Conferences and Reviews

Management of Acute Ischemic Stroke
An Update for Primary Care Physicians

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Few areas of medicine have had as many major advances in recent years as the treatment and prevention of ischemic stroke. During the 1990s—"the decade of the brain"—carotid endarterectomy was demonstrated to be effective for preventing stroke in patients with significant carotid stenosis. Large clinical studies have documented the effectiveness of new antiplatelet agents and oral anticoagulant therapy for stroke prevention in specific patient groups, and recently tissue plasminogen activator was approved for the treatment of acute ischemic stroke. Because the use of these new therapies is restricted to specific patient subgroups, the accurate determination of the cause of stroke is now mandatory. Fortunately, advances in diagnostic methods, including cardiac and vascular ultrasonographic techniques and brain imaging, facilitate the determination of the stroke subtype in most patients. Additional advances in stroke treatment and prevention are on the immediate horizon. New therapeutic agents, including neuroprotective medications, and new treatment modalities such as cerebral angioplasty are promising investigational therapies.

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Stroke is one of the most common neurologic conditions, with an incidence of about 500,000 new cases per year in the United States alone. Primary care physicians are frequently the first medical contacts and principal care providers for stroke patients. Therefore, an understanding of recent advances in stroke management is essential for primary care practitioners.

Stroke Etiology

Cerebral hemorrhage accounts for only about 15% of all stroke cases. Brain hemorrhages typically result from the rupture of an intracranial artery or a congenital aneurysm or vascular malformation. The topic of this review, ischemic stroke, represents the vast majority (about 85%) of stroke cases and occurs following an embolic or thrombotic occlusion of an extracranial or intracranial cerebral artery. Thrombotic stroke typically results from thrombus formation initiated by atherosclerotic plaque. Embolic stroke results from the embolization of atherosclerotic debris or thrombotic material into a brain vessel from a more proximal vascular lesion—such as an atherosclerotic plaque in the aorta, carotid, or vertebral artery—or from cardiac embolization. Lacunar strokes result from the occlusion of small, deep-penetrating intracerebral vessels, such as the lenticulostriate vessels, which run from the middle cerebral artery into deep brain structures, or basilar branch arteries that perfuse much of the brain stem. Atherosclerosis and cardiogenic embolization account for most ischemic strokes; uncommon causes of stroke include hypercoagulable states, vasculitis, arterial dissection, certain drugs, and infectious processes (Table 1).

Stroke Symptoms

Stroke symptoms typically occur suddenly, and the symptoms vary considerably depending on the specific region of brain injury. Carotid artery syndromes occur when this vessel or one of its major intracranial branches is occluded, causing ischemic injury to the ipsilateral cerebral hemisphere or retina. Common symptoms include unilateral weakness or sensory loss, expressive or receptive language disorders, confusion, cognitive or behavioral disorders, visual-spatial difficulties, gaze preferences, and visual field defects (Table 2). Strokes involving the posterior circulation (vertebral or basilar artery distribution) can damage the brain stem, cerebellum, midbrain, thalamus, or occipital or inferior temporal lobes. Common symptoms include unilateral or bilateral motor or sensory symptoms, oculomotor abnormalities, decreased alertness, vertigo, ataxia, and unilateral or bilateral vision loss (Table 2). Tentative lesion localization is possible in most stroke patients based on the presenting neurologic symptoms and signs. The subsequent diagnostic evaluation will be substantially influenced by the initial localization.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic/y
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NINDS = National Institute of Neurologic Disorders and Stroke
t-PA = tissue plasminogen activator

Diagnosis of Stroke

No routine or standard diagnostic algorithm is applicable to all patients with stroke because the diagnostic evaluation must be tailored to the specific clinical features of individual patients. The goals of the diagnostic evaluation are to determine the location and extent of brain injury, establish the specific cause of the stroke, and identify relevant coexisting medical conditions.

Initial Evaluation

Patients who have stroke symptoms should be urgently transported to an emergency medical facility for immediate evaluation (Figure 1). The initial assessment should verify cardiovascular stability and adequate oxygenation and include a brief initial history and neurologic examination to clarify the time symptoms occurred and estimate the degree of neurologic impairment (cognitive, motor, sensory, and visual functions). This initial evaluation should focus on determining if the patient may be a candidate for immediate therapy with tissue plasminogen activator (t-PA). If the patient is a candidate for thrombolytic therapy, the remainder of the initial evaluation must be completed emergently and focus on determining if the patient meets the specific inclusion and exclusion criteria for thrombolytic therapy (discussed later).

