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Ischemic Stroke: Evaluation, Treatment, and Prevention

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Ischemic Stroke: Evaluation, Treatment, and Prevention

Matthew Brandon Maas, MD, and Joseph E. Safdieh, MD

INTRODUCTION

This manual is the second half of a 2-part review of ischemic stroke. In part 1, the pathophysiology of stroke was reviewed from both a cellular and systemic perspective. An organized framework was developed to discuss the important characteristics of diseases implicated in causing ischemic stroke based on their mechanism of injury. Part 2 of this review provides an overview of the evaluation and management of ischemic stroke. Because of the broad heterogeneity of stroke mechanisms, strategies are presented to systematically screen for contributory risk factors. Management techniques are presented from acute stabilization to secondary prevention, covering important topics such as vascular reperfusion therapies, in-hospital care, relevant surgical procedures, and rehabilitation. This manual concludes with a series of case-based questions that apply the concepts presented throughout parts 1 and 2.

STROKE EVALUATION AND MANAGEMENT

Stroke care is commonly divided into 2 phases. The initial phase is the urgent time period that begins when the patient first presents to clinical attention. Because the brain is poorly resilient to deprivation of oxygen and metabolic substrates, time to intervention is critically important. The organizing principle of the initial phase of stroke care is to perform a limited evaluation with a focus on obtaining data necessary for making decisions about time-sensitive treatments. This includes an abbreviated history of the patient's presenting symptoms and past medical history, a focused general and neurologic examination, basic laboratory studies, and rapid baseline neuroimaging. Stabilization and therapeutic interventions ensue during this phase of care.

In the second phase, care started during the initial phase continues on an inpatient basis as a thorough evaluation of the patient is undertaken. The accumulation of additional data allows for a more accurate determination

of the etiology of the ischemic event and further exploration of risk factors. Patients presenting with transient ischemic attack (TIA) are at significant risk for stroke¹ and should undergo the same evaluation as patients admitted for stroke, with the intent of identifying risk factors for primary prevention.² A multidisciplinary approach is required to avoid further medical consequences of stroke (eg, aspiration pneumonia) and to establish a plan for rehabilitation. Outpatient care supports continuing rehabilitation efforts and ongoing risk factor modification.

ACUTE EVALUATION AND STABILIZATION

Several basic evaluation and management procedures should be rapidly undertaken for every patient presenting with suspected acute ischemic stroke.³ The extent of the evaluation depends on the likelihood of encountering a positive finding, the pretest probability. For example, the pretest probability of a significant finding on a hypercoagulability panel for a stroke patient is high for a young woman with a history of thrombosis and multiple spontaneous fetal losses but low for an elderly patient with poorly controlled risk factors and a severe ipsilateral carotid stenosis.

Stabilization

The first step in acute stroke management is to ensure that the patient is stabilized, brought promptly to an appropriate emergency department (ED), and rapidly evaluated. It has been demonstrated that outcomes are better for patients treated at designated stroke centers.³ As in all emergency situations, the initial approach to the patient requires a survey of the patient's airway, breathing, and circulatory function. Severe dysphasia and diminished level of arousal are not rare in acute stroke, and some patients may require intubation to protect their airway and minimize aspiration. An abbreviated examination will consist of assessment of vital signs, survey for evidence of trauma, and a focused cardiovascular system assessment.

History and Neurologic Assessment

A neurologic assessment should be sufficiently thorough to identify major deficits. Use of a standardized

Table 1. Criteria for Intravenous Tissue Plasminogen Activator (tPA) Within 3 Hours*

Indications	Contraindications	Warnings [†]
Age ≥ 18 yr	SBP > 185 mm Hg or DBP > 100 mm Hg despite intervention to lower it	Glucose > 400 or < 50 mg/dL
Significant deficit expected to result in long-term disability	Seizure at onset (if unclear whether the deficits are postictal or ischemic)	Very severe stroke (NIHSS > 22)
Noncontrast CT scan showing no hemorrhage or well-established new infarct	Major surgery within 14 days	Documented left heart thrombus
Acute ischemic stroke symptoms with a clearly defined onset or time last known well < 3 hr from time tPA is to be given	Stroke, intracranial or spinal surgery, or serious head trauma within 3 mo	Bacterial endocarditis
	History of intracranial hemorrhage or known vascular malformation or brain tumor with elevated hemorrhage risk	Post-MI pericarditis
	Internal bleeding within 21 days	Pregnancy
	Arterial puncture at a noncompressible site within 7 days	Rapidly improving deficits
	Platelet count < 100,000/mm ³ , PTT > 40 sec, PT > 15 sec or INR > 1.7, or known bleeding diathesis	Life expectancy < 1 yr due to medical comorbidities
	Suspicion of SAH	

CT = computed tomography; DBP = diastolic blood pressure; INR = international normalized ratio; MI = myocardial infarction; NIHSS = National Institutes of Health Stroke Scale; PT = prothrombin time; PTT = partial thromboplastin time; SAH = subarachnoid hemorrhage; SBP = systolic blood pressure.

*Use of tPA within 3 to 4.5 hours of stroke onset is not approved by the U.S. Food and Drug Administration, and the criteria for use in that time window are stricter.

[†]These conditions increase the risk of unfavorable outcomes but are not contraindications.

scale, such as the National Institutes of Health Stroke Scale (NIHSS), facilitates the process by considering the most important domains of neurologic function and by providing a well-recognized score to represent the magnitude of acute disability. The NIHSS examination can yield a good impression of the potential localization of the lesion. (A copy of the NIHSS scoring form and instructions for its use are available at www.ninds.nih.gov/doctors/NIH_stroke_scale.pdf.) During the initial assessment, the patient's medical history should be reviewed. In particular, medical risk factors associated with stroke and the patient's medications are important. The circumstances and symptoms at onset can be elicited from the patient or bystanders and may raise suspicion for a stroke mimic, such as seizure. Lastly, several acute stroke interventions are time-sensitive. Therefore, establishing the time of onset is of utmost importance.

Diagnostic Testing

Once the patient is in stable condition and the focused history and examination are complete, several basic tests are obtained. An electrocardiogram (ECG) should be done in every patient. Laboratory studies should include a basic chemistry panel, complete blood count, prothrombin time (PT), partial thromboplastin time (PTT), and cardiac enzymes. A toxicology screen, pregnancy test, and arterial blood gas measurements may be useful in selected patients. Finally, brain imaging must be obtained rapidly. At a minimum, noncontrast head computed tomography (CT) is required to exclude hemorrhage and to assess for developing

signs of infarction. Some centers have the capacity to obtain CT- and/or magnetic resonance (MR)-based angiography and perfusion imaging as well as magnetic resonance imaging (MRI) sequences useful in evaluating acute stroke, such as diffusion-weighted imaging. It is critical to note that obtaining imaging studies other than a noncontrast head CT may assist in decision making but should not be used in such a way that may prohibit appropriate patients from receiving thrombolytic therapy in a timely manner. American Heart Association guidelines suggest that initial history and physical examination, phlebotomy for laboratory studies, and ECG be completed within 25 minutes of the patient's arrival in the ED; that neuroimaging be obtained within 45 minutes of arrival; and that a final reassessment and decision about the appropriateness of thrombolytic therapy be completed within 1 hour.⁴

ACUTE REVASCLARIZATION THERAPIES

Three categories of acute revascularization therapies are in clinical use: intravenous (IV) thrombolysis, intra-arterial thrombolysis, and mechanical revascularization. Intra-arterial thrombolysis and mechanical revascularization are accomplished by percutaneous catheter approach.

