACEIs or angiotensin II receptor blockers may have added benefit in providing vascular protection beyond their ability to lower blood pressure.[57,58]

Anticoagulation

Although several large randomized trials have examined the use of IV or subcutaneous heparin in acute stroke, none demonstrated a benefit of heparin in preventing stroke progression or improving neurologic outcomes compared to aspirin or placebo.[59,60] The Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[61,62] evaluated the use of low-molecular-weight heparinoid (danaparoid) or heparin (nadroparin) for treatment of acute ischemic stroke and failed to show a significant benefit.

SURGICAL MANAGEMENT

Carotid Endarterectomy/Carotid Stenting

Several groundbreaking trials in the early 1990s showed that carotid endarterectomy (CEA) performed within 2 years of a TIA or stroke is beneficial in patients with symptomatic ipsilateral carotid stenosis of 70% or more.[63,64] However, controversy remains over the timing of CEA after acute stroke. Several studies demonstrated good outcomes in patients with CEA within days to weeks after stroke, particularly in patients with mild-to-moderate stroke, stable neurologic examination, and small infarct size on neuroimaging.[65,66] The routine practice of waiting 4 to 6 weeks after stroke before performing CEA may not be necessary. In fact, patients may have a risk of recurrent stroke of up to 10% during the waiting period.[67] Use of CEA in asymptomatic patients with carotid stenosis of 60% or more may offer modest benefit.[68,69]

Only one trial has demonstrated that the efficacy of carotid artery stenting (CAS) is comparable to CEA in high-risk patients.[70] In this study, use of CAS with an emboli-protection device among patients with severe carotid stenosis and coexisting conditions was not inferior to CEA.[70] Several ongoing trials and registries are examining the benefit of CAS in patients with symptomatic or asymptomatic carotid disease.[71]

Hemicraniectomy

Patients with massive hemispheric strokes or "malignant" MCA territory infarction leading to intracranial hypertension and tissue shifts have poor outcomes and mortality rates between 50% and 78%.[72,73] Mortality remains high despite aggressive medical therapies, such as hyperventilation, mannitol, barbiturate coma, and hypothermia. Decompressive hemicraniectomy, first proposed in the 1950s and recently performed in a large series with early decompression (ie, within 24 hr), was shown to reduce overall mortality and improve stroke outcomes by avoiding brainstem compression and herniation syndrome.[74,75] In a retrospective review of hemicraniectomy for massive MCA stroke, Gupta et al[74] found that age is an important factor for predicting better functional outcomes; however, timing of surgery, hemisphere infarcted, presence of signs of herniation before surgery, or involvement of other vascular territories did not predict outcomes. Worse outcomes have been seen with older age, more severe neurologic deficit at admission, and longer duration of mechanical ventilation and intensive care stay but not with timing of decompressive surgery.[75]

NEUROENDOVASCULAR INTERVENTIONS FOR HYPERACUTE AND RECURRENT ISCHEMIC STROKE

Although IV rt-PA has been shown to significantly improve outcomes,[3] only 2% to 5% of stroke patients receive this therapy.[76,77] There are several important limitations to IV rt-PA that have discouraged its broader use, including relatively low recanalization rates in large vessel occlusion,[78] contraindications such as anticoagulation therapy or recent major surgery, and risk of intracerebral hemorrhage. Catheter-based intra-arterial thrombolysis for acute ischemic stroke has the potential to overcome these limitations. Recent technical advances in the flexibility and steerability of microguidewires and the compliance of microcatheters have made intracranial endovascular access increasingly feasible and safe. In August 2004, the FDA approved the Mechanical Embolus Removal in Cerebral Ischemia (MERCI; Concentric Medical, Mountainview, CA) device to treat vessel thrombosis.[4,5] The ischemic penumbra is potentially salvageable if blood flow is restored within the first few hours after stroke.[79] Three broad strategies for revascularization of the acutely occluded cerebral artery using endovascular technique include thrombolysis, thrombectomy, and augmented thrombolysis.[80]

Intra-arterial Thrombolysis

Intra-arterial thrombolysis delivers thrombolytic agents directly into thrombus occluding the intracranial artery. The advantages of this technique are higher drug concentrations at the thrombus site and decreased systemic concentration, possibly reducing hemorrhagic risk. Recanalization of the artery is checked by repeat angiogram.