Preliminary laboratory studies are initiated (complete blood count, chemistry profile, prothrombin time, and activated partial thromboplastin time) and an electrocardiogram obtained. If hypoglycemia is suspected, a fingerstick blood glucose test should be done immediately. Urgent brain imaging is usually obtained with a computed tomographic (CT) scan of the brain rather than with magnetic resonance imaging (MRI) because CT is better tolerated by severely ill patients, can usually be done more rapidly, and is more sensitive for determining whether an acute stroke is ischemic or hemorrhagic. In selected patients, however, an MRI scan may be preferred as the initial brain imaging study. For medically stable patients who are not candidates for thrombolytic therapy and do not have symptoms or signs suggestive of subarachnoid hemorrhage, MRI has advantages over CT because it can identify ischemic lesions earlier, particularly small infarcts and lesions in the brain stem or cerebellum. The option of simultaneously obtaining magnetic resonance angiography (MRA) of cervical or intracranial vessels is an additional advantage of MRI.

Therapy for Acute Stroke

Emergent Supportive Interventions

Hypotension, hypoxia, hypoglycemia, and fever can exacerbate ischemic brain injury. Therefore, emergency treatment of stroke includes optimizing oxygenation and blood pressure and correcting hypoglycemia and hyperthermia. In general, hypertension should not be treated in patients with acute stroke because cerebral autoregulation is impaired in ischemic brain tissue, and blood pressure reductions may decrease blood flow in ischemic brain regions. Antihypertensive medications may be required in selected patients, however, including those who are candidates for thrombolytic therapy (discussed later) or patients with certain associated medical

TABLE 1.—*Conditions That Can Cause Stroke*

Condition	*Examples*
Cerebrovascular lesions	Atherosclerosis: extracranial, intracranial, aortic arch
	Arterial dissection: traumatic or spontaneous
	Vasculitis: immune-mediated, infectious, drug-induced
	Fibromuscular dysplasia
	Migraine
	Moyamoya syndrome
High-risk cardiac disorders	Atrial fibrillation: chronic or paroxysmal
	Myocardial infarction, especially large anterior infarcts
	Cardiomyopathies: dilated or ischemic
	Prosthetic heart valves: mechanical or bioprosthetic
	Rheumatic mitral stenosis
	Paradoxic embolism
	Endocarditis: infectious, immunologic, paraneoplastic
	Intracardiac tumors: atrial myxoma
Hypercoagulable states	Coagulation factor deficiencies: protein C, protein S, antithrombin III
	Antiphospholipid antibodies
	Hyperviscosity syndromes: immune-mediated, polycythemia, leukocytosis, thrombocytosis
	Sickle cell disease
	Hypercoagulability associated with systemic neoplasm

TABLE 2.—*Common Symptoms and Signs of Stroke*

Territory Infarcts	*Symptoms and Signs*
Carotid artery	Contralateral weakness, sensory disturbance, or homonymous hemianopsia
	Gaze preference: eyes deviate toward the injured hemisphere
	Language dysfunction: expressive or receptive aphasias
	Neglect syndromes, especially with right parietal lesions
	Behavioral disorders: confusion, agitation
	Ipsilateral monocular visual loss
Vertebrobasilar artery	Unilateral or bilateral weakness, sensory disturbance, or visual field deficits
	Oculomotor abnormalities: diplopia, gaze palsies, nystagmus
	Decreased coordination: appendicular or truncal ataxia
	Altered level of consciousness: stupor, coma
	Memory disturbances
	Vertigo

disorders (coexistent acute myocardial infarction, hypertensive encephalopathy, cerebral hemorrhage, or aortic dissection). In addition, the cautious use of antihypertensive medications is generally recommended for patients with extreme elevations of blood pressure (systolic blood pressure >220 mm of mercury, mean arterial pressure >130 mm of mercury).[1] If antihypertensive medications are required, agents that may cause abrupt drops in blood pressure, such as sublingual calcium channel blockers, should be avoided. The use of short-acting agents (such as labetalol hydrochloride) is often recommended.

Thrombolytic Therapy

In June 1996, t-PA was approved by the Food and Drug Administration for the treatment of selected patients with acute ischemic stroke. This approval was prompted by the results of the National Institute of Neurologic Disorders and Stroke (NINDS) t-PA stroke trial. This study randomly assigned 624 patients to treatment with intravenous t-PA or placebo within three hours of the onset of stroke.[2] Restrictive inclusion and exclusion criteria were used to carefully select patients for this study (Table 3), and a relatively low dose of t-PA (0.9 mg per kg with a maximum dosage of 90 mg) was used.

TABLE 3.—*National Institute of Neurologic Disorders and Stroke Protocol Patient Selection Criteria for the Administration of Tissue Plasminogen Activator for Acute Stroke*

Inclusion criteria
- Age 18 years or older
- Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- Time of symptom onset well established to be <180 min before treatment would begin

