An Updated Review on Ischemic Stroke

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A 63-year-old white man with a history of hypertension, gastroesophageal reflux, and coronary arterial disease (myocardial infarction 14 years prior) was brought by his girlfriend into the local hospital emergency department for evaluation of new-onset confusion. The patient's girlfriend stated that he was in his normal state of health until the morning of admission when he awoke with mental status changes. He was not making sense with his words and could not follow simple commands or answer questions appropriately. His speech was fluent but his pattern suggested a disorganized, nonsensical pattern of speech. He was able to shower and dress himself without assistance. The girlfriend stated that the patient had not complained of chest pain, shortness of breath, headache, abdominal pain, visual changes, fever, chills, nausea, vomiting, change in bowel movements, or dysuria. He has no personal or family history of psychiatric illness, no known drug allergies, and takes loratidine as needed approximately three times a week. He does not smoke or engage in illicit drug use but drinks two or three glasses of wine daily. His father died at the age of 61 from a myocardial infarction, and his mother had Alzheimer's disease.

Vital signs on admission include a pulse of 76 per minute, blood pressure of 181/103 mmHg, respiratory rate of 18 per minute, and a pulse oximetry revealing 98% saturation on no supplemental oxygen. He was afebrile, and head, neck, cardiopulmonary, abdominal, and extremity exams were normal except for the presence of trace pretibial edema. Neurological exam revealed normal sensory findings and motor strength, although the exam was limited secondary to the patient's difficulty in following commands. Reflexes were normal throughout, and cranial nerve testing and gait observance revealed no abnormalities. He seemed disoriented to name, time, place, and situation, but had significant expressive aphasia which impaired his ability to communicate. Pertinent laboratory findings on admission include a white blood cell count of 5,000/μL with normal differential, hemoglobin of 15.8 g/dL, hematocrit of 46.0% (39-49%), and platelet count of 158,000/μL (150,000-450,000). Complete metabolic profile and coagulation studies were within normal limits. An electrocardiogram done in the emergency department revealed evidence of an old inferior myocardial infarction and left ventricular hypertrophy. His chest radiograph demonstrated an increased cardiac silhouette without pulmonary infiltrates or effusions. A computed tomographic (CT) scan of the head showed no evidence of hemorrhage or infarction.

The patient received continuous cardiac monitoring and was followed with serial neurological examinations. He was treated with full-dose aspirin therapy, and he

CME INFORMATION

TARGET AUDIENCE

The November/ December Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, and psychiatrists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, microbiology, clinical presentation, diagnosis, treatment, and prevention of ischemic stroke.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of 1 category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Masri has nothing to disclose.
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received low molecular weight heparin for prophylaxis against venous thrombosis. He was not a candidate for thrombolytic therapy due to the unknown duration of his symptoms. The blood pressure was closely monitored and was not lowered acutely because of the high suspicion of a cerebrovascular event. In order to rule out other causes of delirium, determinations of TSH, RPR, ESR, and ABG were made, and blood and urine cultures were obtained. All of these were unrevealing. A diffusion-weighted MRI of the brain demonstrated an early subacute infarct involving the posterior left external capsule, left insular cortex, and left parietal lobular region. A region of signal dropout at the left middle cerebral arterial trifurcation was seen on magnetic resonance angiography corresponding to the area of infarction seen on MRI. A diagnosis of an expressive aphasia was made, and the speech and occupational therapy services were consulted. The patient improved markedly throughout his hospital course, and he was able to have extended conversations prior to discharge. A fasting lipid profile revealed an elevated LDL cholesterol of 287 mg/dL, a normal HDL cholesterol of 50 mg/dL, and a slightly elevated serum triglyceride level of 184 mg/dL. Statin therapy was initiated and continued after discharge. There was no evidence of stenosis on carotid arterial ultrasound examinations and a transthoracic echocardiogram demonstrated a left ventricular ejection fraction of 30%, inferior wall hypokinesis, left ventricular hypertrophy, and no thrombus. Subsequent transesophageal echocardiogram confirmed the absence of a thrombus or patent foramen ovale. He was also started on an ACE inhibitor and arrangements were made for an outpatient cardiac catherization. At follow-up, the patient had no residual motor or speech deficits and was back at work full time.