IV Thrombolysis

At present, only IV thrombolysis is approved by the U.S. Food and Drug Administration (FDA) for treatment of acute ischemic stroke. IV thrombolysis should be given to all eligible patients. **Table 1** summarizes the

appropriate indications and contraindications, as approved by the FDA, as well as warnings for conditions associated with unfavorable outcomes. Alteplase, a recombinant tissue plasminogen activator (tPA), is approved for treatment of ischemic stroke up to 3 hours from known onset of symptoms in a select population of adult patients. The major risk of IV thrombolysis is cerebral and systemic hemorrhagic complications. There are many contraindications to the treatment, all of which correlate to elevated risk of bleeding complications.⁵ A recent clinical trial has demonstrated efficacy of alteplase up to 4.5 hours from symptom onset in a more strictly selected group of patients.⁶ Thrombolysis using agents other than alteplase has been investigated. Although some of these agents have shown promising results, none are available in routine clinical care.

Intra-arterial Thrombolysis

Intra-arterial thrombolysis has the benefit of exposing the systemic circulation to a much smaller dose of a thrombolytic agent and therefore diminishing the rate of systemic bleeding complications, but at the expense of an increased rate of cerebral hemorrhage. Intra-arterial thrombolysis may be appropriate for patients who are unable to receive IV treatment due to systemic bleeding risks (eg, recent surgery) and may be effective in patients with a stroke duration of 6 hours or more. Use of CT- or MR-based angiographic and perfusion imaging may be helpful in selecting patients most likely to benefit. An ideal patient would be one with a small infarct core (which can be estimated by CT angiography source images or diffusion-weighted MR images) but a large area of perfusion impairment, indicating a large penumbra of tissue at ongoing risk for progressing to infarction.⁷⁻⁹

Mechanical Revascularization

Mechanical revascularization may incorporate any of several techniques, including mechanical disruption of the thrombus with the catheter or guide wire, thrombectomy with a device developed for that purpose, angioplasty of the vessel, and stent placement.¹⁰ Clinical trials and case series suggest that all of these techniques may be appropriate and improve outcomes in a carefully selected subset of acute stroke patients, but confirmation in further clinical trials is needed. Currently, the MERCI device has been approved by the FDA to extract a thrombus from an occluded intracranial artery.¹¹

INPATIENT MANAGEMENT OF ACUTE STROKE COMPLICATIONS

Blood Pressure and Induced Hypertension

Acute stroke triggers an intrinsic hypertensive re-

sponse that diminishes over the course of days.^{12,13} In patients with TIA and mild to moderate infarcts, blood pressure elevates, then returns to a stable baseline level 24 hours after admission. In patients with severe cerebral infarcts, blood pressure may remain elevated beyond 7 days poststroke.¹⁴ In the context of acute stroke, normal cerebral autoregulation in the affected area is impaired and the hypertensive response may facilitate improved perfusion to the ischemic penumbra. Aggressive antihypertensive treatment has been shown to worsen outcomes and may cause infarct progression.¹⁵ In practice, the hypertensive response is monitored and permitted up to a level of approximately 220 mm Hg systolic or 120 mm Hg diastolic. When required, blood pressure reduction should be targeted to a moderate 15% over the first 24 hours.^{15,16} Patients who have received thrombolysis are at significantly increased risk for intracerebral hemorrhage and require stricter control of blood pressure. Maintaining blood pressure below 185/110 mm Hg is recommended using labetalol, nitroglycerin paste, and sodium nitroprusside.

There is also some evidence for induced hypertension as a method of improving perfusion. As in the case of revascularization treatments, patients with a large infarct core to perfusion mismatch may benefit from techniques to facilitate perfusion. Animal models and human pilot studies have demonstrated improved perfusion and a trend toward improved outcomes in patients with arterial occlusions. The common approach is to apply a stepwise sequence of treatments of increasing intensity to achieve a systolic blood pressure of 160 mm Hg or a 20% increase over admission blood pressure. Initially, patients are given isotonic IV fluids for volume expansion. Midodrine and fludrocortisone may be useful, although the effect of each is relatively small and delayed. The α_1 -adrenergic agents phenylephrine and norepinephrine both have been used in pilot studies with reported success.^{17,18}

Oropharyngeal Dysfunction

Patients with stroke may have significant oropharyngeal dysfunction and therefore may be at high risk for aspiration. All patients should remain nil per os until their swallowing function is assessed. For patients with no evidence of oropharyngeal dysfunction on neurologic examination, a bedside swallowing test is sufficient. For any patient with evidence of impairment, a formal swallowing evaluation is indicated before allowing oral intake. Some patients require intubation. The efficacy of use of supplemental oxygen has not been proven other than to maintain oxygen saturation at 92% or above, although studies of hyperbaric oxygen and a recent pilot trial of 100% normobaric oxygen indicate

the potential for improved outcomes.¹⁹ Current recommendations are to use supplemental oxygen only as needed to treat hypoxia.³

Fever and Hypothermia

Fever has been associated with poor outcomes in stroke.²⁰ All patients with fever or other signs of infection should be fully evaluated for an infectious source. Fever should also be treated with antipyretic medications (eg, acetaminophen). Although animal studies support the prospect of hypothermia to treat acute stroke and benefit has been shown following global anoxia due to cardiac arrest, evidence is lacking for the use of cooling for acute stroke.²¹

Glycemic Control

Several studies indicate that hyperglycemia contributes to poor outcomes following acute stroke. The presence of hyperglycemia may be a stress response and marker of stroke severity, but persistent hyperglycemia exceeding 200 mg/dL in the first 24 hours after stroke independently predicts infarct expansion and poor neurologic outcomes.²² Numerous trials in the critical care literature have reported a lower incidence of complications in critically ill patients with well-controlled blood glucose levels. Treatment with insulin to avoid significant hyperglycemia is recommended.³

Hemorrhagic Transformation and Seizures

Hemorrhagic transformation occurs frequently with ischemic stroke. The rate of hemorrhagic transformation has been estimated at 5% using older CT imaging,²³ but more sensitive gradient echo MR studies have shown petechial hemorrhage to be much more common. The rate of hemorrhage reported in the placebo arm of a thrombolysis trial published in 2008 was 17.6% using CT or MRI.⁶ Thrombolysis increases the risk for cerebral hemorrhage, as does larger infarct volume. Antiplatelet and anticoagulant treatments are withheld in the context of new hemorrhage, and large volume hemorrhage should be considered for surgical evacuation. Significant hemorrhage increases the risk of seizures after stroke, which is otherwise uncommon. There is no role for prophylactic anticonvulsant medications in otherwise uncomplicated ischemic stroke.

