CME ARTICLE

Ischemic Stroke: Acute Management and Secondary Prevention

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AUDIENCE
This article is intended for all clinicians caring for patients who have had an ischemic stroke.

GOAL
To review advances in the management and treatment of ischemic stroke, focusing on acute treatment, diagnostic workup, and secondary prevention.

OBJECTIVES
1. Describe the initial management of ischemic stroke.
2. Review current recommendations for the use of thrombolytic therapy in ischemic stroke.
3. Discuss strategies for preventing recurrent stroke.

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Stroke is the third leading cause of death in the United States.[1] Each year in the United States, approximately 700,000 people have an acute stroke; one third of these are fatal and the remainder often produce significant morbidity. Stroke also has considerable economic consequences, with an estimated combined direct and indirect cost of $39 billion in the United States in 1996.[2] Most strokes (85%) are ischemic and originate from a thromboembolic source.[3] Over the past decade, significant advances in the management of ischemic stroke have provided an opportunity to prevent stroke, improve outcome, and impact costs. In this article, we review the diagnosis and management of ischemic stroke, focusing on recent developments in acute treatment and secondary prevention.

··· ETIOLOGY ···

Ischemic stroke commonly results from 1 of 2 mechanisms, either an embolic occlusion or a thrombosis that originates at an atherosclerotic plaque within the arterial intracerebral circulation. In general, intracerebral thrombosis involving either large- or small-vessel disease accounts for approximately two thirds of ischemic stroke and embolic events account for the remaining one third.[4] The heart is the most frequent source of emboli in patients with atrial fibrillation, valvular heart disease, or dilated cardiomyopathy. Alternatively, emboli can originate from arterial plaques in the aorta, carotid or basilar arteries, or rarely the venous circulation. Other causes of ischemic stroke, although uncommon, include vasculitis, syphilis, endocarditis, and venous thrombosis from hypercoagulable states such as proteins C or S deficiency, antithrombin III deficiency, factor V Leiden mutation, factor II mutation, or antiphospholipid syndrome.

··· CLINICAL PRESENTATION ···

The hallmark of ischemic stroke is the manifestation of focal neurologic deficits, the nature of which depends on the site of the cerebrovascular occlusion. Although the brain has anterior-posterior collateral circulation via the circle of Willis, the carotid or anterior cerebral circulation primarily supplies the optic nerve and the frontal, temporal, and parietal lobes. Consequently, stroke in the anterior distribution can cause monocular blindness, hemianopsia, gaze preference, expressive or receptive aphasia, unilateral weakness or hemiparesis, unilateral sensory deficits, or, rarely, decreased level of consciousness.[5] Occlusion in the basilar artery or posterior system, which primarily supplies the occipital lobe, the brainstem, and the cerebellum, can produce unilateral or bilateral weakness, complete hemianopsia or cortical blindness, diplopia, dysarthria, ataxia, dysphagia, vertigo, or sensory deficits. Coma can occur with large posterior infarcts. As shown in Table 1, the differential diagnosis of ischemic stroke is extensive. However, a careful history, physical examination, screening laboratory tests, and imaging studies can often quickly narrow the diagnosis.

··· EVALUATION ···

The major goals of the initial evaluation of suspected stroke are to determine the extent of the neurologic deficit, to classify the event as hemorrhagic or ischemic, and to determine the optimal immediate therapy. Because current treatment options are often time-dependent, patients with suspected ischemic stroke should be transported immediately to an emergency room for evaluation and stabilization. Unfortunately, the public is poorly informed regarding the symptoms of stroke and people often delay seeking medical attention.[6-8] Campaigns are under way to improve the public's knowledge of and response to stroke symptoms.[9,10]

The initial history should focus on the time of onset of neurologic symptoms, risk factors for stroke (Table 2), medications, bleeding risks, and presence of heart disease. A neurologic examination using the National Institutes of Health[11] or other stroke scale can help determine the extent of the neurologic deficit and the patient's eligibility for thrombolytic treatment. Additionally, a focused cardiopulmonary examination should be performed to assess for hemodynamic stability, left ventricular dysfunction, arrhythmia, valvular disease, and the presence of carotid bruit.

A noncontrast computed tomographic (CT) scan of the head is the imaging modality of choice in the initial evaluation of suspected ischemic stroke. The purpose of the initial CT scan is typically not to diagnose the ischemic lesion but rather to exclude other causes of focal acute neurologic deficit, such as hemorrhage, abscess, or tumor. Compared with magnetic resonance imaging, CT is more sensitive in detecting intracranial blood, can be more rapidly and less expensively performed, and is more readily available. Computed tomographic scans can detect nearly all intracerebral blood and 95% to 98% of all acute subarachnoid hemorrhage. CT scans cannot usually delineate new ischemic infarcts within the first 24 hours of symptom onset, however, unless the

Table 1. Differential Diagnosis of Ischemic Stroke*

Clinical Entities with Focal Deficits	
Ischemic stroke	
Intracerebral or cerebellar hemorrhage	
Subarachnoid hemorrhage	
Subdural or epidural hematoma	
Brain abscess or tumor	
Bell's palsy	
Seizure with or without Todd's paralysis	
Multiple sclerosis	
Peripheral vestibular disease	
Hypertensive encephalopathy	
Temporal arteritis	
Aortic dissection	
Clinical Entities without Focal Deficits	
Electrolyte disturbances:	Hyper- or hyponatremia
	Hypercalcemia
Metabolic abnormalities:	Hyper- or hypoglycemia
	Hypercapnia
	Hypoxemia
	Hepatic failure
	Renal failure
Drug intoxication	
Seizure	
Central nervous system infection	
Hypertensive encephalopathy	
Generalized cerebral ischemia resulting from profound shock	
Bilateral chronic subdural hematoma	
Subarachnoid hemorrhage	

*Ordered from most to least common.

stroke is large and accompanied by cerebral edema or mass effect. Magnetic resonance imaging is superior to CT for detecting posterior fossa pathology and can be performed if these conditions are suspected and the initial noncontrast head CT scan is unrevealing.[12] Emerging techniques in neuroimaging will enable clinicians to identify zones of infarction acutely as well as clearly delineate the penumbra or region of ischemic tissue surrounding the core of the infarction. Magnetic resonance perfusion/diffusion techniques, single photon emission computed tomography (SPECT) scanning, and xenon CT can detect potentially viable peri-infarct ischemia, but their utility, cost effectiveness, and overall role in the initial evaluation of stroke await clinical trials and the results of studies with emerging therapies directed at neuron salvage.[13]

As outlined in Table 3, additional studies in the initial evaluation of stroke are geared toward determining the cause of the stroke, any contraindications to thrombolytic therapy, and the presence of other comorbid conditions. These tests should be performed concurrently with the initial clinical evaluation and CT imaging.