Exclusion criteria
- Evidence of intracranial hemorrhage on pretreatment computed tomography (CT)
- Only minor or rapidly resolving stroke symptoms
- Clinical presentation suggestive of subarachnoid hemorrhage, even with normal CT
- Active internal bleeding
- Known bleeding diathesis, including but not limited to
  - Platelet count <100 × 10^9/liter(<100,000/mm^3)
  - Patient has received heparin within 48 hours and has an elevated aPTT (>upper limit of normal for laboratory)
  - Current use of oral anticoagulants (such as warfarin sodium) or recent use with an elevated prothrombin time >15 seconds
- Within 3 months of any intracranial operation, serious head trauma, or previous stroke
- History of gastrointestinal or urinary tract hemorrhage within 21 days
- Recent arterial puncture at a noncompressible site
- Recent lumbar puncture
- On repeated measurements, systolic blood pressure >185 mm of mercury or diastolic blood pressure >110 mm of mercury at the time treatment is to begin, or patient requires aggressive treatment to reduce blood pressure to within these limits
- History of intracranial hemorrhage
- Abnormal blood glucose level (<2.8 or >22.2 mmol/liter [<50 or >400 mg/dl])
- Post–myocardial infarction pericarditis
- Patient observed to have seizure at the same time as the onset of stroke symptoms occurred
- Known arteriovenous malformation or aneurysm

aPTT = activated partial thromboplastin time

Patients were required to have a substantial neurologic deficit and a stroke onset time that was clearly documented to be within three hours (180 minutes) of drug administration. A CT scan was done to document that there was no evidence of brain hemorrhage before treatment. Patients could not be entered into the study if their blood pressure was higher than 185/110 mm of mercury. A cautious use of antihypertensive medications was allowed for patients with severe hypertension at stroke onset. Other exclusion criteria included recent major surgical procedure, stroke, or head trauma or substantial risk factors for bleeding. Patients receiving anticoagulants were also excluded; however, antiplatelet therapy at the time of stroke onset was acceptable.

Eligible patients were treated with intravenous t-PA or placebo. A tenth of the total dosage was administered as a bolus, immediately followed by a one-hour infusion. Following the administration of t-PA, patients were closely observed in a special care unit, and protocols were followed to maintain blood pressures below 185/110 mm of mercury, to monitor neurologic changes closely, and to detect intracranial hemorrhage. Neither antiplatelet agents nor anticoagulants were administered for 24 hours after treatment with t-PA. Patients who received t-PA had a significant improvement in neurologic and functional outcomes compared with patients who received placebo. Patients treated with t-PA were 30% more likely to have a full recovery or only minimal disability at the three-month follow-up. This degree of benefit was seen despite a 6.4% rate of symptomatic cerebral hemorrhage in the t-PA group compared with a 0.6% rate in the placebo group. Mortality was also slightly, but not significantly, reduced in the t-PA group (17% versus 21%).

At present, t-PA therapy is recommended for patients who meet the restrictive selection criteria employed in the NINDS trial (Table 3).[3,4] Because of the risk of severe brain hemorrhage, this therapy should be administered only by physicians who are thoroughly familiar with patient selection criteria and the protocols for patient monitoring and management following thrombolytic therapy (Figure 2). In addition, a physician who is skilled in interpreting the CT scan must evaluate the head CT before the thrombolytic therapy is administered. Patients and family members should be informed of the risks and benefits of this treatment. Thrombolytic therapy should be used with great caution in stroke patients older than 80 years because the risks and benefits are not well established in this age group.

Streptokinase is not indicated for use in acute stroke. All three of the large randomized trials that evaluated intravenous streptokinase use in patients with acute stroke were terminated prematurely because of an excessive incidence of brain hemorrhage and poor outcomes in streptokinase-treated patients.[5-7] These studies differed from the NINDS t-PA trial in several important ways. Patients were enrolled at later time points after the onset of stroke (usually 3 to 6 hours) and were treated with a comparatively higher dose of the thrombolytic agent. In addition, the patient selection criteria for these trials were not as restrictive as those used in the NINDS t-PA trial.

Other thrombolytic agents and the intra-arterial administration of thrombolytics have not been adequately evaluated to assess their relative risks and benefits in patients with acute stroke. Ongoing clinical trials should clarify which agents are optimal for use in stroke patients and whether certain subgroups will have greater benefit from intra-arterial administration. Studies are also underway to evaluate a longer window of time (up to 5 or 6 hours after stroke onset) for administering intravenous t-PA. At present, however, this therapy should not be given to patients who are not clearly documented to be within three hours of the onset of stroke, except as part of a clinical trial.

Initial Antithrombotic Therapy

Intravenous heparin continues to be one of the most commonly used agents for the treatment of acute stroke despite the fact that no adequate clinical trials have been done to establish its efficacy and safety. The largest modern study of intravenous heparin use in acute stroke entered only 212 patients within 24 hours of the onset of stroke.[8] This trial failed to document an improvement in neurologic outcome or a reduction of stroke progression with heparin therapy. Despite the lack of objective data to support its use, heparin is frequently chosen for patients with progressive stroke, particularly in the vertebrobasilar circulation, and for patients with severe stenosis of large intracranial or extracranial arteries, based on the premise that it can inhibit ongoing arterial thrombosis. Intravenous heparin is also frequently used in patients with acute cardioembolic stroke. Long-term therapy with oral anticoagulants is established to be highly effective for the prevention of cardiac embolism, and the results of several small studies suggest that the use of intravenous heparin may reduce the risk of early stroke recurrence in patients with acute cardioembolic stroke.[9] Early intravenous heparin therapy is generally not recommended for patients with large strokes or uncontrolled hypertension because of an increased risk of brain hemorrhage. The use of a heparin bolus and excessive prolongation of the activated partial thromboplastin time have also been associated with an increased risk of brain hemorrhage.[10]