EPIDEMIOLOGY/PREVENTION

Stroke is the third most common cause of death in the United States and the leading cause of disability in the United States.[1] In the United States, Australia, and Europe, it is estimated that 400 persons per 100,000 over the age of 45 years will have a first stroke each year.[2] However, 75% of strokes occur in less developed areas of the world. In 1990, 3% of the world's disability was attributed to stroke. The increase in the proportion of elderly in the population coupled with the effects of increased smoking patterns in less developed countries has led experts to anticipate a doubling in stroke mortality by 2020. The care related to this diagnosis is among the fastest growing expenses in the health care industry. Yet, stroke research funding lags far behind the funding for cancer and heart disease research.[3] Increased awareness of risk factors will help combat this rise in the incidence of strokes.

There are multiple risk factors for stroke which overlap with the risk factors for ischemic heart disease. Nonmodifiable risk factors include male sex, nonwhite race, the presence of coronary artery disease or congestive heart failure, and a positive family history of stroke or transient ischemic attack. Older age is an independent risk factor for stroke in that 75% of all first strokes occur after the age of 65 years.[3] Modifiable risk factors include hypertension, elevated total cholesterol, smoking, physical inactivity, obesity, diabetes, carotid arterial stenosis, alcohol consumption, and atrial fibrillation.

Hypertension is one of the major independent risk factors for stroke. It has been established through randomized placebo-controlled trials that lowering both systolic and diastolic blood pressure in hypertensive patients decreases relative risk for both ischemic and hemorrhagic strokes by 35-45%.[4] The Systolic Hypertension in the Elderly (SHEP) study demonstrated the benefit of lowering isolated systolic blood pressure even in patients older than 80 years of age.[5] Trials have shown that thiazide diuretics, long-acting calcium channel blockers, ACE Inhibitors, and angiotensin receptor-blockers reduce the risk of stroke. Most studies have shown the greatest benefit with the use of thiazide diuretics to decrease stroke risk. The Veterans Administration trials proved the efficacy of diuretics in reducing the risk of strokes.[6,7] It was thought that this was secondary to the ability of diuretics to decrease systolic blood pressure as seen in the SHEP trial. However, in multiple studies with the same degree of blood pressure reduction, diuretics reduced stroke rate more than other anti-hypertensive agents. For instance, the Perindopril Protection Against Recurrent Stroke (PROGRESS) trial did not show a statistically significant decrease in stroke with ACE inhibitor monotherapy but showed a 43% decrease in stroke reduction with the combination of an ACE inhibitor and a diuretic.[8] This finding was confirmed in the ALLHAT studies, in which the patients receiving the thiazide diuretic, chlorthalidone, for blood pressure control showed a larger decrease in stroke risk than those in the alpha-blocker (19% more strokes) or ACE inhibitor-treated group (15% more strokes).[9,10] These trials support the JNC 7 recommendation that diuretics be first line agents for the treatment of hypertension especially in patients with risk factor for stroke.[11] Other agents that have been shown to decrease the risk of ischemic stroke include calcium channel blockers (Systolic Hypertension in Europe trial)[12] and angiotensin receptor blockers (LIFE trial).[13] The only trial to show a benefit with ACE inhibitor monotherapy was the Heart Outcomes Prevention Evaluation (HOPE) study which demonstrated total stroke risk reduction by 32% with a 3 mmHg lower systolic blood pressure using ramipril in patients having or at high risk for coronary artery disease, a finding not supported by the other studies.[14]

Although there is a clearly established relationship between hypercholesterolemia and risk of coronary artery disease, the relationship between hypercholester-

olemia and risk of stroke is not as well established. Observational studies do suggest that higher total and LDL cholesterol levels are associated with a greater risk of ischemic stroke. The benefit of lowering cholesterol resulting in a reduction in strokes has been shown with statin therapy. One meta-analysis found a 25% reduction (95%CI, 14%-35%) in the risk of fatal and nonfatal strokes with the use of statins.[4] The Heart Protection Study (HPS) incorporated over 20,000 patients between the ages of 40-80 years with coronary disease, other occlusive arterial disease, or diabetes and found that stroke rate was reduced by 25% in the simvastatin group.[15] Similar findings were reported in the Cholesterol and Recurrent Events (CARE) trial in which pravastatin significantly reduced the outcome of stroke by 31%.[16] This benefit was even observed in patients with normal cholesterol levels at baseline. This finding suggests that the statins have a beneficial effect beyond cholesterol lowering, which is supported by the fact that this decrease in stroke risk has not been established using other cholesterol lowering medications.