Table 2. Established Risk Factors for Ischemic Stroke

Prior stroke or transient ischemic attack
Hypertension
Cigarette or cigar smoking
Heart disease
Coronary artery disease
Congestive heart failure
Atrial fibrillation
Valvular disease
Diabetes
Hypercoagulable states
Older age
Male sex
African American or Hispanic race

Table 3. Initial Workup of Suspected Acute Ischemic Stroke

- History and physical examination, including temperature and blood pressure
- Noncontrast head computed tomographic scan
- Twelve-lead electrocardiogram to screen for acute coronary syndromes, atrial fibrillation, and heart disease
- Electrolytes, glucose, and creatinine to detect other causes of central nervous system deficits and identify exclusion criteria for thrombolytics
- Complete blood count, prothrombin time, partial thromboplastin time, and platelets to screen for a bleeding diathesis
- Chest x-ray film to assess for cardiopulmonary disease
- Pregnancy and toxicology screen when clinically appropriate

··· INITIAL MANAGEMENT ···

During the initial evaluation, the patient should receive general care to maintain the airway, support breathing with supplemental oxygen, and monitor circulation. If the initial workup reveals an acute ischemic stroke, appropriate treatment requires a thorough appreciation of the available therapeutic options.

Thrombolytic Therapy

The efficacy of thrombolytic therapy for acute ischemic stroke was demonstrated in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, a controlled trial of 624 patients with ischemic stroke randomly assigned to treatment with either tissue plasminogen activator (t-PA) at a dose of 0.9 mg/kg or placebo within 3 hours of symptom onset. The patients treated with t-PA were 30% more likely to have little or no neurologic deficit compared with those given placebo at 3 and 12 months of follow-up.[14,15] The thrombolytic drug was effective in all ischemic stroke subtypes, and mortality was similar in both groups at 3 months (17% for t-PA versus 21% for placebo). Patients receiving t-PA, however, experienced a significant 10-fold increase in intracranial hemorrhage compared with the control patients (6.6 % versus 0.6%). Hemorrhagic risk was greater in patients who had a higher National Institutes of Health stroke scale score, signs of acute ischemia on the initial CT scan, or evidence of diabetes or hyperglycemia.[16,17] In the NINDS trial, thrombolytic therapy lowered the costs of treatment by decreasing the length of hospital-

ization and reducing the need for nursing home placement.[18] The success of the NINDS trial is due in part to the stringent eligibility criteria used to enroll patients (Table 4). Indeed, fewer than 5 % of evaluated patients met these criteria.

Other studies have not demonstrated a clinical benefit with thrombolytic therapy. The European Cooperative Acute Stroke Study, a randomized, double-blind, placebo-controlled trial, found that patients with acute ischemic stroke treated within 6 hours of symptom onset with t-PA at a dose of 1.1 mg/kg did not have improved neurologic outcome at 3 months compared with control patients.[19] Furthermore, patients treated with t-PA had significantly higher mortality at 3 months (22.4% versus 15.8%) and a greater frequency of large cerebral hemorrhage (19.8% versus 6.5%). The European Cooperative Acute Stroke Study 2, a follow-up trial using a lower dose of t-PA (0.9 mg/kg) given within 6 hours of stroke onset, also showed no improvement in functional outcome at 3 months.[20] Studies examining the efficacy of streptokinase in acute ischemic stroke were halted early when preliminary analyses revealed significantly higher mortality in patients treated with this thrombolytic drug.[21-23] Different times to treatment, CT interpretation standards, and the specific type or dose of thrombolytic agent used likely account for the outcome disparities of these studies and stress the importance of strict eligibility standards. Future study of thrombolytics should focus on clarifying these issues and identifying which patient subpopulations would benefit most from this intervention.[24]

After reviewing the trials on thrombolytics in acute ischemic stroke, the Stroke Council of the American Heart Association and the Food and Drug Administration recommended thrombolytic therapy for patients with acute ischemic stroke who met the eligibility criteria outlined in the NINDS trial.[25] Given the potential risks of thrombolytics, the CT scan should be interpreted by a neuroradiologist and

Table 4. Indications, Contraindications, and Dosing for Thrombolytic Drugs

Indications (all criteria must be met)
Clinical diagnosis of ischemic stroke with a focal deficit
Symptom onset less than 3 h before treatment is started
Age 18 y or older
Contraindications
Intracranial hemorrhage or evidence of large infarction on head computed tomographic scanElevated partial thromboplastin time
Rapidly improving stroke symptoms
Persistent hypertension refractory to initial treatment (systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mm Hg)
Seizure with onset of stroke
Internal bleeding within previous 21 d
Recent acute myocardial infarction
Neurosurgery, major head trauma, or stroke within previous 3 mo
Surgery or biopsy of parenchymal organ within previous 14 d
Lumbar puncture within previous 24 h
History of central nervous system bleeding, arteriovenous malformation, or aneurysm
Warfarin use or coagulopathy with international normalized ratio (INR) > 1.3
Recent arterial puncture
Subarachnoid hemorrhage strongly suspected despite normal head computed tomographic scan
Pregnancy or parturition within previous 30 d
Suspected septic embolus
Platelet count < 100,000µL
Hematocrit < 25%
Elevated partial thromboplastin time
Glucose < 50 or > 400 mg/dL
Dosing
0.9 mg/kg as a 10% bolus over 2 minutes with the remainder infused over 60 minutes, not to exceed a total dose of 90 mg

t-PA administered under the direction of a neurologist.[26] Although chronic aspirin therapy is not a contraindication to the use of thrombolytics, the initial treatment of ischemic stroke with aspirin should be delayed 24 hours in patients receiving thrombolytic therapy. Heparin should not be used in patients receiving thrombolytics. All patients receiving t-PA should be monitored initially in an intensive care unit or stroke unit and their blood pressure should be meticulously controlled. If significant neurologic deterioration occurs during thrombolytic treatment, the thrombolytic infusion should be promptly discontinued and an emergent head CT scan performed to detect intracranial hemorrhage. Blood should be sent for a platelet count, fibrinogen level, and prothrombin and partial thromboplastin time. Fresh frozen plasma and platelets should be given to correct any coagulation abnormality and a neurosurgeon consulted if a hemorrhage amenable to surgical evacuation is identified.[25]

Aspirin

Two large, randomized, placebo-controlled trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), evaluated the efficacy of aspirin given within 48 hours of stroke onset.[27,28] Taken together, these trials demonstrated that aspirin at doses of 160 to 300 mg administered acutely during ischemic stroke prevents, over the ensuing several weeks, 10 deaths or recurrent strokes per 1000 patients treated. These findings are supported by the results of the Multicenter Acute Stroke Trial, which demonstrated a trend toward decreased mortality and recurrent stroke when aspirin was given within 6 hours of initial symptom onset.[22]

Heparin

Although the use of heparin in acute stroke has been a subject of controversy, 2 trials have helped clarify its role in acute ischemic stroke. The International Stroke Trial demonstrated that patients treated with unfractionated heparin at doses of 5000 or 12,500 units subcutaneously twice per day had fewer ischemic but more hemorrhagic strokes at 14 days and therefore received no benefit from heparin compared with placebo.[27] After 6 months of follow-up, there were no significant differences in functional status or death rates between treatment and placebo groups. The Trial of ORG 10172 in Acute Stroke Treatment, a randomized double-blind study that compared the intravenous low-molecular-weight heparinoid danaparoid with placebo, revealed no treatment differences in stroke prevention or clinical outcome at 3 months.[29] In view of these studies, neither low-molecular-weight heparin nor unfractionated heparin should be used routinely in ischemic stroke.