Low-dose subcutaneous heparin (5,000 U twice a day) is effective for preventing deep venous thrombosis in immobilized stroke patients; however, subcutaneous heparin does not appear to be beneficial for preventing stroke recurrence. A large international trial recently evaluated two doses of subcutaneous heparin administered within 48 hours of the onset of stroke. A mild reduction in stroke recurrence was offset by a small increased risk of brain hemorrhage using either low doses (5,000 U twice a day) or high doses (12,500 U twice a day) of subcutaneous heparin.[11]

Low-molecular-weight forms of heparin may be safer and more efficacious for stroke patients. A recent randomized trial from Hong Kong reported substantial improvement in stroke outcome and no increase in the

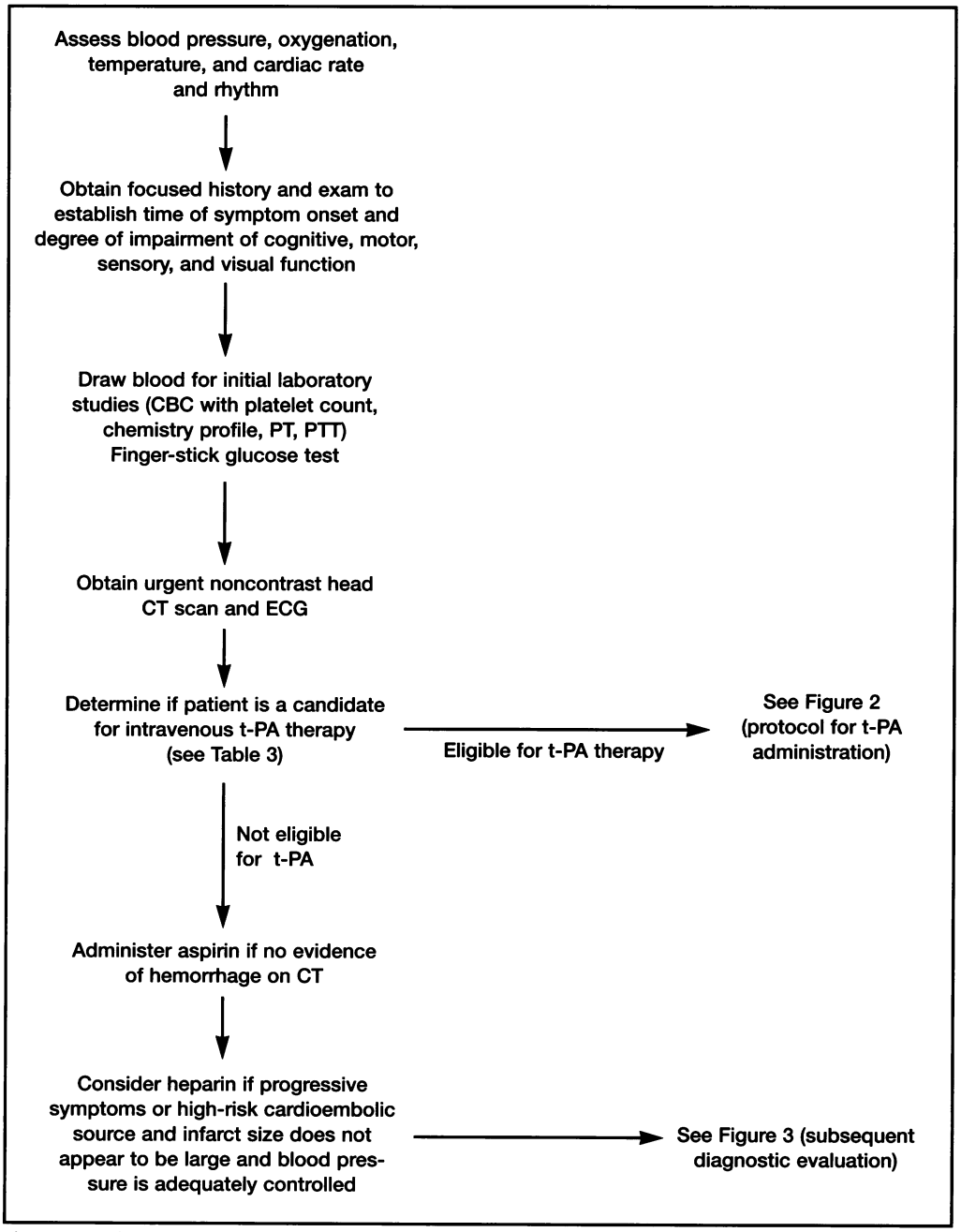

Figure 1.—The initial evaluation of a patient with acute ischemic stroke is shown. CBC = complete blood count, CT = computed tomography, ECG = electrocardiogram, PT = prothrombin time, PTT = partial thromboplastin time, t-PA = tissue plasminogen activator

incidence of hemorrhagic complications among patients treated within 48 hours of stroke onset with subcutaneous nadroparin calcium given for ten days.[12] Further evaluation of nadroparin in patients with acute stroke is ongoing (this agent is currently not available in the United States). A large North American trial of another low-molecular-weight form of heparin (danaparoid sodium; ORG 10172) is nearing completion.