One of the biggest impacts on stroke reduction is anticoagulation in patients with atrial fibrillation. The mortality rate for patients with atrial fibrillation is double that of age and sex matched patients without atrial fibrillation primarily secondary to a higher incidence of thromboembolic stroke. Abnormal contractions of the atria in this arrhythmia may result in formation of a thrombus. American College of Chest Physicians (ACCP) recommendations for anticoagulation estimated a biannual thromboembolic stroke risk of 2-20% in patients with nonrheumatic atrial fibrillation.[17] Risk of thromboembolic events increases with age >75 years, history of a prior thrombotic event, diabetes, history of hypertension, and poor left ventricular dysfunction. Individuals less than 65 years of age with none of the above risk factors may be anticoagulated with aspirin alone. Those individuals less than 75 years of age with any of the above risk factors are recommended to take warfarin to achieve an INR between 2 and 3. The number needed to treat in this patient population to prevent one stroke is 32.[17] The greatest benefit of warfarin anticoagulation has been seen in patients greater than 75 years of age. The number needed to treat in this patient population to prevent one stroke is 8.[17]

Asymptomatic carotid artery disease is another modifiable risk factor for stroke. Recommendations have been made for carotid endarterectomy based on results of large randomized controlled trials. The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) demonstrated clear benefit of carotid endarterectomy (CEA) in patients with stenosis of 70% or greater.[18,19] Debate continues in patients with asymptomatic carotid stenosis between 50 and 60%. The ACAS and ACST did show benefits of CEA in patients with asymptomatic carotid stenosis of > 60%. The Veterans Administration trial included a smaller number of patients but did show a significant annual risk reduction in stroke risk in patients with carotid stenosis of > 50-60%.[20] Based on the above studies, the current indications for carotid endarterectomy is an asymptomatic patient aged 80 years or younger with a carotid artery stenosis of 60% or greater with 3% or less surgical risk for stroke or death.[21] Indications for carotid endarterectomy in symptomatic men or women aged 80 years or younger is for a carotid artery stenosis of 50% or greater with 6% or less surgical risk for stroke and death.[21] Carotid artery stenting has also been studied as a possible alternative to CEA in high risk patients.

CLINICAL PRESENTATION

Patients with ischemic stroke have a wide variety of clinical presentations, depending largely on the vessel distribution that is compromised. The internal carotid arteries supply the anterior and middle cerebral arteries of the Circle of Willis. The anterior cerebral artery supplies the medial inferior portion of the cerebral cortex as well as the anterior portions of the caudate nucleus, putamen, internal capsule, and hypothalamus. The middle cerebral artery supplies the lateral portion of the cerebral cortex and contributes to perfusion of the internal and external capsule and lentiform nucleus. The vertebral arteries give off the posterior inferior cerebellar arteries and combine to form the basilar artery. This basilar artery ultimately leads to the posterior cerebral arteries that supply the brainstem and thalamus, as well as a majority of the occipital cortex and medial temporal lobe.[22]

The origin of the internal carotid arteries (ICA) at the common carotid artery bifurcation is a common site of atherosclerosis. Since these arteries provide ophthalmic perfusion, patients with occlusion of this arterial bed can present with classic "amaurosis fugax", or transient blindness in the ipsilateral eye. The extent of damage with ICA lesions depends on the integrity of the collateral blood flow through the Circle of Willis, ranging from no neurological deficits if intact to multiple "watershed infarcts" if circulation is compromised. If there is severely diminished collateral circulation, a near complete hemispheric infarction may occur.

Anterior cerebral artery (ACA) occlusion is uncommon but usually presents with motor and sensory deficits in the contralateral lower extremity. Other signs seen include mild hemiparesis of the contralateral arm, urinary and fecal incontinence, and frontal lobe dysfunction manifesting as labile mood and cognitive defects. Bilateral frontal lobe infarcts will unmask primitive reflexes, such as the grasp, suck, and glabellar reflexes.