Cerebral Edema

Cytotoxic edema is a consequence of cerebral infarction but is rarely a source of further neurologic compromise. Two groups of patients show particular risk—those with large infarcts comprising more than one third of a cerebral hemisphere and those with

cerebellar infarcts. Patients with large cerebral hemispheric strokes can experience significant swelling due to edema, possibly exacerbated by reperfusion injury. This occurs most frequently with middle cerebral artery (MCA) or internal carotid artery occlusions and is often referred to as a *malignant MCA stroke*. Increasing intracranial pressure (ICP) decreases cerebral perfusion pressure, leading to progressive infarction of at-risk hypoperfused tissue in the penumbra. When hemispheric swelling reaches a critical point, uncal herniation can occur. In large cerebellar strokes, swelling may lead to brainstem compression and obstructive hydrocephalus due to impingement of the cerebral aqueduct and fourth ventricle. There are few clinical predictors of deterioration due to cerebral or cerebellar edema in stroke other than the size of the infarct.

Significant edema can develop within 24 hours of stroke onset, with peak swelling occurring from 48 to 72 hours after onset. A standard approach is to observe the neurologic status of patients at risk for significant edema in a critical care setting while maintaining the serum sodium concentration in the high-normal range. If patients show radiographic or clinical warning signs of deterioration, hyperventilation and osmotic agents are used as temporizing measures to stabilize appropriate patients for surgical interventions.

Hyperventilation decreases cerebral blood volume by hypocapnia-induced vasoconstriction. Although it is effective in reducing ICP, the reduction in perfusion due to vasoconstriction may cause further infarction from decreased oxygen delivery, increased cerebral oxygen demand, and potentiation of seizure activity.²⁴ Osmotic agents (eg, hypertonic saline, mannitol) quickly reduce ICP but do not continue to be effective for a sufficient period of time to maintain ICP reduction for the duration of problematic swelling. A pooled analysis of 3 randomized controlled trials of decompressive craniectomy for patients with infarction of at least 50% of the MCA territory found a reduction in mortality and increased number of favorable functional outcomes.^{25,26} Likewise, favorable experience has been reported for ventriculostomy placement and for suboccipital craniotomy and evacuation in patients with large cerebellar strokes.²⁷

Mobilization and Rehabilitation

Immobilization following stroke is problematic. Patients hospitalized for stroke are at increased risk for developing deep venous thrombosis (DVT) and pulmonary embolism. In patients without contraindications, subcutaneous anticoagulants at prophylactic doses are used. Pneumatic compression devices are an accepted

Table 2. Risk Factors for First or Recurrent Stroke

Modifiable	Potentially modifiable
Cardiovascular disease	Metabolic syndrome
Coronary heart disease	Alcohol abuse
Congestive heart failure	Hyperhomocysteinemia
Peripheral arterial disease	Drug abuse
Hypertension	Hypercoagulability
Cigarette smoking	Oral contraceptive use
Diabetes mellitus	Periodontal disease
Carotid stenosis	<i>Chlamydia pneumoniae</i> infection
Vertebrobasilar disease	Cytomegalovirus infection
Intracranial arterial disease	<i>Helicobacter pylori</i> seropositivity
Arterial dissection	Acute respiratory or urinary tract infection
Acute myocardial infarction	Elevated biomarkers
Left atrial or ventricular thrombus	CD40 ligand
Valvular heart disease	Interleukin-18
Atrial fibrillation	High-sensitivity C-reactive protein
Patent foramen ovale	Migraine
Sickle cell disease	Elevated lipoprotein(a)
Dyslipidemia	Obstructive sleep apnea
Obesity	
Physical activity	Nonmodifiable
Postmenopausal hormone therapy	Age
	Race
	Sex
	Family history of stroke

Data from Goldstein LB, Adams R, Albers MJ, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:1583–633; and Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke* 2006;37:577–617.

alternative. Early mobilization helps prevent DVT and facilitates rehabilitation efforts. Good nutrition and prompt rehabilitation intervention improve functional outcomes. Consultation with physical, occupational, and speech rehabilitation services is indicated for all patients with new neurologic impairments. Many patients will benefit from ongoing rehabilitation after inpatient hospitalization and should be assessed for acute or sub-acute rehabilitation placement. Medical social workers

and case managers assist the family and medical team with this process.

Goals of Care

All management decisions should be consistent with the overall goals of the patient’s care. The goals of care are established in collaboration with the patient (or surrogate) and family to reflect the best possible outcome consistent with the realistic constraints of the patient’s condition and personal values. In certain cases, patients with profound and likely irreversible impairments or severe medical comorbidities will not be appropriate candidates for aggressive management measures. Palliative care services play a crucial role in circumstances in which patient comfort is of utmost concern.

FURTHER EVALUATION FOR CONTRIBUTORY CAUSES

Once a patient with acute stroke is admitted for management, further evaluation of contributory factors is undertaken to elucidate the mechanism of the stroke and explore risk factors for the sake of optimizing prevention (Table 2).^{28,29}

Neuroimaging

One of the first steps is completing important neuroimaging studies. MRI has become standard for most patients. Aside from being highly sensitive to infarction on diffusion-weighted images, T2 and fluid attenuation inversion recovery (FLAIR) images can reveal evidence of prior cerebrovascular insults, chronic ischemic changes, and microvascular ischemic patterns suggestive of vasculitis or a noninflammatory vasculopathy. CT or MR angiography is used to assess the patient’s extracranial and intracranial circulation for vascular diseases, the most common being atherosclerosis. Duplex ultrasonography is frequently used to assess the extracranial circulation and to characterize atheromatous lesions in the carotid artery. Transcranial Doppler ultrasonography yields information about flow dynamics for vessels comprising and near the circle of Willis.

Cardiac Evaluation

Transthoracic echocardiography (TTE) evaluates cardiac structure and function. Structural abnormalities and poor contractility can increase the risk of cardiogenic embolism. TTE is sufficient for the evaluation of most patients. Transesophageal echocardiography (TEE) is significantly more sensitive than TTE for detecting left atrial thrombi, left atrial spontaneous echo contrast, aortic atheromas, patent foramen ovale (PFO), and valvular strands. TEE can detect potentially significant cardiac sources of embolism in more than

50% of stroke patients without clinically overt heart disease.³⁰ Agitated saline contrast should be used in conjunction with TTE for all patients being evaluated for potential cardiac sources of embolism, and TEE should be performed in younger patients (age < 50 yr) with unexplained stroke.³⁰ Patients should also undergo cardiac rhythm monitoring to screen for arrhythmias that increase stroke risk (eg, atrial fibrillation). Both telemetry monitoring and Holter monitoring are commonly used. Cardiac conditions that pose increased risk for stroke are summarized in **Table 3**.