Aspirin is the only antiplatelet agent whose use has been adequately evaluated in patients with acute stroke. A large international trial recently found that patients treated within 48 hours of the onset of stroke with 300 mg of aspirin per day were less likely to suffer early stroke recurrence than control patients.[11] Similar results were found in a recent trial in China using 160 mg of aspirin.[13] Based on these results, early aspirin therapy can be recommended for patients with acute ischemic stroke who do not receive treatment with t-PA.

Neuroprotective Agents

Recent advances in neuroscience have identified the basic mechanisms that mediate ischemic brain injury.[14-16]

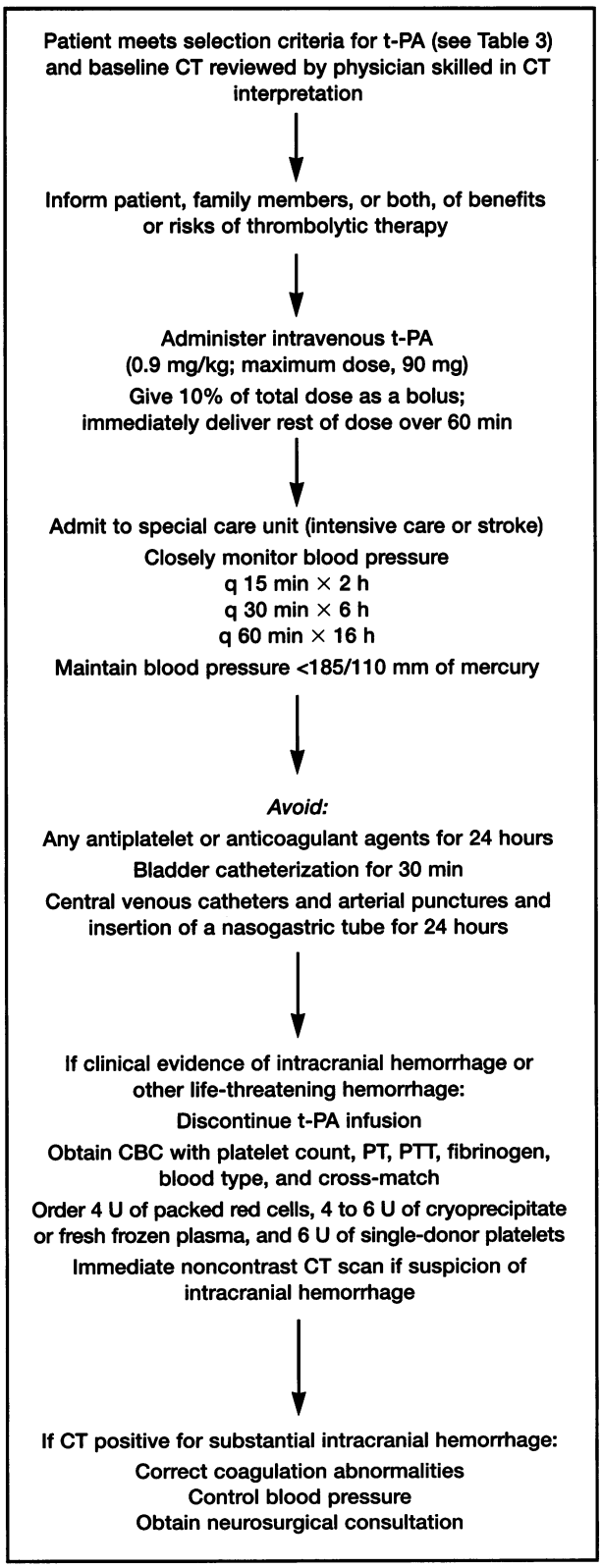

Figure 2.—The protocol for administering intravenous tissue plasminogen activator (t-PA) to patients with stroke is shown. CBC = complete blood count, CT = computed tomography, PT = prothrombin time, PTT = partial thromboplastin time, q = every