Middle cerebral artery (MCA) occlusion accounts for the largest proportion of ischemic strokes. The hallmark of an MCA ischemic stroke is contralateral hemiparesis, mainly affecting the face and arm more than the lower extremity, as well as an ipsilateral hemianopsia. Additional features are dependent on the location of the stroke with left hemispheric lesions causing varying degrees of

aphasia. Involvement of the superior frontal lobe can lead to expressive, or Broca's, aphasia, while more posterior lesions involving the temporal or parietal lobe can lead to receptive, or Wernicke's, aphasia. Right hemispheric lesions, on the other hand, can present with contralateral neglect. Deviation of gaze toward the side of the lesion can be seen in both MCA and ACA occlusions, but this finding usually resolves 48-72 hours after stroke onset. Complete or near complete MCA occlusion is the type of infarction most likely to lead to herniation, which is more common in younger patients with less cortical atrophy and decreased tolerance for cerebral edema.[23]

Posterior cerebral artery (PCA) occlusion has variable presentations depending on the degree of hypoperfusion and collateral flow. The usual visual defect is a contralateral homonymous hemianopsia or superior or inferior quadrantanopsia. Macular or central vision is usually spared secondary to collateral flow from the MCA. The patient can also present with contalateral facial and body hemianesthesia with diminished sensation on the affected side. These patients can also exhibit visual-spatial deficits, which can lead to difficulty in navigating the environment or driving a car.

Occlusions of the various branches of the vertebrobasilar system can result in cranial nerve dysfunction, nausea, vomiting, dysphagia, dysarthria, and varying degrees of paralysis. Patients with brainstem infarcts commonly present with "crossed" sensory deficits, involving the ipsilateral face and contralateral body. There are numerous brainstem infarct stroke syndromes which result in varying combinations of deficits. One example is lateral medullary infarction, known as Wallenberg's syndrome, which can produce the above symptoms as well as ipsilateral ataxia and Horner's syndrome. Vertebrobasilar insufficiency, unlike ACA or MCA occlusion, can also present with loss of consciousness[24], sometimes mimicking syncope.

DIAGNOSIS

Clinicians must arrive at an appropriate diagnosis in a timely manner since delayed treatment can worsen morbidity and mortality. A thorough history and physical exam and proper imaging are essential. The American Stroke Association recommends initially obtaining a CT scan of the brain in order to assess for the presence of an acute hemorrhage. During the first hours, few infarcts can be seen on CT scan. They become visible later. The infarct appears as a dark hypodense wedge-shaped area which may be associated with mass effect. It is important to note that approximately 50% of infarcts never become visible on CT.[3] More severe strokes (medium to large cortical infarcts) are more likely to be seen on CT scan as compared to milder strokes (lacunar and small cortical infarcts). Magnetic resonance imaging demonstrates acute infarction earlier than CT scanning. As a matter of fact, the advent of diffusion-weighted imaging (DWI) with MRI allows the visualization of the size and location of ischemia or infarction within minutes. Newer studies have shown a correlation between the acute DWI lesion and the final infarct size and neurologic outcomes.[25] Perfusion-weighted images (PWI), on the other hand, are taken after a rapidly injected bolus of intravenous contrast agent. A delay in the contrast arriving to the area constitutes an area of hypoperfusion. Early in the presentation of stroke, the PWI lesions are larger than DWI lesion. With recent studies, it appears that the size of the PWI lesion correlates more closely with the severity of the early clinical deficit.[25] These new imaging techniques may help impact guidelines for use of thrombolytics and in estimating prognosis.

TREATMENT

There are several basic medical principles that guide the management of patients with ischemic stroke. All patients should receive continuous cardiac monitoring with frequent neurological examinations to evaluate for evolving changes. Patients should receive adequate hydration and any evidence of fever should be treated with antipyretics and evaluated with appropriate cultures and imaging. Hyperglycemia and hypoxia should be corrected with insulin and oxygen as needed. To prevent infection, Foley catheters should be removed as soon as possible.[26] The American Stroke Association also recommends early mobilization to prevent complications such as aspiration pneumonia, venous thromboembolism, pressure ulcers, and contractures.[27] Oral intake should not be initiated until an evaluation of swallowing is performed. Deep venous thrombosis prophylaxis should be provided by pharmacologic or mechanical means. Initial evaluation should include CT scan of head without contrast to exclude hemorrhage as soon as possible and an EKG. Serology should include cardiac markers if indicated, complete blood cell and platelet count, complete metabolic profile, coagulation studies, and fasting lipid profile.[28]