Although heparin should not be used routinely in ischemic stroke, its use is often advocated in the special settings of cardioembolic stroke, ischemic stroke in evolution, and posterior circulation ischemia. Although substantial evidence supports chronic anticoagulation to prevent stroke in atrial fibrillation[30] and to a lesser extent in severe cardiomyopathy after anterior myocardial infarction,[31] the practice of acutely heparinizing cardioembolic stroke has no proven outcome advantage and in fact may increase hemorrhagic conversion and perhaps morbidity. Consequently, to balance the benefit of secondary prevention from chronic anticoagulation against the risk of hemorrhagic conversion, an observation period of 72 hours followed by a repeat head CT scan is prudent before initiating therapeutic anticoagulation for cardioembolic stroke.[32] The efficacy of heparin for stroke in evolution has not been studied in randomized controlled trials, although several small observational studies of heparin in this setting have revealed high rates of stroke progression despite intravenous heparin therapy.[33,34] Finally, there are few data from randomized trials supporting the use of heparin in posterior ischemic stroke. In the International Stroke Trial, patients with posterior strokes who received heparin tended to have worse outcomes than did control patients.[27] We recommend consulting a neurologist before using heparin therapy in these settings.

Management of Hypertension

Blood pressure is often elevated in ischemic stroke but in general should not be acutely lowered because of the risk of inducing hypoperfusion and extending the infarct. Blood pressure often returns to pre-stroke levels with 3 to 4 days. In most cases, patients already maintained on antihypertensive medication should continue their therapy during the peri-stroke period. Patients with extreme elevations of blood pressure (systolic blood pressure > 230 mm Hg or diastolic blood pressure > 130 mm Hg) should undergo gradual reduction of blood pressure. The exceptions to this strategy that warrant more aggressive blood pressure management occur when ischemic stroke is accompanied by use of thrombolytics, myocardial infarction, severe congestive heart failure, or aortic dissection.[25,35] Controversy exists over the optimal medication for

the acute treatment of hypertension when emergent therapy is needed. Labetalol is fairly short-acting, easy to administer, and does not cause central nervous system arterial or venous dilation that can increase intracranial pressure. Nitroprusside is a potent vasodilator, easy to titrate, and effectively controls high blood pressure. This drug should be reserved for refractory hypertension, however, because it can cause intracranial hypertension.[36]

Stroke Units

Stroke units provide coordinated and specialized care for stroke patients by using pathways for diagnosis, treatment, complication prevention, and rehabilitation.[37] This hospital-based system typically consists of a multidisciplinary team of neurologists, nurses, social workers, and physical, occupational, and speech therapists. Stroke units improve short and long-term survival, functional outcome, and quality of life compared with general medical ward care.[38-40] Most of these benefits are imparted regardless of patient age or stroke severity. Consequently, stroke units are cost effective[41] and should be organized if the resources are available.

··· DEVELOPING THERAPIES ···

Glucose Control

Among diabetic and nondiabetic patients, hyperglycemia during an acute ischemic stroke has been associated with a poor prognosis in most but not all studies.[42,43] Reperfusion treatment and the subtype of stroke (lacunar versus nonlacunar) may alter the effects of hyperglycemia.[17] The appropriate standard of care (ie, "tight" versus routine glucose control) awaits the results of ongoing randomized trials evaluating the efficacy of glucose control during acute stroke.[44]

Fever

Prospective studies have revealed that patients in whom fever develops within 7 days of an acute stroke have a worse outcome during the first few months of follow-up than do those who do not develop a fever.[45,46] Although definitive results of interventional trials to treat fever in stroke are currently lacking, empiric antipyretic therapy with acetaminophen is inexpensive, safe, and based on biologically sound theory.[47]

Specific Neuroprotective Therapy

Many neuroprotective therapies have been shown to decrease infarct size in animal stroke models. The efficacy of most of these agents, however, has not been confirmed in human studies. Currently, trials are ongoing to evaluate a wide variety of potential neuroprotective treatments, such as antioxidants, cytoprotective agents, and calcium channel antagonists.[24,48]

··· PROGNOSIS ···

The course and recovery after acute ischemic stroke is quite variable. Up to one third of patients with an acute ischemic stroke ultimately die from the stroke, but approximately 50% of those who survive regain complete independence in their activities of daily living. Although the eventual outcome depends on a heterogeneous collection of factors, many of the most significant determinants can be assessed early in the presentation. In the most rigorous trials, early predictors of a poor prognosis include older age, previous stroke, depressed level of consciousness, disorientation to place and time, low activities of daily living score, extent and density of paralysis, urinary incontinence, poor sitting balance, and lack of social support.[49] Formal stroke scales can be used to independently predict outcome, although no specific stroke scale is clearly superior in this regard.[50]

··· SECONDARY PREVENTION ···

After the acute care of ischemic stroke, the focus turns toward optimizing function and preventing recurrent stroke. Early rehabilitative efforts are important because functional improvement after stroke occurs primarily within the first few months.[51] For secondary prevention, patients can generally benefit from many different therapies. The efficacy of some treatments, however, depends on the cause of the stroke. Consequently, a workup to determine the underlying etiology is necessary, especially if the course of therapy may be altered. Clinicians should also remember that stroke patients are at equally high risk of cardiac disease, which should be appropriately managed.