Assessment of Metabolically Associated Risks

In addition to general laboratory studies, several other tests are frequently obtained. Glycosylated hemoglobin A_{1c} (HbA_{1c}) and morning fasting glucose levels are used to screen for diabetes, and a lipid profile is obtained to assess for dyslipidemia. Lipoprotein(a) [Lp(a)] is attributed to have atherogenic and prothrombotic properties and has been associated with stroke based on these properties. There is considerable population variability in Lp(a) levels due to genetic variation in apolipoprotein(a).³¹ Testing for Lp(a) level is not routinely used in clinical practice as no specific treatment is available. Hyperhomocysteinemia has been associated with atherosclerotic vascular disease and an increased risk of stroke, but the benefit of treatment is controversial.³² Homocysteine level can be checked by a simple blood test.

Assessment for Coagulopathy

Patients with a history of clotting abnormalities or young patients with stroke should be assessed for hypercoagulability. Sickle cell disease, a hemoglobinopathy, is usually apparent in childhood and is a frequent cause of stroke in children. The abnormalities are apparent on a routine complete blood count and differential. Hypercoagulability can be the result of an inherited thrombophilia, a systemic inflammatory or autoimmune process, or cancer. Some aspects of the patient's coagulation profile may be perturbed in the context of acute stroke, requiring testing at a later time. The results of coagulopathy tests do not change the management of a substantial number of cases,³³ and diagnostic yield of coagulopathy testing is low in unselected patients. Therefore, testing should be pursued only in the context of high clinical suspicion, or when routine diagnostic evaluations are negative.^{34,35} Common coagulopathies and suggested testing strategies are summarized in **Table 4**.^{36,37} Investigations into other possible genetic coagulopathies such as fibrinogen polymorphisms, factor XIII gene, and platelet glycoprotein anomalies are ongoing, but these tests have

Table 3. Sources of Cerebral Emboli

High-risk sources	Low-risk sources
Left atrial thrombus	Mitral annular calcification
Left ventricular thrombus	Patent foramen ovale
Atrial fibrillation	Atrial septal aneurysm
Paroxysmal atrial fibrillation	Atrial septal aneurysm and patent foramen ovale
Sick sinus syndrome	Left ventricular aneurysm without thrombus
Sustained atrial flutter	Spontaneous left atrial echo contrast (smoke)
MI ≤ 1 mo prior	Pulmonary arteriovenous malformation
Rheumatic mitral or aortic valve disease	
Bioprosthetic or mechanical heart valves	Variable-risk sources
Chronic MI with ejection fraction < 28%	Hypercoagulable state
Symptomatic congestive heart failure with ejection fraction < 30%	Inherited thrombophilia
Dilated cardiomyopathy	Antiphospholipid antibodies
Nonbacterial thrombotic endocarditis	Cancer
Infective endocarditis	
Papillary fibroelastoma	
Left atrial myxoma	
Arterial dissection	

MI = myocardial infarction. (Data from Ay H, Furie KL, Singhal A, et al. An evidence-based causative classification system for acute ischemic stroke. *Ann Neurol* 2005;58:688–97; and Doufekias E, Segal AZ, Kizer JR. Cardiogenic and aortogenic brain embolism. *J Am Coll Cardiol* 2008;51:1049–59.)

not been established in clinical practice.^{38,39} Cancer induces a hypercoagulable state leading to nonbacterial thrombotic endocarditis and embolic stroke.^{40,41} In rare cases, acute stroke may bring a cancer patient to clinical attention, at which time an underlying neoplastic condition is identified.

Assessment for Vasculopathy

Patients with suspected vasculopathy (idiopathic, inflammatory, or vasospastic) may require 4-vessel catheter cerebral angiography if the findings on noninvasive imaging are equivocal. Detailed diagnostic criteria exist for these conditions. Some are based on single tests, such as hemoglobin electrophoresis for sickle cell disease and Notch3 gene testing for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Unless an obvious precipitant (eg, cocaine, subarachnoid hemorrhage [SAH]) or a clear syndrome (eg, moyamoya disease) is present, further testing may be required. Based on clinical suspicion, the laboratory panel could include erythrocyte sedimentation rate, C-reactive protein, complement levels, cryoglobulins, immune complexes, antibody screening (antinuclear antibody [ANA], anti-neutrophil cytoplasmic antibodies, rheumatoid factor,

Table 4. Hypercoagulability Testing

Coagulopathy	Testing Strategy
Hereditary coagulopathies	Test at least 2 mo poststroke, off warfarin for 2 wk and heparin for 24 hr. Use functional assay for ATIII, PC, and PS to screen, and confirm with quantitative test. Use aPTT-based assay to screen for APCR and confirm by factor V Leiden genotyping. Obtain G20210A genotyping for PGM. Consider repeating tests in 1 mo to confirm.
Antithrombin III (ATIII)	
Protein C (PC)	
Protein S (PS)	
Activated protein C resistance (APCR)	
Prothrombin gene mutation (PGM)	
Acquired coagulopathies	Test at least 2 months poststroke when there is no evidence of systemic inflammation or infection. Use ELISA for ACL antibodies and β_2 glycoprotein to screen, repeated in 1 mo to confirm. Evaluate for LA by aPTT, DRVVT, KCT, or TTI test and confirm with mixing tests and either HPP or PNT.
Anticardiolipin (ACL) antibodies	
Anti- β_2 glycoprotein antibodies	
Lupus anticoagulant (LA)	
Cancer	Relevant signs and symptoms

aPTT = activated partial thromboplastin time; DRVVT = dilute Russell viper venom test; ELISA = enzyme-linked immunosorbent assay; HPP = hexagonal phase phospholipid; KCT = Kaolin clotting time; PNT = platelet neutralization test; TTI = tissue thromboplastin inhibition. (Data from Bushnell CD, Goldstein LB. Diagnostic testing for coagulopathies in patients with ischemic stroke. *Stroke* 2000;31:3067–78; and Bushnell CD, Goldstein LB. Physician knowledge and practices in the evaluation of coagulopathies in stroke patients. *Stroke* 2002;33:948–53.)

anticardiolipin antibody), angiotensin-converting enzyme (ACE), and serum protein electrophoresis. Further specific or confirmatory testing may be required, such as immunofluorescence for specific ANAs in the case of a positive ANA enzyme-linked immunosorbent assay screen. Serum and cerebrospinal fluid microbial studies may be necessary to screen for infections such as syphilis, viral hepatitis, and herpesviruses. Finally, a biopsy of the leptomeninges, brain parenchyma, or other body site may be required for confirmation.^{42–44}

SECONDARY PREVENTION OF ISCHEMIC STROKE

RISK FACTOR MANAGEMENT

Many risk factors for ischemic stroke have been identified. The majority of known risk factors are closely associated with the risk of atherosclerotic vascular disease, hypercoagulability, or cardiac sources of embolism. Nonmodifiable risk factors include the increased risk of stroke associated with aging, a higher prevalence of stroke among African Americans and Native Americans

compared with other races, male sex, and a family history of stroke.⁴⁵

Some factors are modifiable by behavioral changes, medications, and surgically based interventions.^{28,29} Certain measures for secondary prevention of stroke are initiated during the inpatient stay and are adjusted in outpatient follow-up, and other treatments are pursued after the patient has undergone some rehabilitation. Attempts at lifestyle modification should be made for all patients with behaviorally associated risk factors (eg, cigarette smoking, obesity, dietary intake, and physical inactivity). Moderate alcohol consumption may have a mildly beneficial effect, but excessive consumption increases the risk of stroke.