The use of thrombolytic therapy in the management of acute ischemic stroke is of particular importance. The landmark article on the use of thrombolytics in ischemic stroke was published in 1995 by the National Institute of Neurologic Disorders and Stroke (NINDS) and Stroke rt-PA Stroke Study Group.[29] This study showed a clinically significant benefit at 3 months and 1 year when intravenous tissue plasminogen activator (TPA) was given to patients with ischemic strokes who presented within 3 hours of onset of symptoms. The TPA was given in a dose of 0.9 mg/kg (maximum 90 mg) with 10% given as an initial bolus and the rest infused over 60 minutes.[29] The eligibility criteria included patients older than 18 years of age with ischemic stroke of less than 3 hours duration who demonstrated persistent neurological deficit beyond sensory impairment or ataxia. If the patient awoke with neurological symptoms, as in our case pa-

tient, the onset of symptoms is assumed to be when the patient was last known to be of normal health, i.e., before falling asleep. The benefit of the administration of thrombolytics between 3 and 6 hours of presentation has been evaluated in several subsequent studies, including ECASS I[31], ECASS II[32], and the ATLANTIS trials[33], and has failed to show a consistent benefit. At present, the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy does not support a recommendation for intravenous TPA in the 3- to 6-hour window but does give a Grade 2C recommendation (no randomized trials but consensus opinion of experts) for the use of intra-arterial thrombolysis with TPA for MCA occlusion and basilar artery thrombosis in this subset of patients.[30] Streptokinase, on the other hand, has not been approved for use in acute ischemic stroke.

Historical exclusion criteria for the use of thrombolytic therapy include major surgery within 14 days, history of stroke, MI, or head trauma within 3 months, history of intracerebral hemorrhage, gastrointestinal or genitourinary bleeding within 21 days, or arterial or lumbar puncture within the previous seven days. Clinical exclusion criteria include both very minor or very severe neurological deficits, signs of resolving deficits, seizure at onset of stroke, persistent blood pressure of greater than 185/110 mmHg despite treatment, pregnancy or lactation, active bleeding, or symptoms suggestive of acute MI or subarachnoid hemorrhage. Laboratory exclusion criteria include INR greater than 1.5 on warfarin, prolonged PTT on heparin, platelet count less than 100,000 units, or serum glucose less than 50 mg/dl or greater than 400 mg/dl. Radiologic exclusion criteria include evidence of hemorrhage or involvement of greater than one-third of the MCA territory.[34]

Antiplatelet therapy, including aspirin, dipyridamole, and clopidogrel, has consistently been shown to be beneficial in all patient populations who have no contraindications for their use. Aspirin has been the subject of several clinical stroke trials and should be started within 48 hours of stroke onset.[35,36,37] There has been no published data to suggest adverse outcomes in delaying therapy up to 48 hours after onset of stroke symptoms. It has been shown to reduce the rate of recurrent ischemic stroke. It has also shown to be as effective as warfarin therapy in preventing future vascular events for patients with recent TIA or stroke and evidence of intracranial arterial stenosis.[38] Ticlopidine was shown to have similar efficacy but is not used much anymore due to its association with neutropenia and TTP. The ESPS-2 study showed the combination of dipyridamole and aspirin reduced the risk of stroke by 23% compared to aspirin alone, although the dose of aspirin used in this study, 25 mg twice daily, was controversial.[39] As for clopidogrel, the CAPRIE study showed an 8.7% relative risk reduction for clopidogrel versus aspirin in regards to ischemic stroke, MI, or vascular death.[40] However, the recent MATCH trial failed to show a decrease in the rate of ischemic events with the combination of clopidogrel plus aspirin versus clopidogrel alone but the combination did lead to a statistically significant increase in major bleeding.[41] At present, all three agents are acceptable options as initial antiplatelet therapy.

The role of heparin in the treatment of acute ischemic stroke is unclear. Most trials with full-dose intravenous, subcutaneous, or low molecular weight heparins have failed to show any benefit over antiplatelet therapy.[42] These heparin products, however, are associated with a substantially higher risk of hemorrhagic transformation of the cerebral infarct. The main role of heparin in this subset of patients is for DVT prophylaxis, which can be initiated simultaneously with antiplatelet therapy. If thrombolytics are used, heparin can be started 24 hours after the administration of thrombolytics. Multiple studies have failed to show a benefit in starting heparin acutely in patients with cardioembolic ischemic stroke secondary to atrial fibrillation.[43] Although secondary prevention of warfarin in this subset of patients is clearly accepted, the optimal time to initiate anticoagulation in acute ischemic stroke is still under debate.