Carotid Disease

Approximately 15% of ischemic strokes are caused by emboli originating from the extracranial carotid arteries.[4] After an ischemic stroke or transient ischemic attack caused by a carotid embolus, the degree of carotid stenosis is a reasonable predictor of the risk for recurrent stroke. Thus in patients

with a nondisabling stroke or transient ischemic attack in the carotid distribution that does not originate from a suspected cardiac source, duplex ultrasonography is indicated to assess the degree of stenosis. In well-trained hands, this test is 90% to 95% sensitive for detecting significant carotid stenosis.[52] Based on randomized, controlled trials, in patients with 70% or greater (severe) stenosis without complete occlusion, carotid endarterectomy (CEA) provides an absolute 10% to 15% decrease and a relative 50% decrease in the risk of recurrent ipsilateral stroke at 2 years follow-up.[53-55] For those with moderate stenosis (50% to 69%), CEA provides a much more modest reduction in the risk of ipsilateral disabling stroke (7% absolute and 30% relative decrease at 5 years).[54] Carotid endarterectomy generally is not beneficial in patients with stenosis less than 50%. For appropriate patients, CEA is clearly cost effective and might even be cost saving compared with medical management.[56]

When clinicians assess the value of CEA for specific patients, several points deserve special attention. First, most of the risk of recurrent stroke or death in those undergoing CEA occurs up front and is associated with the surgery, compared with the more gradual yet persistent risk of stroke and death in medically treated patients. As a result, the "crossover" toward a significant surgical benefit generally occurs in the first year after the incipient event for those with severe stenosis but not until 4 to 5 years for those with moderate stenosis.[54] Second, because only a minority of medically treated patients with moderate or severe stenosis suffer a recurrent ipsilateral stroke, recent studies have attempted to identify specific subgroups of patients who would benefit most from CEA. These studies suggest that those with higher grade stenoses, atheroma plaque irregularity or ulceration, stroke or transient ischemic stroke within 2 months, cerebral rather than ocular event, male sex, absence of peripheral vascular disease, systolic blood pressure less than 180 mm Hg, and nonoccluded contralateral internal carotid artery preferentially benefit from CEA.[57,58] Finally, the appropriate selection of the surgeon, hospital, and patient is important to achieve an optimal outcome. The trials that demonstrated the efficacy of CEA for symptomatic stenosis had a perioperative risk of stroke or death of less than 6%. These rates may not be achievable in routine settings because of patient selection or surgical skill, a concern given the twofold increase in CEA that occurred between 1991 and 1996.[59-61] Thus only patients with sufficiently low operative risk should be selected to undergo surgery. Furthermore, surgeons and hospitals that perform a greater volume of CEA cases have lower rates of complications and incur less cost compared with those that perform fewer of these procedures.[62,63]

Cardiac and Aortic Disease

At least 20% of ischemic strokes originate from an embolic cardiac or aortic source.[4] In the appropriate clinical setting, a patient's readily determined clinical characteristics, such as atrial fibrillation, severe dilated cardiomyopathy, or left-sided mechanical heart valve, may impute a cardioembolic cause such that further etiologic workup is unnecessary because anticoagulation is generally indicated in these cases regardless of the imaging results. In these patients, warfarin therapy to maintain the international normalized ratio (INR) between 2.0 and 3.0 (2.5 to 3.5 for most mechanical valves) collectively decreases the absolute risk of recurrent stroke by 8% and the relative risk by 67% and provides substantial cost savings.[64,65]

In patients with ischemic stroke who do not have significant ipsilateral carotid stenosis (≥50%) or the aforementioned high-risk cardioembolic conditions, often grouped as stroke of indeterminate etiology, the diagnostic workup for a possible cardiac cause of stroke is evolving.[66] Transthoracic echocardiography (TTE) has traditionally been the primary diagnostic tool used to assess cardioembolic risk. In this indeterminate group, TTE identifies a potential cause of stroke in 15% of persons with concomitant clinical heart disease and in approximately 5% of those without heart disease.[4,67] More recently, transesophageal echocardiography (TEE), a modality with improved cardiac and aortic-root imaging ability, has been demonstrated to substantially improve the detection of aortic atheroma, patent foramen ovale, left atrial thrombus, left atrial spontaneous echo contrast, and atrial septal aneurysm, findings that have been associated with an increased risk of ischemic stroke.[67,68]

Despite these associations and the superior sensitivity of TEE, the usefulness of TEE depends on its ability to improve treatment. In a study by Rauh et al,[69] the results of TEE led to the initiation of anticoagulant therapy in an additional 10% of patients. Furthermore, recent studies suggest that the risk of recurrent stroke may be reduced by oral anticoagulant therapy in patients with aortic arch atheroma, especially those with mobile ulcerated plaques greater than 4 mm.[70-72] In addition, paradoxical embolus from deep venous thrombosis via moderate-to-large patent foramen ovale appears to be a real, although uncommon, cause of stroke in this indeterminate group.[73-76] In patients with patent

foramen ovale, lower extremity venography may be necessary to detect venous thrombosis because these patients often have no symptoms from their thrombosis, a condition known to decrease the sensitivity of lower extremity duplex.[73,74] Finally, cost analysis of various algorithms for echocardiographic use indicate that compared with selective or no echocardiographic workup, TTE alone, or combinations of TTE and TEE, first-line TEE in all patients in this indeterminate group appears to be cost effective by reducing the risk of recurrent stroke.[77] Thus echocardiography, especially TEE, should be strongly considered in patients with an indeterminate cause of stroke, although the clinician and patient should appreciate that treatment decisions based on TEE may rely on emerging but still limited data.

Additional Etiology Evaluation

Numerous additional modalities to identify the cause of stroke are available and continue to develop, although their role in guiding therapy and their cost effectiveness are often unclear. These diagnostic techniques include transcranial Doppler to detect intra- or extracranial arterial stenosis and occult emboli, magnetic resonance angiography or conventional angiography to evaluate the cerebral vasculature, magnetic resonance imaging to better image the brain, laboratory tests to identify hypercoagulable states, and ambulatory electrocardiographic monitoring in patients suspected of having occult arrhythmia, such as paroxysmal atrial fibrillation, contributing to the risk of cardiac embolism. Neurologic expertise and an individual case-by-case approach help to maximize the benefit of these studies.

··· GENERAL PREVENTIVE THERAPY ···

Aside from CEA for significant carotid stenosis and anticoagulation with warfarin for high-risk thrombotic states, several therapies can be generally recommended to prevent recurrent ischemic stroke.

Blood Pressure Control

Both diastolic and systolic hypertension are associated with an increased risk of stroke regardless of age or sex. Treatment of hypertension decreases the relative risk of stroke by approximately 25% and the absolute risk by 2% and is cost effective.[78,79] In general, elderly patients appear to benefit most from diuretic therapy, those with coronary disease from β-blocker therapy; and those with cardiomyopathy from angiotensin converting enzyme inhibitor and β-blocker therapy.

Smoking Cessation

Smoking is associated with a twofold increase in the risk of stroke, a risk that can be reduced to nearly that of a nonsmoker with successful cessation.[80-83] This benefit begins fairly soon after smoking cessation and increases with time. Consequently, safe and typically cost-effective interventions to improve smoking cessation rates that include physician counseling, behavioral therapy, nicotine replacement therapy, or bupropion treatment should be instituted in stroke patients who smoke.[83-86]

Antiplatelet Therapy

Antiplatelet therapy, primarily in the form of aspirin, has been a cornerstone of secondary stroke prevention, although recent developments have expanded current treatment options and future possibilities. Aspirin, which inhibits the cyclooxygenase pathway, reduces the relative risk of recurrent cardiovascular disease in general by 25% and stroke specifically by approximately 15%.[87,88] Because a wide range of aspirin dosages (50 to 1300 mg/day) has produced benefit, the optimal dose is undetermined. The Food and Drug Administration currently recommends a daily dosage of 50 to 325 mg; this lower dose range may produce fewer gastrointestinal adverse effects and offers the theoretic advantage of superior platelet inhibition.