A cascade of biochemical reactions initiated by an excessive activation of neuronal excitatory amino acid receptors leads to a toxic influx of calcium into neurons. Excessive intracellular calcium can trigger a host of detrimental reactions, including the activation of phospholipases and proteases, the generation of free radicals, and lipid peroxidation. The intracellular formation of nitric oxide also appears to be an important mediator of ischemic neuronal injury. This "neuronal injury cascade" offers multiple sites for the pharmacologic protection of the brain from ischemic injury. New medications have been developed to attenuate or interrupt the neuronal injury reactions, and many of these agents have been found highly effective in reducing brain injury in experimental stroke models. Several of these neuroprotective agents are currently in the final stages of clinical evaluation in stroke patients, and highly encouraging results have been obtained in preliminary trials. These medications not only appear to be effective for limiting the degree of brain injury caused by ischemic stroke but also may lengthen the time window available for administering thrombolytic agents. For example, a large North American study of the neuroprotective agent lubeluzole recently reported that patients treated within six hours of stroke onset had improvement in neurologic outcome without suffering serious adverse effects.[17] Lubeluzole appears to act by inhibiting neuronal injury mediated by intracellular nitric oxide. Other promising neuroprotective strategies include *N*-methyl-D-aspartate antagonists that block the excessive activation of excitatory amino acid receptors.[18] It is likely that neuroprotective agents will be available for general clinical use within the next several years.

Subsequent Diagnostic Studies

After the initial diagnostic tests are done and emergent supportive interventions and therapies have been administered, more detailed diagnostic testing is done to clarify the cause of the stroke (Figure 3). For patients with ischemic lesions in the carotid distribution, an evaluation of the cervical carotid artery is usually essential. Patients with mild neurologic deficits or rapid recovery may be candidates for early carotid endarterectomy if a severe (≥70%) ipsilateral carotid stenosis is detected. Carotid imaging is also helpful for patients who are not candidates for carotid endarterectomy because it may clarify the cause of the stroke and influence blood pressure management or anticoagulant therapy. Carotid duplex ultrasonography is typically the most accurate and inexpensive method for imaging the carotid bifurcation. In many laboratories, carotid ultrasonography has an accuracy of 90% to 95%[19]; accuracy varies considerably among different laboratories, however.[20] Ultrasonography is more accurate for assessing severe lesions than for mild to moderate stenoses, although it cannot reliably differentiate a very severe stenosis from a carotid occlusion. Magnetic resonance angiography and spiral CT angiography are alternative techniques for evaluating the carotid bifurcation and can also evaluate the distal carotid artery and major intracranial vessels. These regions can also be imaged with transcranial Doppler,