Hypertension

Numerous clinical trials have documented a reduction in stroke from management of hypertension. Antihypertensive treatments are often implemented after 48 hours for permissive hypertension. The currently accepted treatment goal is blood pressure less than 120/80 mm Hg. Unless a patient has a prior history of heart disease, diabetes, kidney disease, or stroke, lifestyle changes alone are advocated for pressures up to 140/90 mm Hg. Beyond that, the choice of antihypertensive medication is less significant than the degree of blood pressure normalization, and certain medications may be indicated due to other medical comorbidities. In general, a diuretic alone or in combination with an ACE inhibitor is recommended.

Metabolic Risks

Near normal glycemic control improves outcomes for diabetic patients. The goal for HbA_{1c} is 7% or lower. Glycemic control with a goal of normoglycemia should continue indefinitely.

Patients with dyslipidemia (elevated low-density lipoprotein [LDL] or low level of high-density lipoprotein [HDL]) or atherosclerosis benefit from cholesterol-lowering medications. The recent SPARCL trial has demonstrated the benefit of intensive statin treatment after TIA or stroke, even in patients without known coronary heart disease.⁴⁶ Based on this and prior studies, statins are the preferred class of lipid-lowering medication and may have beneficial effects in patients with vascular disease beyond lowering cholesterol. Niacin is effective in raising HDL levels but is poorly tolerated in some patients. The treatment goal is an LDL level less than 100 mg/dL, or in the case of high-risk patients with multiple risk factors, an LDL level less than 70 mg/dL. In most patients, statin medication treatment is started or increased to more intensive dosing while the patient is in the hospital.

The treatment of hyperhomocysteinemia is controversial. Individual trials of vitamin supplementation to reduce homocysteine concentrations have shown minimal efficacy, although a recent meta-analysis of 8 randomized trials has found that folic acid supplementation reduces the risk of stroke by 18%.³² Treatment by supplementation of folate, vitamin B₆, and vitamin B₁₂ is inexpensive and reasonable.

Antithrombotic Medications

Antithrombotic therapy is a cornerstone in the treatment of ischemic stroke. The 2 fundamental approaches are antiplatelet agents and anticoagulants. The cumulative experience gained from many large-scale secondary prevention trials has clarified the indications for antithrombotic treatment for a variety of conditions, although considerable doubt still exists as to the “best” antiplatelet agent when cost, efficacy, and adverse effects are considered. Anticoagulation with warfarin for a target international normalized ratio (INR) range of 2 to 3 is recommended for patients with cardioembolic stroke risk due to atrial fibrillation, acute myocardial infarction with left ventricular thrombus, rheumatic mitral valve disease, or prosthetic heart valves. Use of concurrent antiplatelet treatment is limited to patients with ischemic coronary artery disease or patients who experience recurrent embolism while adequately treated with warfarin. Either warfarin or antiplatelet agents are suggested for patients with cardiomyopathy.⁴⁷ In practice, most patients with low ejection fraction ($\leq 35\%$) due to cardiomyopathy are treated with warfarin.

Antiplatelet treatment is preferred for patients with mitral annular calcification, mitral valve prolapse, aortic valve disease, or noncardioembolic stroke or TIA. The common, clinically available antiplatelet agents are aspirin, aspirin in combination with extended-release dipyridamole, and clopidogrel. Several trials testing these medications alone, in combination, and head-to-head have found small but potentially meaningful differences in beneficial and adverse outcomes. Based on those studies, the combination of aspirin and dipyridamole or clopidogrel monotherapy is suggested as the best treatment option.⁴⁷ Those treatment regimens failed to show a difference in efficacy in a recently completed major head-to-head trial, and they have both been shown to be slightly superior to aspirin alone.⁴⁷ The combination of aspirin and clopidogrel is not recommended in the absence of other compelling indications due to increased risk of bleeding complications without a significant benefit in secondary prevention.⁴⁷

The evidence for optimal treatment is less clearly established for particular causes of stroke for which many

large randomized controlled trials are not available. For patients with arterial dissection, either anticoagulation or antiplatelet treatment may be used, although antiplatelet agents are preferred beyond 6 months. Anticoagulation is often used for the first several months if the dissection is symptomatic, or even longer if recurrent ischemic events occur. Stenting is considered for patients refractory to medical management.^{29,48} The presence of a PFO alone is not an indication for anticoagulation. There are limited data with no completed randomized controlled trials on the efficacy of surgical or transcatheter PFO closure. PFO closure may be considered²⁹ in cases of recurrent cryptogenic stroke despite optimal medical therapy. If other coagulopathic risk factors are present, or there is an associated atrial septal aneurysm, anticoagulation may be considered. Some patients with inherited or inflammatory coagulopathy will require anticoagulation based on the occurrence of venous thrombosis or arterial occlusive disease in other organs. In patients without such compelling comorbidities, either antiplatelet or anticoagulant treatment is reasonable, but patients with recurrent thrombotic events usually require anticoagulation.³

Except for patients who have received thrombolysis, antiplatelet medications are started immediately upon presentation. Aspirin is recommended over clopidogrel in the acute phase. There is no clear evidence to support the use of emergent anticoagulation to prevent stroke worsening, and initiation of anticoagulation is generally delayed in patients with large volume strokes due to an elevated risk for hemorrhagic transformation.

TREATMENT OF VASCULOPATHY

A detailed discussion of the treatment of the vasculitides and rare vasculopathies is beyond the scope of this review. In general, once the diagnosis of an inflammatory vasculitis is confirmed, the condition is treated in 2 steps. First, an induction regimen is given to achieve initial control of the inflammatory process. Most commonly, a high dose of a corticosteroid is used, first intravenously followed by transition to an oral formulation, sometimes in conjunction with cyclophosphamide. The induction treatment is given for approximately 3 months. Next, the maintenance phase consists of a baseline immunosuppressive regimen. Steroid-sparing cytotoxic medications such as azathioprine and methotrexate are commonly used. In particular cases, IV immunoglobulin, plasmapheresis, and other immunomodulatory agents are effective.⁴²⁻⁴⁴ Many of the rare vasculopathies are difficult to treat. Treatment of progressive disorders typically consists of an antithrombotic medication and surgical approaches to revascularization.

SURGICAL INTERVENTIONS

Surgical interventions in stroke care consist of ventriculostomy placement and decompressive craniotomies to manage the effects of swelling in the context of acute stroke, acute revascularization techniques, vascular interventions for secondary prevention, and extracranial to intracranial neovascularization surgeries for progressive vasculopathies. Ventriculostomy placement and decompressive surgeries (for cerebral edema) and acute revascularization procedures were previously discussed.