Newer antiplatelet agents of the thienopyridine class, ticlopidine and clopidogrel, work by inhibiting the binding of adenosine 5´-diphosphate to its platelet receptor, thereby decreasing platelet aggregation.[89] Ticlopidine at a dosage of 250 mg twice daily is marginally but significantly better than aspirin in preventing recurrent stroke yet is substantially more expensive, has been associated with the development of thrombotic thrombocytopenic purpura, and produces neutropenia in 1% to 2% of patients, necessitating bimonthly blood count monitoring.[89,90] Despite these characteristics, one study suggested that ticlopidine may be cost effective compared with aspirin.[91] Clopidogrel appears to be comparable to aspirin in preventing recurrent stroke. Unlike ticlopidine, clopidogrel does not cause neutropenia, but it is considerably more expensive than aspirin.[92]

Because the thienopyridines and other antiplatelet agents inhibit platelet aggregation through mechanisms distinct from those of aspirin, combination antiplatelet therapy may potentially provide greater benefits than therapy with a single agent. Indeed, a recent study demonstrated that the combination of slow-release dipyridamole 400 mg/day and aspirin 50 mg/day decreased the relative risk of recurrent stroke an additional 15% compared with aspirin alone.[93]

Other combinations await study. Consequently, aspirin at 50 to 325 mg/day is considered first-line antiplatelet therapy. Patients who do not respond to aspirin alone should be treated with a combination of low-dose aspirin and dipyridamole, switched to clopidogrel, or have clopidogrel added to their aspirin regimen. Finally, antiplatelet therapy should generally be withheld from patients receiving anticoagulation treatment, although in rare instances combined use may be indicated.

Cholesterol Reduction

Although there is little epidemiologic evidence linking elevated cholesterol levels to the risk of stroke,[94] recent meta-analyses of secondary endpoints have consistently demonstrated a 30% relative reduction in stroke rates among patients with coronary artery disease who receive lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors.[95-97] Although unproved, this benefit might also extend to persons with isolated cerebrovascular disease and no coronary artery disease. With few exceptions,[98] other lipid-lowering therapies, including fibrates, resins, and dietary interventions that are typically associated with smaller cholesterol reductions, do not appear to be similarly effective.[95] Although the mechanism of benefit awaits elucidation, HMG CoA reductase inhibitors may reduce the risk of stroke by decreasing coronary artery disease, slowing the progression of cerebral atherosclerosis and stabilizing atheromatous plaques, or exerting anti-inflammatory effects.[99,100] Furthermore, lipid-lowering treatment appears to be cost effective.[101] In light of these data, patients with ischemic stroke should generally be evaluated and treated for lipid abnormalities.

Homocysteine Reduction

Extreme elevations of homocysteine as found in homocystinuria, a collection of rare inherited metabolic disorders, appear to promote atherosclerosis.[102] Furthermore, even modest elevations of homocysteine, which are seen in the general population, have been linked to cardiovascular disease and stroke in epidemiologic studies.[103] This association appears to be independent of other established cardiovascular risks and is largely attributable to deficiencies of folic acid, an essential cosubstrate in the metabolism of homocysteine.[104] Indeed, treatment with folic acid lowers homocysteine levels regardless of homocysteine or folic acid status.[105] Ongoing randomized trials will determine whether treatment of hyperhomocystinemia with folic acid therapy prevents cardiovascular disease.[106] Until the results of these trials become available, it may be sensible to encourage patients who have had a stroke to supplement their diet with 0.4 to 1 mg/day of folic acid, a reasonably safe and inexpensive intervention.[107]

Hormone Replacement Therapy

Although estrogens and progestins affect vascular reactivity, lipid profiles, and coagulation factors,[108] hormone replacement therapy (HRT), either given as unopposed estrogen or an estrogen-progestin combination, has not consistently been associated with a beneficial or detrimental effect on the risk of ischemic stroke.[109-113] Thus, although most information derives from cohort or case-control primary-event investigations and not randomized, controlled secondary-prevention studies, HRT currently should not be initiated to reduce the risk of recurrent stroke nor should it necessarily be discontinued in a patient receiving HRT for a separate indication.

Physical Activity

Taken together, numerous studies have not demonstrated that physical activity definitely decreases the risk of ischemic stroke.[114-120] Because physical activity favorably affects hypertension and other cardiovascular risk factors, however, a program that encourages attainable physical activity is a reasonable approach and may ultimately reduce the risk of recurrent stroke.[114]

Glucose Control

Diabetes and impaired glucose tolerance are well-established risk factors for ischemic stroke.[121,122] In randomized, controlled trials, tight glucose control, when compared with conventional treatment, successfully prevented microvascular disease in both type 1 and 2 diabetes.[123,124] Although the degree of hyperglycemia is associated with macrovascular complications, there is little direct evidence in type 2 diabetes that tight glucose control reduces macrovascular disease, the primary cause of morbidity and mortality in this group.[123,125] Future trials may clearly establish the macrovascular advantages of tight control, although successful management of established risks, such as hypertension and smoking, are likely to provide greater benefit.[126]

··· CONCLUSION ···

Ischemic stroke continues to be a major public health problem with substantial personal and societal costs. Recent therapeutic advances have provid-

ed an opportunity to improve the acute treatment and secondary prevention of ischemic stroke. Only with clinician and public awareness of these and future developments will better care for ischemic stroke be realized.