Blood pressure should not be acutely lowered in ischemic stroke to avoid decreasing cerebral perfusion pressure. However, extreme elevations of blood pressure can have dangerous consequences and are absolute contraindication for thrombolyic therapy. Diastolic blood pressures greater than 140 mmHg can be treated with intravenous nitroglycerin up to a maximum of ten micrograms per kilogram per minute. Systolic blood pressures greater than 180 mmHg and diastolic blood pressures greater than 105 mmHg can be treated with labetolol, either through repeated 10-20 mg boluses (maximum 150 mg) or an intravenous drip (maximum: 8 mg/min). If the blood pressure does not fall below this cutoff value with treatment, the patient should not receive thrombolytic therapy. On the other hand, patients not receiving thrombolytics who present with systolic blood pressure greater than 220 mmHg, diastolic blood pressure greater than 120 mmHg, or mean arterial blood pressure greater than 130 mmHg should receive repeated boluses of labetolol or be placed on a nitroprusside drip to lower the blood pressure.[44] The American Stroke Association recommends a 10-15% reduction of the presenting blood pressure in these patients.[27]

Rehabilitation after an acute ischemic stroke is a major determinant in the patient's future quality of life. Inpatient rehabilitation consisting of either physical, speech, and/or occupational therapy, is indicated for patients with disability who cannot return home but are able to participate in therapy for at least 3 hours daily. Medicare covers home-based rehabilitation for at least 2 weeks after discharge and up to 3 additional months of therapy at an outpatient facility.[2] Barriers to successful rehabilitation include insurmountable neurological deficits, depression, sleep disorders, osteoarthritis, and cardiopulmonary disease.[45]

REFERENCES

1. Fleming K, Brown R. Secondary prevention strategies in ischemic stroke: Identification and optimal management of modifiable risk factors. *Mayo Clin Proc* 2004;79:1330-1340.
2. Dobkin B. Rehabilitation after stroke. *N Engl J Med* 2005;352:1677-1684.
3. Warlow C, Sudlow C, Dennis M, et al. Stroke. *The Lancet* 2003;362:1211-1224.
4. Straus S, Majumdar S, McAlister F. New evidence for stroke prevention. *JAMA* 2002;288:1388-1395.
5. The SHEP Cooperative Research Group. Prevention of Stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991:265:3255-3264.
6. The Veterans Administration Cooperative Study Group on Antihypertensive agents. Effects of treatment on morbidity and mortality in hypertension: results in patients with diastolic blood pressure averaging 115 through 129 mmHg. *JAMA* 1967;202: 1028-1034.
7. The Veterans Administration Cooperative Study Group on Antihypertensive agents. Effects of treatment on morbidity in hypertension. II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970;213:143-152.
8. PROGRESS Management Committee. Blood pressure lowering for the secondary prevention of stroke: rationale and design for PROGRESS. *J Hypertens Suppl* 1996;14:S41-S46.
9. The ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlorthalidone: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000;283:1967-1975.
10. ALLHAT officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:1981-1997.
11. Chobanian A, Bakris G, Black H, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;289:2560-2572.
12. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomized double-blinded placebo-controlled Systolic Hypertension in Europe Trial (Syst-Eur). *Lancet* 1998;352:1347-1351.
13. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention for the Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002;359:994-1003.
14. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular eventsin high-risk patients. *N Engl J Med* 2000;342:145-153.
15. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:7-22.
6. Sacks FM, Pfeffer MA, Moye LA, et al. For the Cholesterol and Recurrent Events Trial investigators. The effect of Pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-1009.
17. Albers GW, Dalen JE, Laupacis A, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 2001;119:194S-206S.
18. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421-1428.
19. Halliday A, Mansfield A, Marro J, et al. Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomized controlled trial. *Lancet* 2004;363:1491-1502.
20. Hobson RW II, Weiss DG, Fields WS, et al. Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med* 1993;328:221-227.
21. Brott T, Brown R, Meyer F. Carotid revascularization for prevention of stroke: Carotid Endarterectomy and carotid artery stenting. *Mayo Clin Proc* 2004;79:1197-1208.
22. Marx, *Rosen's Emergency Medicine: Concepts and Clinical Practice*, 5th edition. Carlsbad, Ca: Mosby, Inc;2002:1434-1438.
23. Goldman, *Cecil's Textbook of Medicine*, 22nd edition, Philadelphia, Pa: W.B. Saunders Co; 2004:2281-2290.
24. Goetz, *Textbook of Clinical Neurology*, 2nd edition. Elsevier, 2003:412-417.
25. Albers G. Advances in intravenous thrombolytic therapy for treatment of acute stroke. *Neurology* 2001;57:S77-S81.
26. Broderick J, Hack W. Treatment of acute ischemic stroke, Part II: Neuroprotection and medical management. *Circulation* 2002;106:1736-1740.
27. Klijn C, Hankey G. Management of acute ischemic stroke: new guidelines from the American Stroke Association and European Stroke Initiative. *Lancet Neurology* 2003;2:698-701.
28. Zweiffer R. Management of acute stroke. *South Med J* 2003;96:380-385.
29. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333: 1581-1587.
30. Albers G, Amarenco P, Easton D, et al. Antithrombotic and thrombolytic therapy for ischemic stroke, The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:483S-512S.
31. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;274:1017-1025.
32. Hacke W, Kaste M, Fieschi C, et al. Randomized double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischemic stroke (ECASS II). *Lancet* 1998;352:1245-1251.
33. Clark W, Albers G, Madden K, et al. The rtPA (alteplase) 0 to 6-hour stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. *Stroke* 2000;31:811-816.
34. Quality Standards Subcommittee, American Academy of Neurology. Practice advisory: Thrombolytic therapy for acute ischemic stroke: Summary statement. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 1996;47:835-839.
35. CAST Collaboration Group. CAST: randomized placebo-controlled trial of early aspirin use in 20,000 patients with acute ischemic stroke. *Lancet* 1997;349:1641-1649.
36. Coull B, Williams L, Goldstein L, et al. Anticoagulants and antiplatelet agents in acute ischemic stroke. *Neurology* 2002;59:13-22.