Interventional options for secondary prevention of stroke include carotid endarterectomy (CEA) and percutaneous transluminal angioplasty and stenting (PCTA/S) of the carotid, vertebral, basilar, and intracranial arteries. The indication for these procedures is atherosclerosis in the vast majority of cases, although PCTA/S is also used for fibromuscular dysplasia (FMD) and a minority of arterial dissection cases. CEA has been in standard surgical practice for many years, and efficacy has been demonstrated in several large trials.^{49–52} Medically based secondary prevention has improved substantially since the time of these investigations, and it is unclear if the magnitude of benefit of surgery over best medical management would be as great in the context of current practice.

The technology and technique employed in carotid angioplasty and stenting (CAS) continue to evolve. Early clinical trials comparing CAS with CEA were limited by inclusion of inexperienced CAS operators or stent placement in a minority of patients undergoing angioplasty, or by CAS without the use of a distal embolism protection device.^{53–55} Some studies are ongoing, but difficulty in randomizing patients to CEA has slowed or stopped some attempts at a head-to-head comparison.⁵⁶ Five CAS studies were stopped early, and heterogeneous design makes overall interpretation difficult.⁵⁷

CEA is recommended for patients with a TIA or stroke ipsilateral to severe (70%–99%) carotid stenosis.²⁹ The benefit of CEA is less apparent for patients with moderate (50%–69%) stenosis. In such cases, CEA is more clearly indicated in the context of factors that predict greater benefit, such as age 75 years or older, male sex, and ischemic symptoms within the last 2 weeks. Regardless of whether the degree of stenosis is moderate or severe, patients who undergo surgery within 2 weeks experience better outcomes. Pending the outcome of further trials, CAS is currently recommended for patients with severe stenosis in whom the surgical approach is difficult or who pose significant surgical risk due to medical comorbidities.²⁹

Neovascularization procedures include direct anastomosis by creation of an extracranial to intracranial artery bypass, the most common being superficial temporal

artery to middle cerebral artery (STA-MCA) bypass or indirect bypass, such as encephaloduroarteriosynangiosis (EDAS), encephaloduromyosynangiosis (EDMS), or a combined encephaloduroarteriomyosynangiosis (EDAMS). For EDAS and EDMS, either an arteriovenous pedicle of the arterial tree of the superficial temporal artery (arteriosynangiosis) or the deep temporal artery-supplied temporalis muscle (myosynangiosis) is brought through the skull and placed as an onlay over the dura, usually over the MCA territory. It is thought that the ischemic milieu in the cerebral hemisphere releases factors promoting angiogenesis between the poorly perfused distal arterial tree of the cerebral arteries and the well-perfused superior temporal artery or temporalis tissue. Neovascularization procedures are well studied in moyamoya disease. In children with moyamoya disease, either direct or indirect techniques can be effective at preventing TIA and stroke, and the combination of STA-MCA bypass and EDAMS is frequently used.^{58–61} In adults, neovascularization following an indirect procedure has been found to be less robust and effective, and direct bypass is preferred.^{62,63}

CLINICAL VIGNETTES

In this section, cases are presented that apply the material on the pathophysiology, evaluation, and management of ischemic stroke covered in this 2-part review. The cases and questions highlight fundamental concepts and provide a means for deeper discussion of select topics.

QUESTIONS

Questions 1–5 refer to the following case.

A 47-year-old woman with a history of hypertension, smoking, and a TIA that occurred 2 years prior presents to the ED with difficulty speaking. She has taken an aspirin daily since her TIA and also takes lisinopril for blood pressure control. She has a long-standing prescription for sumatriptan tablets, which she takes as needed for migraine headaches. Her lipid profile at her last yearly checkup showed an LDL cholesterol level of 110 mg/dL and HDL level of 60 mg/dL. The patient reports that she experienced a typical migraine headache that morning. It started with the aura that precedes about half of her headaches in which she sees sparkles and distorted shapes for approximately 10 minutes. She took a sumatriptan tablet but still felt exhausted once the headache pain calmed. By her report, it is not unusual for her to feel tired after a headache and to take a nap to sleep off the residual nausea

and sensitivity to light. The patient notes that some time after the headache began to improve, she had a difficult time typing because her left hand felt “sloppy.” Her friend in the next cubicle at work told her she was slurring her words. The patient says that she thought these symptoms were due to her headache. She remembers that at the time of her TIA 2 years ago, the ED physician thought her symptoms of numbness on the right side of her body might have been due to a migraine as well. She waited for about an hour for the symptoms to pass, but they did not improve. She decided to seek medical care at the insistence of her supervisor.

- 1. Which statement regarding the patient’s medication regimen is least accurate?**
 - (A) Considering her other past medical history, use of a statin would have been recommended after her TIA
 - (B) Considering her past medical history, she should not have been taking sumatriptan
 - (C) While aspirin was an acceptable choice for initial therapy, there is evidence to recommend aspirin combined with dipyridamole over aspirin alone
 - (D) While aspirin was an acceptable choice for initial therapy, there is evidence to recommend aspirin combined with clopidogrel over aspirin alone
 - 2. MRI of the brain shows an ischemic stroke in the right internal capsule. Echocardiography demonstrates a PFO. What is the most likely pathologic mechanism based on the given information?**
 - (A) Cardioembolism
 - (B) Hypercoagulability
 - (C) Lipohyalinosis
 - (D) Migraine-induced
 - (E) Paradoxical embolization
 - 3. Reviewing the FLAIR images from this patient’s MRI, there is a substantial burden of white matter microvascular ischemic changes. Several chronic, small, subcortical lacunar-type lesions are seen. The patient is asked about her family history and reports that her father has had strokes and developed early dementia. What further testing would be most relevant for this patient based on this new information?**
 - (A) Factor V Leiden genotyping
 - (B) G20210A genotyping
 - (C) Hemoglobin electrophoresis
 - (D) Immunofluorescence for β 2-glycoprotein
 - (E) Mitochondrial DNA genotyping at base pair (bp) 3243
 - (F) Notch3 genotyping
 - 4. What feature of white matter disease is highly prevalent in CADASIL but rare in age-related change and other white matter diseases?**
 - (A) Corpus callosum involvement
 - (B) Extensive anterior temporal involvement
 - (C) Extensive parietal lobe involvement
 - (D) Extensive subcortical involvement
 - (E) Pontine involvement
- Questions 5 and 6 refer to the following case.**
- A 52-year-old man presents to the ED complaining of a 5-minute episode of left-sided numbness. He reports that yesterday he experienced a 10-minute episode of blindness in his right eye. He states that he has not been to a doctor in years but believes he is completely healthy. As stated, he has no significant past medical history. He is physically active, jogs twice a week, and recently started taking a yoga class. He does not smoke and drinks minimally on a social basis. He takes a daily multivitamin and no other medications. On review of systems, the patient notes that he has had a moderate-intensity, constant left-sided headache for the last 48 hours. He attributes the headache to a neck strain because the right side of his neck has been aching since his yoga class the day the headache started. On examination, the following abnormalities are noted: the left pupil is larger than the right pupil, and the left palpebral fissure is wider than the right. No bruits are present. Of note, his blood pressure is 175/112 mm Hg. CT angiography of the neck demonstrates a dissection of the right internal carotid artery extending from just above the carotid bulb to 1 cm below the petrous segment. The dissection is causing severe stenosis. In addition, a “string of beads” appearance is noted in portions of the left carotid artery and throughout the right carotid artery, but without hemodynamically significant stenosis in areas other than the dissection site.
- 5. Given the patient’s clinical presentation and imaging findings, what underlying anomaly is suspected?**
 - (A) Buerger’s disease
 - (B) Ehlers-Danlos type IV
 - (C) FMD
 - (D) Takayasu’s arteritis
 - 6. What is the preferred treatment option for this patient at this time?**
 - (A) CEA
 - (B) Clopidogrel 75 mg daily
 - (C) Heparin, transitioning to warfarin with a goal INR of 2 to 3

- (D) Percutaneous angioplasty and no antithrombotic treatment for at least 3 months
- (E) Percutaneous angioplasty with stent placement over the dissection with clopidogrel 75 mg daily

Questions 7–9 refer to the following case.