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··· REFERENCES ···

1. *Heart and Stroke Facts. Statistical Supplement.* Dallas, TX: American Heart Association; 1996.
2. Taylor TN, Davis PH, Torner JC, et al. Lifetime cost of stroke in the United States. *Stroke* 1996;27:1459-1466.
3. *Heart and Stroke Facts. Statistical Supplement.* Dallas, TX: American Heart Association; 1998.
4. Cerebral Embolism Task Force. Cardiogenic brain embolism. The second report of cerebral embolism task force. *Arch Neurol* 1989;46:727-743.
5. Benbadis SR, Sila CA, Cristea RL. Mental status changes and stroke. *J Gen Intern Med* 1994;9:485-487.
6. Kotheri R, Sauerbeck L, Jauch E, et al. Patients' awareness of stroke signs, symptoms, and risk factors. *Stroke* 1997;28:1871-1875.
7. Jorgensen HS, Nakayama H, Reith J, et al. Factors delaying hospital admission in acute stroke: The Copenhagen Stroke Study. *Neurology* 1996;47:383-387.
8. Pancioli AM, Broderick J, Kotheri R, et al. Public perception of stroke warning signs and knowledge of potential risk factors. *JAMA* 1998;279:1288-1292.
9. Marler JR, Jones RW, Emr M. *Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke.* Bethesda, MD: The National Institute of Neurological Disorders and Stroke, National Institutes of Health; 1997.
10. Alberts M, for the Stroke Belt Consortium. The Stroke Belt Consortium. *J Stroke Cerebrovasc Dis* 1996;6:54-59.
11. Brott T, Adams HP, Olinger CP, et al. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke* 1989;20:864-870.
12. Gilman S. Imaging of the brain. *N Engl J Med* 1998;338:812-820.
13. Lutsep HL, Albers GW, DeCrespigny A, et al. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol* 1997;41:574-580.
14. The National Institute of Neurologic Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-1587.
15. Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. *N Engl J Med* 1999;340:1781-1787.
16. The NINDS rt-PA Stroke Study Group. Symptomatic intracerebral hemorrhage after t-PA for stroke. *Stroke* 1997;28:272. Abstract.
17. Demchuk AM, Morgenstern LB, Krieger DW, et al. Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. *Stroke* 1999;30:34-39.
18. Fagan SC, Morganstern LB, Petetta A, et al. Cost effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology* 1998;50:883-890.
19. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: The European Cooperative Stroke Study (ECASS). *JAMA* 1995,274:1017-1025.
20. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Austrailasian Acute Stroke Study Investigators. *Lancet* 1998;352:1245-1251.
21. Multicenter Acute Stroke Trial-Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 1996;335:145-150.
22. Multicenter Acute Stroke Trial-Italy (MAST-1) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995;346:1509-1514.
23. Donnan GA, Davis SM, Chambers BR, et al. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA* 1996;276:961-966.
24. Fisher M, Bogousslavsky J. Further evolution toward effective therapy for acute ischemic stroke. *JAMA* 1998;279:1298-1303.
25. Guidelines for thrombolytic therapy for acute stroke. A supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1996;27:1711-1718.
26. Caplan LR. Stroke treatment: Promising but still struggling. *JAMA* 1998;279:1304-1306.
27. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): A randomized trial of aspirin, subcutaneous heparin, both or neither among 19,435 patients with acute ischemic stroke. *Lancet* 1997;349:1569-1581.
28. Chinese Acute Stroke Trial Collaborative Group. CAST: Randomized placebo controlled trial of early aspirin use in 20,000 patients with acute ischemic stroke. *Lancet* 1997;349:1641-1649.
29. Adams HP, for the TOAST investigators. Low molecular weight heparinoid ORG 10172 (danaparoid) and outcome after acute ischemic stroke. *JAMA* 1998;279:1265-1272.
30. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;154:1449-1457.
31. Feinberg WN. Anticoagulation for prevention of stroke. *Neurology* 1998;51(suppl 3): S20-S22.
32. Rothrock JF, Hart RG. Antithrombotic therapy in cerebrovascular disease. *Ann Intern Med* 1991;115:885-895.
33. Haley EC, Kassell NF, Torner JC. Failure of heparin to prevent ischemic infarction. *Stroke* 1988;19:10-14.
34. Slivka A, Levy D. Natural history of progressive ischemic

stroke in a population treated with heparin. *Stroke* 1990;21:1657-1662.
35. Adams HP, Brott TG, Crowell RM, et al. Guidelines for the management of patients with acute ischemic stroke. A statement for health care professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994;25:1901-1914.
36. Murphy C. Hypertensive emergencies. *Emerg Med Clin North Am* 1995;13:973-1005.
37. Harvey RL. Commentary on "Stroke unit care improved survival and function for 5 years after an acute stroke." ACP Journal Club March/April 1998;128:2. Abstract of: Indredavik B, Slordahl SA, Bakke F, Rokseth R, Haheim LL. Stroke unit treatment. Long-term effects. *Stroke* 1997;28:1861-1866.
38. Stroke Unit Trialists' Collaboration. Collaborative systematic review of randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ* 1997;314:1151-1159.
39. Indredavik B, Slordahl SA, Bakke F, Rokseth R, Haheim LL. Stroke unit treatment. Long-term effects. *Stroke* 1997;28:1861-1866.
40. Indredavik B, Bakke F, Slordahl SA, et al. Stroke unit treatment improves long-term quality of life. A randomized controlled trial. *Stroke* 1998;29:895-899.
41. Odderson IR, McKenna BS. A model for management of patients with stroke during the acute phase. Outcome and economic implications. *Stroke* 1993;24:1823-1827.
42. Weir CJ, Murray GD, Dyker AG, Lees KR. Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study. *BMJ* 1997;312:1303-1309.
43. Wass CT, Lanier WL. Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996;71:801-812.
44. Scot JF, Robinson GM, French JM, et al. Glucose potassium insulin infusions in the treatment of acute stroke patients with mild to moderate hyperglycemia: The glucose insulin in stroke trial (GIST). *Stroke* 1999;30:793-799.
45. Azzimondi G, Bassein L, Nonino F, et al. Fever in acute stroke worsens prognosis. *Stroke* 1995;26:2040-2043.
46. Castillo J, Davalos A, Marrugat J, Noya M. Timing of fever related brain damage in acute ischemic stroke. *Stroke* 1998;29:2455-2460.
47. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: A significant clinical concern. *Stroke* 1998;29:529-534.
48. Becker KJ. Emerging medical therapy of acute stroke. *Top Emerg Med* 1997;19:79-88.
49. Kwakkel G, Wagenaar RC, Kollen BJ, Lankhorst CJ. Predicting disability in stroke: A critical review of the literature. *Age Aging* 1996;25:479-489.
50. Orgogozo JM. Advantages and disadvantages of neurological scales. *Cerebrovasc Dis* 1998;8(suppl 2):2-7.
51. Cifu DX, Stewart DG. Factors influencing functional outcome after stroke: A critical review of rehabilitation interventions. *Arch Phys Med Rehabil* 1999;55:1742-1748.
52. Council of Scientific Affairs. Doppler sonographic imaging of the vascular system: Report of the Ultrasonography Task Force. *JAMA* 1991;265:2382-2387.
53. The North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade stenosis. *N Engl J Med* 1988;313:1191-2000.
54. The North American Symptomatic Carotid Endarterectomy Trial Collaborators. Benefit of carotid endarterectomy in patients with symptomatic moderate or high grade stenosis. *N Engl J Med* 1998;339:1415-1425.
55. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial. *Lancet* 1998;351:1379-1387.
56. Holloway RG, Benesch CG, Rahilly CR, Courtright CE. A systematic review of cost-effectiveness research of stroke evaluation and treatment. *Stroke* 1999;30:1340-1349.
57. Rothwell DM, Warlow CD. Prediction of benefit from carotid endarterectomy in individual patients: A risk-modeling study. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1999;353:2105-2110.
58. Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: A systematic review. *BMJ* 1997;315:1571-1577.
59. Wong JH, Findlay JM, Suarez-Almazor ME. Regional performance of carotid endarterectomy: Appropriateness, outcomes, and risk factors for complications. *Stroke* 1997;28:891-898.
60. Dyken ML. Controversies in stroke–past and present: the Willis Lecture. *Stroke* 1993;24:1251-1258.
61. Tu JV, Hannan EL, Anderson GM, et al. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med* 1998;339:1441-1447.
62. Hannan EL, Popp AJ, Tranmer B, et al. Relationship between provider volume and mortality for carotid endarterectomy in New York State. *Stroke* 1998;29:2292-2297.
63. Pearce WH, Parker MA, Feinglass J, et al. The importance of surgeon volume and training in outcomes for vascular surgical procedures. *J Vasc Surg* 1999;29:768-778.
64. European Atrial Fibrillation Trial Study Group. Secondary prevention in nonrheumatic atrial fibrillation after transient ischaemic or minor stroke. *Lancet* 1993;342:1255-1262.
65. Gage BF, Cardinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA* 1995;274:1839-1845.
66. Manning WJ. Role of transesophageal echocardiography in the management of thromboembolic stroke. *Am J Cardiol* 1997;80:19D-28D.
67. Pearson AC. Transthoracic echocardiography versus transesophageal echocardiography in detecting cardiac sources of embolism. *Echocardiography* 1993;10:397-403.
68. Albers GW, Comess KA, DeRook, et al. Transesophageal echocardiographic findings in stroke subtypes. *Stroke* 1994;25:23-28.
69. Rauh R, Fischereder M, Spengel FA. Transesophageal echocardiography in patients with focal cerebral ischemia of unknown cause. *Stroke* 1996;27:691-694.