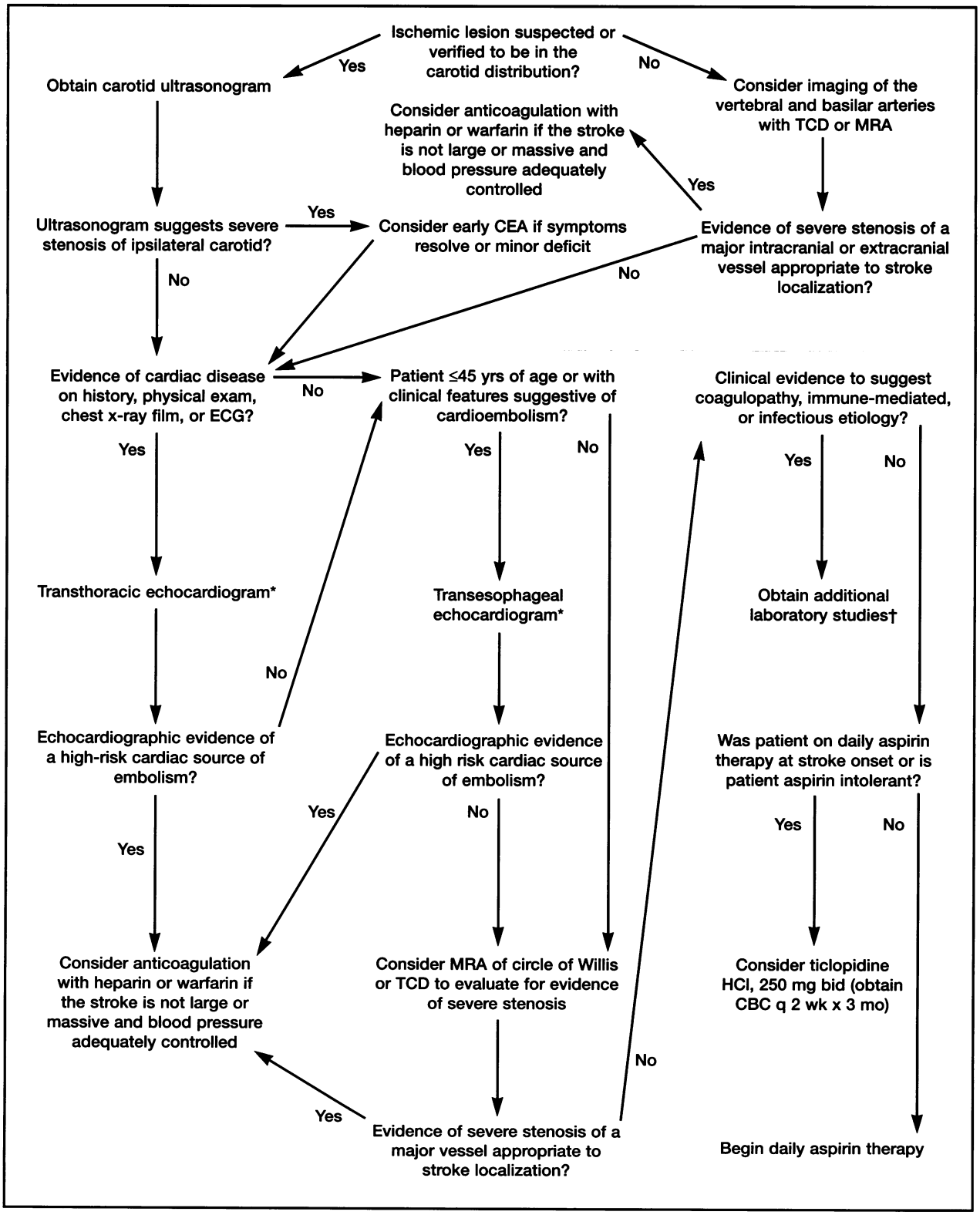

Figure 3.—The algorithm shows the subsequent evaluation and treatment recommendations for patients with stroke. *Echocardiography may not be required for patients with previously diagnosed and stable high-risk cardiac disorders (such as atrial fibrillation) for whom warfarin sodium therapy will be indicated regardless of echocardiographic findings. †Consider laboratory evaluation for hypercoagulable states (see Table 1), infectious diseases, or immune-mediated disorders. bid = twice a day, CBC = complete blood count, CEA = carotid endarterectomy, ECG = electrocardiogram, HCl = hydrochloride, MRA = magnetic resonance angiogram, q = every, TCD = transcranial Doppler

which provides physiologic information about blood flow velocity that is not available with CT or MRA. Other limitations of MRA include an overestimation of the degree of arterial stenosis and the inability to discriminate severe stenoses from complete occlusions.

For patients with vertebrobasilar ischemia, the vertebral arteries and basilar artery can be imaged noninvasively with CT, MRA, or transcranial Doppler. If further clarification of lesion location or severity is required in either the anterior or posterior circulation, conventional cerebral angiography can provide excellent visualization of all of the major intracranial and extracranial cerebral vessels. Angiography is more sensitive than the noninvasive techniques for clarifying the specific cause and severity of vascular lesions (atherosclerosis, dissection, vasculitis, aneurysm).

For patients with clinical evidence of heart disease—previous cardiac disorders, abnormal cardiac examination or chest radiography, or substantial electrocardiographic abnormalities—a transthoracic echocardiogram is usually indicated. This generalization does not apply to patients with previously documented stable cardiac disorders who have undergone echocardiography and for whom anticoagulation therapy will be indicated regardless of the echocardiographic findings—for example, patients with atrial fibrillation, notable valvular disease, or severe cardiomyopathy. For patients with no clinical evidence of heart disease, the yield of transthoracic echocardiography is less than 3%.[9] Transesophageal echocardiography is frequently reserved for young patients (<45 years old) and persons with stroke of unclear origin after routine diagnostic studies and transthoracic echocardiography are done. Although transesophageal echocardiography has a high yield for detecting possible cardioembolic sources such as spontaneous echo contrast, aortic atherosclerosis, atrial septal aneurysm, and patent foramen ovale, the identification of these lesions often does not influence subsequent management.[21]

Additional laboratory studies are obtained if there is a suspicion of a coagulopathy or an infectious or immune-mediated disorder. Specific studies that are often helpful include antiphospholipid antibodies, protein C, protein S, antithrombin III, sedimentation rate, antinuclear antibody tests, and syphilis serologic tests. Lumbar puncture is not routinely indicated in patients with ischemic stroke, but it may be warranted when there is suspicion of a small subarachnoid hemorrhage, a central nervous system infection, vasculitis, or multiple sclerosis.

Stroke Prevention

Following the diagnosis and initial treatment, attention can be focused on preventing stroke recurrence. Treatable stroke risk factors should be reviewed with the patient and efforts made to modify existing risk factors (Table 4).[22] Patients with significant carotid stenosis should be considered for carotid endarterectomy (discussed later).

TABLE 4.—*Modifiable Stroke Risk Factors*

Stroke Risk Factor	*Estimated Relative Risk*
Hypertension	4.0–5.0
Cardiac disease	2.0–4.0
Atrial fibrillation	5.6–17.6
Diabetes mellitus	1.5–3.0
Cigarette smoking	1.5–2.9
Alcohol abuse	1.0–4.0
Hyperlipidemia	1.0–2.0

*Adapted from Sacco.[22]

Antiplatelet Agents

Numerous studies have documented that aspirin is effective for preventing stroke recurrence in both male and female patients who have suffered an ischemic stroke or transient ischemic attack.[23] Unfortunately, clinical trials have not clarified the optimal dosage of aspirin, and experts continue to debate whether low or high doses should be recommended. At present, there is no compelling evidence to support a specific dosage recommendation. Dosage ranges from 30 to 1,300 mg per day are currently considered acceptable, with most physicians in the United States opting for 325 mg per day.[24]