A 32-year-old woman is brought to the ED by ambulance for evaluation of suspected stroke. She is accompanied by her husband. An initial survey shows that her vital signs are stable and she is protecting her airway. She is in normal sinus rhythm. General physical examination is unremarkable. On neurologic examination, the following deficits are noted: aprosodic speech, a rightward gaze palsy overcome by oculocephalic maneuver, left lower facial droop, dense weakness of the left arm with mild left leg weakness, severely diminished sensation in the left face and body to all modalities, and left-sided neglect. Her NIHSS score is 11. The witnessed onset of this patient's deficits was at 3:15 pm. The husband reports that the patient has no known past medical history other than an uneventful pregnancy 2 years prior. He does note that she has had chronic complaints of lightheadedness as well as a few "spells" of numbness and clumsiness in the past. She takes no medications. After a focused evaluation, a noncontrast head CT is obtained. A small area of encephalomalacia is noted in a superficial area of the high frontal convexity, consistent with a chronic MCA-anterior cerebral artery (ACA) watershed infarct. Chemistry panel, complete blood count, PT, and PTT are all within normal limits. The time is now 6:30 pm.

7. At this point, what is the best management option for the patient?

- (A) Administer IV tPA
- (B) Administer a weight-based load of IV heparin and continue, titrating to a PTT of 60–80 sec
- (C) Administer aspirin 325 mg as chew and swallow
- (D) Obtain catheter angiography with intent to perform a thrombectomy if appropriate
- (E) Obtain CT or MR angiography and perfusion imaging

8. CT angiography and CT perfusion images are obtained. The CT angiography shows severe narrowing in the distal internal carotid arteries and proximal MCAs and ACAs bilaterally. The superior division of the right MCA terminates abruptly, consistent with a persistent occlusion. Abnormal microvascular enhancement is seen near the anterior portion of the circle of Willis bilaterally. The superficial temporal arteries are prominently visualized bilaterally.

This angiographic appearance could be consistent with all of the following conditions EXCEPT:

- (A) FMD
- (B) Moyamoya disease
- (C) Primary angiitis of the central nervous system (CNS)
- (D) Sickle cell disease
- (E) Wegener's granulomatosis

9. Assuming that this patient has moyamoya disease, which of the following is likely to offer the most benefit?

- (A) Antiplatelet treatment
- (B) EDAMS
- (C) Oral anticoagulation
- (D) Percutaneous transluminal angioplasty
- (E) STA-MCA bypass

ANSWERS

- 1. (D). While aspirin was an acceptable choice for initial therapy, there is evidence to recommend aspirin combined with clopidogrel over aspirin alone.** Based on her medical history with hypertension, smoking, and a likely TIA 2 years ago as risk factors, treatment with a statin for a goal LDL level below 100 mg/dL would be recommended. Treatment of patients with stroke risk factors but no known coronary heart disease was recently evaluated in the SPARCL trial, which demonstrated efficacy in preventing both stroke and cardiac events.⁴⁶ Use of triptans is contraindicated in patients with a history of ischemic cardiac, cerebrovascular, or peripheral vascular disease as well as in patients with basilar or hemiplegic migraine. The product label for sumatriptan includes TIA as a cerebrovascular ischemic condition. While the combination of dipyridamole and aspirin is supported over aspirin alone in clinical trials, the combination of clopidogrel and aspirin increases the risk of hemorrhage and is not recommended unless another specific indication is present.^{64–68}
- 2. (C) Lipohyalinosis.** Lacunar infarcts, caused by thrombosis of small penetrating vessels, are typically less than 2 cm in diameter. Pathology of these vessels demonstrates lipohyalinosis and/or microatheromatosis, which is strongly associated with hypertension.⁶⁹ The presence of a PFO raises the possibility of paradoxical embolization. A number of studies have asserted a possible association between PFO and migraine, but a large epidemiologic study published recently does not support this association.⁷⁰ Both PFO and migraine are common in the baseline population. This patient requires further evaluation

before a conclusive determination of the etiology of her stroke can be made. PFO is present in 15% to 25% of the population, and its presence alone is not compelling evidence for an embolic stroke process. Given the patient's history of hypertension and smoking and the lacunar syndrome presentation, small vessel thrombosis is more likely than embolization.

3. **(F) Notch3 genotyping.** The syndrome of early dementia, leukoariosis, migraine headaches, and subcortical strokes is highly suggestive of CADASIL. Lacunar infarct syndromes occur commonly in patients with CADASIL, and migraine is present in one third of affected individuals.⁷¹ Patients with migraine can also show some nonspecific deep white matter T2 hyperintensities, but migraine alone would not cause substantial leukoariosis. G20210A and factor V Leiden genotyping is used to test for prothrombin gene mutation and activated protein C resistance, respectively. Both are causes of hypercoagulability. This patient has given no other history of thrombophilia to suggest a coagulopathy, and as noted, the presence of PFO alone is not strongly suggestive of paradoxical embolism. Mitochondrial DNA genotyping can be used to test for mitochondrial encephalomyopathy lactic acidosis and stroke-like (MELAS) episodes; approximately 80% of cases are caused by a mutation at bp 3243.⁷² MELAS episodes include early dementia and stroke-like episodes with a high prevalence of migraine, but the age of onset is typically under 20 years, and myopathy should be present. Hemoglobin electrophoresis would be useful in evaluating for sickle cell disease, and β 2-glycoprotein is a factor in the pathogenesis of antiphospholipid antibody syndrome.

Patients with CADASIL frequently accumulate leukoariosis in the periventricular white matter. Patchy or confluent leukoariosis can be seen as T2/FLAIR hyperintensity in many types of microvascular ischemic pathologies. In the general population, white matter changes are seen most commonly in the context of hypertension and diabetes in conjunction with aging.