70. Labovitz AJ, for the STEPS Investigators. Transesophageal echocardiography and unexplained cerebral ischemia: A multicenter follow-up study. *Am Heart J* 1999;137:1082-1087.
71. Dressler FA, Craig WR, Castello R, Labovitz AJ. Mobile aortic atheroma and systemic emboli: Efficacy of anticoagulation and influence of plaque morphology on recurrent stroke. *J Am Coll Cardiol* 1998;31:134-138.
72. Ferrari E, Vidal R, Chevallier T, Baudouy M. Atherosclerosis of the thoracic aorta and aortic debris as a marker of poor prognosis: Benefit of oral anticoagulants. *J Am Coll Cardiol* 1999;33:1317-1322.
73. Lethen H, Flachskampf F, Schneider R, et al. Frequency of deep vein thrombosis in patients with patent foramen ovale and ischemic stroke or transient ischemic attack. *Am J Cardiol* 1997;80:1066-1069.
74. Stollberger C, Slany J, Schuster I, et al. The prevalence of deep venous thrombosis in patients with suspected paradoxical embolism. *Ann Intern Med* 1993;119:461-465.
75. Meacham RR 3rd, Headley AS, Bronze MS, Lewis JB, Rester MM. Impending paradoxical embolism. *Arch Intern Med* 1998;158;438-448.
76. Steiner MM, Di Tullio MR, Rundek T, et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998;29:944-948.
77. McNamara RL, Lima JAC, Whelton PK, Powe NR. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: A cost-effectiveness analysis. *Ann Intern Med* 1997;127:775-787.
78. The INDANA (Individual Data Analysis of Antihypertensive Intervention Trials) Project Collaborators. Effective antihypertensive treatment in patients having already suffered from stroke: Gathering the evidence. *Stroke* 1997;28:2557-2562.
79. Brown AD, Garber AM. Cost effectiveness of coronary heart disease prevention strategies in adults. *PharmacoEconom* 1998;14:27-48.
80. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ* 1989;298;789-794.
81. Wannumethee SC, Shaper AC, Whinoap PH, Walker M. Smoking cessation and the risk of stroke in middle aged men. *JAMA* 1995;274:155-160.
82. Shinton R. Lifelong exposures and the potential for stroke prevention: The contribution of cigarette smoking, exercise, and body fat. *J Epidemiol Community Health* 1997;51:138-143.
83. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke. *Circulation* 1997;96:3243-3247.
84. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release buproprion, nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340:685-691.
85. Stapleton JA, Lowin A, Russell MA. Prescription of transdermal nicotine patches for smoking cessation in general practice: Evaluation of cost-effectiveness. *Lancet* 1999;354:210-215.
86. Curry SJ, Grothaus LC, McAfee T, Pabinak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. *N Engl J Med* 1998;339:673-679.
87. Collaborative overview of randomised trials of antiplatelet therapy-1: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories. *BMJ* 1994;308:81-106.
88. Algra A, van Gijn J. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia. *J Neurol Neurosurg Psychiatry* 1996;60:197-199.
89. Sharis PJ, Cannon CP, Loscalzo J. The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998;129:394-405.
90. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med* 1989;321:501-507.
91. Oster G, Huse DM, Lacey MJ, Epstein AM. Cost-effectiveness of ticlopidine in preventing stroke in high-risk patients. *Stroke* 1994;25:1149-1156.
92. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-1339.
93. Diener HC, Cunha L, Forbes C et al. European Stroke Prevention Study II: Dipyridamole and acetyl salicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
94. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13 000 strokes in 450 000 people in 45 prospective cohorts. *Lancet* 1995;346:1647-1653
95. Bucher HC, Griffith LE, Guyatt GH. Effect of HMGcoA reductase inhibitors on stroke. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 1998;128:89-95.
96. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* 1997;278:313-321.
97. Crouse JR 3d, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med* 1997;157:1305-1310.
98. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. Veterans Affair High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;341:410-418.
99. Illingworth DR. New risk factors for coronary heart disease. *Am J Med* 1999;107:19S-21S.
100. Crouse JR 3d, Byington RP, Hoen HM, Furberg CD. HMG-CoA reductase inhibitor therapy and stroke risk reduction: An analysis of clinical trials data. *Atherosclerosis* 1998;138:11-24.
101. Grover SA, Coupal L, Paquet S, Zowall H. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease: Forecasting the incremental benefits of preventing coronary and cerebrovascular events. *Arch Intern Med* 1999;159:593-600.
102. Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 1985;37:1-31.
103. Eikelboom JW, Lonn E, Genest J Jr, et al.