37. 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.
38. Chimowitz M, Lynn M, Howlet-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352:1305-1316.
39. Diener H, Cunha L, Forbes C, et al. European Stroke Prevention Study: 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
40. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;348:1329-1339.
41. Diener HC; Bogousslavsky J; Brass LM. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-337.
42. Adams H, Brot T, Furlan A, et al. 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. *Circulation* 1996;94: 1167-1174.
43. Berge E, Abdelnoor M, Nakstad P, et al. Low molecular weight heparin versus aspirin in patients with acute ischemic stroke and atrial fibrillation: a double-blind randomized study. *Lancet* 2000;355:1205-1210.
44. Cummins R. Acute stroke. *Textbook of Advanced Cardiac Life Support*. Dallas, Tx: American Heart Association; 1997:10-28.
45. Eriksson M, Asplund K, Glader E, et al. Self-reported depression and use of anti-depressants after stroke: a national survey. *Stroke* 2004;35:936-941.

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The **Clinical Case of the Month** is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical Students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions.

CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 344. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to December 31, 2006. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

1. All of the following are known modifiable risk factors for stroke *except*:
   a) Hypertension
   b) Smoking cigarettes
   c) Elevated total cholesterol
   d) Rapid weight loss
   e) Atrial fibrillation

2. True or False. Though hypertension is an independent risk factor, lowering blood pressure decreases relative risk for both ischemic and hemorrhagic stroke by only 2.5%.

3. True or False. The mortality rate for patients with atrial fibrillation is doubled that of age and sex matched patients without atrial fibrillation primarily secondary to a higher incidence of thromboembolic stroke.

4. All of the following statements are true except:
   a) The greatest benefit of warfarin anticoagulation has been seen in patients greater than 75 years of age with atrial fibrillation.
   b) Middle cerebral artery occlusion accounts for the largest proportion of ischemic strokes.
   c) Antiplatelet therapy has consistently been shown to be beneficial in all patients with ischemic strokes who have no contraindications for its use.
   d) Blood pressure should be acutely lowered by 50% in the first hour after ischemic stroke in order to optimize cerebral perfusion pressure.
   e) Rehabilitation after an acute ischemic stroke is a major determinant in the patient's future quality of life.