4. **(B) Extensive anterior temporal involvement.** The pons is a common location for age-related white matter disease. Extensive parietal lobe involvement is not common in CADASIL but can be seen in age-related change as well as over 93% of cases of progressive multifocal leukoencephalopathy (PML).⁷³ Corpus callosum and subcortical involvement is seen frequently in CADASIL but can be present in a variety of other conditions including multiple sclerosis, vasculitis,

and PML. Extensive anterior temporal involvement is present in the vast majority of CADASIL cases but is rare in age-related white matter disease and other adult diseases of the white matter.⁷⁴

5. **(C) FMD.** The finding of a string of beads appearance on angiography of the carotid arteries and the incidence of a carotid dissection raises suspicion for FMD.⁴⁸ Ehlers-Danlos type IV can lead to carotid dissection but is unlikely to produce an irregular vascular hyperplasia leading to a string of beads appearance. Patients with Takayasu's arteritis can show a similar angiographic appearance and experience the same ischemic symptoms, but actively affected patients are usually younger and have peripheral claudication, malaise, and other systemic inflammatory symptoms.⁴⁴
6. **(C) Heparin, transitioning to warfarin with a goal INR of 2 to 3.** High-quality data establishing the efficacy of various treatments used in patients with carotid dissection are limited, although substantial consensus exists for some important points. The relevant points to consider in making decisions about the management of patients with carotid dissection are: (1) Does the dissection involve the intracranial portion of the carotid artery? (2) Has the patient experienced ischemic symptoms? and (3) Has the patient experienced ischemic symptoms despite adequate antithrombotic therapy? There is little evidence to demonstrate better efficacy of anticoagulation versus antiplatelet therapy in this population. For patients with ischemic symptoms, most expert reviews suggest anticoagulation for the first 3 to 6 months followed by antiplatelet therapy. In patients without ischemic symptoms, antiplatelet treatment may be reasonable as the initial starting therapy.³

Internal carotid artery dissections that extend to the intracranial segments require special consideration. Subintimal dissection can lead to a false lumen, but hemorrhage is still contained within the vessel itself. Subadventitial dissection may allow some blood to escape the vessel. In the cervical segment, this leakage is contained by a hematoma that quickly forms. In the intracranial segments, subadventitial dissection can lead to SAH. For that reason, anticoagulation is generally considered to be contraindicated, and antiplatelet agents are used with caution.⁷⁵ Open surgical repair and percutaneous interventions are reserved for patients who have experienced ischemic symptoms despite adequate antithrombotic treatment.⁷⁶ Percutaneous angioplasty is also a useful treatment for patients with stenosis due to FMD alone.⁴⁸ In this patient,

stenosis is only reported at the site of dissection, and the vast majority of carotid dissections heal well with conservative medical management. Angioplasty is a reasonable consideration if hemodynamically significant stenosis persists after a reasonable period of medical management (at least 6 mo).

7. **(E) Obtain CT or MR angiography and perfusion imaging.** This question is challenging in the face of newly emerging data and rapidly evolving approaches to nonstandard care. Based on current FDA approval, tPA is not indicated for treatment of ischemic stroke beyond 3 hours from onset. However, a large randomized trial has recently been published demonstrating efficacy for treating ischemic stroke in select patients treated between 3 and 4.5 hours from onset.⁷⁷ This patient meets the selection criteria used in that trial. A meta-analysis of several other thrombolysis trials including similar patients during that timeframe found a similar magnitude of benefit.⁷⁸ At present, neither the FDA nor the organizations responsible for consensus guidelines for stroke treatment have endorsed the use of tPA beyond 3 hours. Heparin has not been found to prevent worsening or improve outcomes when given in the acute phase, although the practice was common in the past and may still have a role in carefully selected individuals with particular conditions that place them at high risk for embolism, such as intracardiac thrombus. The administration of aspirin in the acute setting is recommended for most patients. Data on the acute use of clopidogrel and dipyridamole is lacking.³

Several trials are ongoing to evaluate the role of endovascular treatments in acute stroke. The MERCI device is approved for extraction of intra-arterial thrombi, but the benefit of thrombectomy on long-term outcomes is not established.³ Angiographic and perfusion imaging have become established as important tools in the selection of patients likely to benefit from endovascular intervention.⁷⁹ Angiography can identify occluded proximal arteries amenable to catheter-based treatment. Perfusion imaging, especially in conjunction with CT angiography source image or diffusion-weighted imaging estimates of infarct core, can identify cases with a significant volume of salvageable tissue at risk due to persistently diminished perfusion. While MR and CT perfusion techniques identify relative and absolute abnormalities in brain perfusion, the critical thresholds that discriminate between irreversible infarct core, penumbra, and benign oligemia have not been accurately established.⁸⁰ At present, there is no definitive best answer to this question, except

to note that endovascular intervention has become an accepted alternative for individuals with ischemic stroke beyond 3 hours of onset, and the selection of appropriate candidates by CT or MR angiography and perfusion imaging findings is preferred.

8. **(E) Wegener's granulomatosis.** The angiographic findings described here are highly suggestive of moyamoya disease. Large vessel vasculopathy with proximal collateralization by small vessels is also seen in sickle cell disease, primary angiitis of the CNS, and FMD. Intracranial angiography in those conditions may be indistinguishable from moyamoya disease. Patients with FMD will usually show extracranial manifestations, and sickle cell disease is readily diagnosed by other findings. Although a moyamoya pattern is uncommon in primary angiitis of the CNS, most patients also show signs of microvascular disease and inflammatory histology on brain biopsy. The pathology of Wegener's granulomatosis is limited to small vessels, and a moyamoya pattern of vasculopathy has not been reported.
9. **(E) STA-MCA bypass.** Although TIA and ischemic stroke are the most common manifestations of moyamoya disease in children, intracranial hemorrhage is the most common feature in adults. The hemorrhage is attributed to rupture of the friable small collateral vessels that form as a consequence of disease progression. Oral anticoagulation is unduly risky. Antiplatelet treatment may reduce the risk of ischemic symptoms in the short term but significantly increase the risk of hemorrhage. Furthermore, medical management does not slow the progression of the vasculopathy. Although there are case reports of the use of angioplasty in early moyamoya disease, this patient's condition is too advanced for such a procedure to be an effective long-term treatment strategy. STA-MCA bypass and EDAMS indirect bypass are both used to treat moyamoya disease by revascularizing the distal arterial tree of the MCA and ACA territories. Although both procedures appear to be effective in children, experience has shown that STA-MCA bypass is preferred in adults.^{62,63}

SUMMARY

Proper evaluation and management of patients with stroke is a major concern given the high burden of this condition on public health. In the acute phase, management begins with a rapid diagnostic survey to facilitate delivery of time-sensitive treatments, such

as thrombolysis. Further management explores the patient's underlying risk factors through select laboratory, cardiac, and radiographic studies. At the same time, complications such as swallowing dysfunction and cerebral edema are monitored and treated, and the patient is engaged early in a suitable rehabilitation program using a multidisciplinary approach. Finally, prevention of further ischemic events is accomplished by modification of risk factors. A growing body of clinical research continues to clarify and expand the array of available stroke therapies, requiring care providers to continuously refresh their knowledge base to ensure optimal care for their patients.

BOARD REVIEW QUESTIONS

Test your knowledge of this topic. Go to www.turner-white.com and select Neurology from the drop-down menu of specialties.

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