Homocyst(e)ine and cardiovascular disease: A critical review of the epidemiologic evidence. *Ann Intern Med* 1999;131:363-375.
104. Selhub J, Jacques PF, Rosenberg IH, et al. Serum homocysteine concentrations in the Third National Health and Nutrition Examination Survey (1991-1994): Population reference ranges and contribution of vitamin status to high serum concentrations. *Ann Intern Med* 1999;131:331-339.
105. Lowering blood homocysteine with folic acid based supplements: Meta-analysis of randomised trials. Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998;316:894-898.
106. Clarke R, Collins R. Can dietary supplements with folic acid or vitamin B6 reduce cardiovascular risk? Design of clinical trials to test the homocysteine hypothesis of vascular disease. *J Cardiovasc Risk* 1998;5:249-255.
107. Graham I. Homocysteine in health and disease [editorial]. *Ann Intern Med* 1999;131:387-388.
108. Barrett-Connor E. Hormone replacement therapy. *BMJ* 1998;317:457-461.
109. Petitti DB, Sidney S, Quesenberry CP, Bernstein A. Ischemic stroke and use of estrogen and estrogen/progestogen as hormone replacement therapy. *Stroke* 1998;29:23-28.
110. Fung MM, Barrett-Connor E, Bettencourt RR. Hormone replacement therapy and stroke risk in older women. *J Women's Health* 1999;8:359-364.
111. Pedersen AT, Lidegaard O, Kreiner S, Ottesen B. Hormone replacement therapy and the risk of non-fatal stroke. *Lancet* 1997;350:1277-1283.
112. Sourander L, Rajal T, Raiha I, et al. Cardiovascular and cancer morbidity and mortality and sudden cardiac death in postmenopausal women on oestrogen replacement therapy. *Lancet* 1998;352:1965-1969.
113. Psaty BM, Heckbert SR, Atkins D, et al. A review of the association of estrogens and progestins with cardiovascular disease in postmenopausal women. *Arch Intern Med* 1993;153:1421-1427.
114. Evenson KR, Rosamond WD, Cai J, et al. Physical activity and ischemic stroke risk. The Atherosclerosis Risk in Communities Study. *Stroke* 1999;30:1333-1339.
115. Sacco R, Gan R, Boden-Albala B, et al. Leisure-time physical activity and ischemic stroke risk: The Northern Manhattan Stroke Study. *Stroke* 1998;29:380-387.
116. Bijnen F, Caspersen C, Feskens E, et al. Physical activity and 10-year mortality from cardiovascular diseases and all causes. *Arch Intern Med* 1998;158:1499-1505.
117. Kiely D, Wolf P, Cupples L, et al. Physical activity and stroke risk: The Framingham Study. *Am J Epidemiol* 1994;140:608-620.
118. Abbott R, Rodriguez B, Burchfiel C, Curn J. Physical activity in older middle-aged men and reduced risk of stroke: The Honolulu Heart Program. *Am J Epidemiol* 1994;139:881-893.
119. Ellekjaer E, Wyller T, Sverre J, Holmen J. Lifestyle factors and risk of cerebral infarction. *Stroke* 1992;23:829-834.
120. Us Department of Health and Human Services. *Physical Activity and Health; A Report of the Surgeon General.* Washington, DC: CDC, National Center for Chronic Disease Prevention and Health Promotion; 1996.
121. Laakso M, Lehto S. Epidemiology of macrovascular disease in diabetes. *Diabetes Rev* 1997;5:294-315.
122. Conutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: A metaregression analysis of published data from 20 studies of 95,783 individuals followed 12.4 years. *Diabetes Care* 1999;22:233-240.
123. UK Prospective Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-853.
124. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.
125. Lawson ML, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. *Diabetes Care* 1999;22:35-42.
126. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes* 1999;48:937-942.

CME QUESTIONS: TEST #060002

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Instructions

After reading the article "Ischemic Stroke: Acute Management and Secondary Prevention," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is 1 hour. CME credits are distributed on a yearly basis.

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1. To be eligible for rt-PA treatment of ischemic stroke, a patient must

a) have definite onset of symptoms for less than 3 hours
b) not have taken aspirin for at least the previous 72 hours
c) be less than 70 years of age
d) have no prior history of stroke

2. In appropriate patients, rt-PA treatment for acute ischemic stroke

a) reduces mortality
b) improves functional outcome
c) is not cost effective
d) should be administered and initially monitored in a general ward setting

3. All of the following factors appear to increase the risk of thrombolytic-associated intracranial hemorrhage except

a) elevated blood glucose or diabetes
b) severe neurological deficit based on the stroke scale score
c) evidence on initial computerized tomography (CT) scan of acute brain ischemia
d) younger age

4. Currently, for patients presenting with acute ischemic stroke, heparin

a) should be used routinely to keep the partial thromboplastin time (PTT) between 60 and 90 seconds
b) should be initiated immediately if the patient is found to be in atrial fibrillation
c) increases the risk of hemorrhagic conversion without improving outcome in most cases
d) should be administered preferentially instead of aspirin

5. In acute ischemic stroke, urgent blood pressure control is rarely indicated except in the setting of

a) thrombolytic treatment
b) those patients with a prior history of hypertension
c) concurrent acute myocardial infarction, congestive heart failure, or aortic dissection
d) a and c

6. Following ischemic stroke from a carotid artery embolus, carotid endarterectomy (CEA) is most likely to benefit patients who

a) have a high degree of stenosis in the carotid artery ipsalateral to the ischemic lesion
b) are found on imaging to have an ulcerated or irregular stenotic atheroma
c) generally have a low surgical risk
d) have the procedure performed by a surgeon and hospital with a large experience in CEA
e) all of the above

(CME QUESTIONS CONTINUED ON NEXT PAGE)

CME TEST FORM
AJMC Test #060002

Ischemic Stroke:
Acute Management
and Secondary
Prevention

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(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

7. All of the following statements concerning ticlopidine are true except

a) ticlopidine is an antiplatelet agent used for the secondary prevention of ischemic stroke that is at least as effective as aspirin in the secondary prevention of ichemic stroke
b) ticlopidine has an uncommon but potentially serious side effect of neutropenia that mandates routine blood count screening
c) ticlopidine has superceded aspirin as the first line antiplatelet treatment for the secondary prevention of ischemic stroke
d) the potential risks and benefits of ticlopidine in combination with aspirin or other antiplatelet agents remain uncertain

8. Therapy that has been shown to definitively lower the risk of ischemic stroke includes

a) tight blood glucose control among persons with Type 2 diabetes
b) hormone replacement therapy in women
c) warfarin anticoagulation in patients with atrial fibrillation
d) increased levels of physical activity or exercise

9. Treatment of hyperlipidemia with HMG CoA reductase inhibitors

a) lowers the risk of stroke among those with established coronary artery disease
b) likely reduces the risk of ischemic stroke by multiple biological mechanisms
c) is a reasonable therapeutic approach for patients with isolated cerebrovascular disease (no clinical coronary artery disease)
d) all of the above

10. Patients on aspirin therapy with recurrent nonembolic ischemic stroke should

a) have their dose of aspirin increased.
b) discontinue aspirin and start warfarin therapy
c) discontinue aspirin and initiate clopidogrel, or maintain aspirin and add clopidogrel
d) continue aspirin and add dypiridamole
e) c or d