Ticlopidine hydrochloride is the only other currently available antiplatelet agent with conclusively demonstrated efficacy for preventing stroke. Ticlopidine is slightly more effective than aspirin, but it is associated with more frequent adverse effects, including substantial neutropenia in about 1% of patients.[25] Therefore, aspirin is generally recommended as the initial antiplatelet agent for most stroke patients. Ticlopidine is typically chosen for patients who suffer a stroke or transient ischemic attack despite aspirin therapy or for persons who are aspirin intolerant.[26]

Clopidogrel, a new antiplatelet agent, was recently found to have efficacy and safety similar to 325 mg a day of aspirin for preventing stroke.[27] This agent has not yet received approval from the Food and Drug Administration. Although previous studies did not find dipyridamole to be effective for stroke prevention, a recent large trial found that a combination of dipyridamole and aspirin was considerably more effective than the use of aspirin alone for preventing stroke. The clinical implications of these results are currently unclear, and concerns have recently been raised regarding the conduct of this trial.[28]

Long-term oral anticoagulation with warfarin sodium (international normalized ratio, 2.0 to 3.0) is the treatment of choice for most patients who suffer a cardioembolic stroke. The safety and efficacy of oral anticoagulation has been demonstrated most clearly for patients with atrial fibrillation.[29] Anticoagulation is widely recommended for patients who suffer a cardioembolic stroke from most high-risk cardiac causes, including acute myocardial infarction, severe cardiomyopathy, and substantial valvular heart disease. A slightly greater intensity of anticoagulation (international normalized ratio, 2.5 to 3.5) is suggested for stroke prevention in patients with mechanical heart valves. Anticoagulation is not indicated for patients with stroke caused by septic emboli, except in patients with mechanical heart valves.

The role of oral anticoagulation in ischemic stroke of noncardioembolic causes has not been adequately evaluated in clinical trials. The use of oral anticoagulant therapy is frequently recommended for patients who suffer an ischemic stroke despite adequate antiplatelet therapy, and recent preliminary data suggest that oral anticoagulation may be more effective than antiplatelet therapy for patients with symptomatic intracranial stenoses.[30] A large trial sponsored by the National Institutes of Health is currently comparing the efficacy of warfarin with aspirin in patients with noncardioembolic stroke subtypes.

Carotid Endarterectomy or Cerebral Angioplasty

Three large randomized, multicenter trials consistently found carotid endarterectomy to be highly beneficial for preventing stroke in patients with symptomatic carotid stenosis of 70% or more who are good surgical candidates.[31–33] Patients with recent transient ischemic attacks or minor strokes were entered into these trials and operated on by surgeons with track records of low perioperative stroke and death rates when performing this procedure. Carotid endarterectomy is not indicated for patients with less than 30% stenosis of the carotid artery.[32] The role of carotid endarterectomy is currently under investigation for patients with moderate (30% to 69%) stenosis; however, one recent European trial did not find evidence of benefit for this subgroup of patients.[34]

The Asymptomatic Carotid Atherosclerosis Study (ACAS) recently found that asymptomatic patients with moderate to severe carotid stenosis (60% to 99%) can benefit from carotid endarterectomy. The degree of benefit in this study, however, was considerably less than that documented for patients with symptoms referable to the carotid lesion.[35] The recurrent stroke risk was reduced from about 2% per year in the medical treatment group to about 1% per year in the surgical treatment group. Therefore, the expected risks and benefits of this procedure should be carefully considered in asymptomatic patients. Patients who are at low surgical risk and have a life expectancy of at least five to ten years are most likely to benefit.

The results from several large series suggest that cerebral angioplasty may be a viable option for stroke prevention in patients with both intracranial and extracranial vascular lesions.[36] This procedure is not yet widely available and is generally restricted to patients who are refractory to maximal medical therapy and are not candidates for carotid endarterectomy. Large randomized trials designed to clarify the efficacy and safety of cerebral angioplasty are currently being organized.

Economic and Public Health Effects

Despite substantial advances in diagnosis, treatment, and prevention, stroke continues to have a major effect on public health. Stroke remains the most common cause of neurologic disability and the third leading cause of death. Estimates of the total cost of stroke vary widely; recent figures suggest an annual cost in the United States of about $30 billion.[37] Because of the high cost of stroke, effective stroke treatment and prevention therapies are highly cost-effective.[38,39] Unfortunately, physicians are often slow to adopt these new therapies. For example, compelling data from several clinical trials have documented the efficacy and safety of oral anticoagulation therapy for preventing stroke in patients with atrial fibrillation, yet this therapy continues to be substantially underused.[40] Preliminary analyses indicate that initial stroke therapy with t-PA is also highly cost-effective; yet, only a small fraction of eligible patients receive thrombolytic therapy for stroke.

Recently approved therapies for stroke and several promising investigational strategies offer hope for a substantial reduction in stroke incidence, disability and death. Extensive physician and patient education programs will be required to implement these new treatments.

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