The Prolyse in Acute Cerebral Thromboembolism (PROACT) I and II trials[81] evaluated use of r-proUK

Table 3. Current Hyperacute Stroke Treatment Time Windows

Intravenous rt-PA:* 0–3 h
Consider low-dose rt-PA + intra-arterial lysis if M1 or large artery occlusion is suspected
Intra-arterial rt-PA: 3–6 hr
Intra-arterial mechanical thrombectomy, MERCI device*/intra-arterial mechanical thrombolysis: 3–8 hr
0–12 hr (maybe 24 hr) for basilar artery occlusion

rt-PA = recombinant tissue plasminogen activator.

*Approved by the US Food and Drug Administration.

in patients with proximal MCA (M1 or M2) occlusions within 6 hours of stroke symptom onset. Patients who received r-proUK achieved significantly higher recanalization rates (66%) and had an increased chance of being independent (40%) at 90 days as compared to the control group (18% and 25%, respectively) ($P < 0.043$); however, the r-proUK group had higher hemorrhagic transformation rates at 24 hours (35% versus 13% in controls). Hemorrhagic transformation resulted in neurologic deterioration in 10% of treated patients versus 2% of controls. Although r-proUK did not receive FDA approval because of the small trial size, intra-arterial thrombolysis is now offered in centers with neurointerventional capabilities for patients who present outside the traditional 3-hour limit for IV therapy (**Table 3**). rt-PA, reteplase, tenecteplase, and urokinase are the thrombolytics currently used.

Ultrasound-enhanced intra-arterial lysis. Combination therapy with low-dose IV rt-PA followed by intra-arterial thrombolysis has been evaluated in clinical trials. Both the Emergency Management of Stroke (EMS)[82] and Interventional Management of Stroke (IMS)[83] studies demonstrated higher recanalization rates, similar mortality rates, and significant likelihood of excellent outcomes at 3 months with combination treatment compared to intra-arterial thrombolytics alone. In the recent IMS-II trial,[84] a catheter (MicroLysUS infusion catheter; EKOS Corporation, Bothell, WA) designed to deliver an ultrasonographic pulse within the clot while a thrombolytic agent is infused through a central port was used in 73 patients who had a cerebral artery occlusion after receiving a modified dose of IV rt-PA. Patients in the IMS-II study had a higher recanalization rate (69%) compared with patients in the first IMS study (56%) and a 1.65 times greater chance of attaining independent status at 90 days.[83] In IMS-II, there were more symptomatic hemorrhages (11%) compared with the first IMS study (6.3%) and the NINDS rt-PA study (6.6%).[3] This device is now being tested in a randomized manner in the IMS-III study to yield more definitive data regarding its use in routine clinical care.

MERCI Concentric Retriever Device

The MERCI device is a platinum-tipped nitinol (nickel titanium) wire consisting of a helix with 5 loops of decreasing diameter.[4,5] The device is straightened while inside a microcatheter and assumes a helical shape when advanced out of the microcatheter. The helix is used to engage and retract occluding thrombus in the cerebral arteries. The MERCI device within the microcatheter is advanced past the clot, deployed and turned with counter-rotary movements to engage the clot, which is pulled into the microcatheter apparatus. The microcatheter is then removed from the arterial system.

In a prospective multicenter, nonrandomized study that evaluated MERCI, 151 patients were enrolled up to 8 hours after stroke symptom onset; the recanalization rates was 46%, significantly higher than expected using historical controls (18%; $P = 0.0001$).[5] Treatment of patients with MERCI resulted in significantly higher chances of being independent, and mortality rates were reduced. In this study, there was an overall 7.8% rate of symptomatic intracranial hemorrhage and a 7.1% rate of device-related complications (ie, vessel perforation, intramural dissection, or distal embolization). More definitive proof of improved stroke outcomes with use of the MERCI device is currently being sought in an National Institute of Health–sponsored, randomized controlled trial called MR RESCUE.

CONCLUSION

Diagnostic and therapeutic advances have significantly improved outcomes in acute ischemic stroke. Patients who present to the emergency department within the therapeutic time window after stroke may benefit from thrombolytic or mechanical retrieval device therapy. Prevention of first or recurrent stroke is achieved through aggressive management of stroke risk factors. Newer endovascular therapies are being developed to extend the treatment window in acute stroke. Combination medical therapy and neurointerventional devices may be the next logical step toward improving outcomes following ischemic stroke. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 48.

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