Transient Ischemic Attack and Acute Ischemic Stroke

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EMPIDEMIOLOGY

The yearly incidence of TIA in the United States has been estimated to be approximately 200,000 to 500,000 but may be higher because of the high frequency of underreporting of these events by medical professionals. The annual incidence of TIA may be less and the annual incidence of stroke may be higher if the tissue-based definition were applied to all patients evaluated for TIA. It has been estimated that the overall incidence rate of TIA is 1.1 per 1000 U.S. population. This incidence increases with age from 0.1 per 1000 for patients younger than 50 years to 11.7 per 1000 for patients older than 80 years. The incidence of TIA also varies with race and gender: it is significantly greater in blacks and men than in whites and women. The greatest incidence of TIA occurred in black men older than 85 years, who had an incidence of 16 events per 1000.

TIAs account for 0.3% of all emergency department (ED) visits, and it is estimated that 8.7% to 30% of patients will have a TIA before stroke. Only 28% of TIA patients arrive via ambulance, and 36% of patients arrive during daylight hours. Emergency physicians (EPs) obtain computed tomography (CT) scans on 56% to 70% of all TIA patients and magnetic resonance imaging (MRI) scans on 7% of TIA patients. Nearly half of all patients with TIA are admitted to the hospital, although there is geographic variability in this practice; another 20% of patients are referred for follow-up. Finally, patients seen in the ED with TIA receive preventive aspirin therapy in 18% of cases, other antiplatelet therapy in 7%, and no preventive therapy in an estimated 42%.

Clearly defined risk factors for stroke and adverse events following a TIA are now well described in the literature, and several groups of investigators have independently developed short-term risk stratification methods applicable to TIA patients in the ED. These investigators reported a 10% rate of stroke in the 90 days following the TIA, with 50% of these strokes occurring in the immediate 48 hours after the TIA.

Recently, the ABCD2 score, which combines elements from existing risk stratification systems, was devised to create a robust prediction standard for determining high-risk populations that will benefit from emergency investigation and therapy to prevent short-term adverse events (Table 100.1). Patients with the following characteristics were at high risk for having a stroke in the next 2 to 90 days: age older than 60 years, blood pressure higher than 140 mm Hg systolic or 90 mm Hg diastolic, clinical features such as unilateral

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weakness or speech disturbance, longer duration of symptoms of TIA, and diabetes.

Ischemic stroke accounts for 80% to 88% of the total strokes occurring annually.\(^{11}\) Each year approximately 795,000 people experience a new or recurrent stroke. It is an important cause of death in the United States and ranks third behind heart disease and cancer.\(^ {13}\)

Approximately 8% to 12% of all patients suffering an ischemic stroke die within 30 days of the initial stroke. Ischemic stroke disproportionately affects the elderly, with a mean age at onset of 70.5 years. Ischemic stroke affects black and Hispanic populations more frequently than white populations. The age-adjusted incidence of first ischemic stroke per 100,000 population is 88 in whites, 149 in Hispanics, and 191 in blacks.\(^ {16}\) Ischemic stroke is an enormous economic burden, with an average 30-day cost of $20,346 for a severe stroke and mean lifetime cost of $140,048.\(^ {16}\) The United States spends approximately $73.7 billion yearly on the direct and indirect cost of stroke care.\(^ {15}\)

### FACTS AND FORMULAS

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S1 = \frac{SV}{BSA}
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8.7% to 30% of stroke patients suffer a TIA before the stroke.  
10% of TIA patients have a stroke in the next 90 days, 25% to 50% of whom will have their stroke within the first 2 days.  
33% of TIA patients with symptoms lasting less than 1 hour will have an infarct shown on diffusion-weighted magnetic resonance imaging.  
50% of TIA patients never report symptoms to a physician.  
19.2% of patients with untreated symptomatic carotid stenosis of greater than 70% will have a stroke in the next 90 days.  
For each minute that reperfusion is delayed, 1.9 million neurons die.

\(TIA\), Transient ischemic attack.

### PATHOPHYSIOLOGY

An ischemic injury involving the central nervous system disrupts normal cerebral blood flow to the brain (40 to 60 mL/100 g brain/min). The extent of injury is based on three principles: the duration of disrupted flow, the flow rate, and collateral circulation. Loss of consciousness occurs within 10 seconds and cell death within minutes of disrupted cerebral circulation.

Cerebral tissues with blood flow between 12 and 20 mL/100 g brain/min are termed the ischemic penumbra. These cells are at risk for permanent injury but have the ability to recover if flow is reestablished. When cerebral blood flow falls below 10 mL/100 g brain/min, electrical activity ceases and cell death occurs. Many areas of the brain may be protected by collateral circulation between the anterior and posterior circulation through vessels that make up the circle of Willis.

Classification of TIAs is important because the pathophysiology and risk for recurrent stroke differ among the subtypes. The five mechanisms described are large artery atherosclerosis, cardioembolism, small vessel disease, other rare determined cause, and undetermined cause.\(^ {9,18}\)

Large artery atherosclerosis is defined as greater than 50% narrowing of vessel caliber. It accounts for 15% of all ischemic strokes and is the most common cause of low-flow TIA. Symptoms are the result of thrombus formation in a ruptured atherosclerotic plaque. The most commonly affected vascular territories are the origin of the internal carotid and intracranial portion of the internal carotid (siphon), the middle cerebral artery stem, and the junction of the vertebral and basilar arteries. It is found more commonly in men and has a greater incidence in African and Hispanic populations. Patients with large artery atherosclerosis have a higher recurrence rate than do patients with other stroke subtypes: 4%, 12.6%, and 19.2% at 7, 30, and 90 days, respectively.\(^ {17}\) These patients have transient or stuttering symptoms in the same vascular territory. Symptoms and disability may be less severe than those in patients with cardioembolic stroke.\(^ {14}\)

Cardioembolic disease represents 20% to 25% of ischemic cerebrovascular events. The most common sources are abnormal cardiac rhythm, abnormal left ventricular wall motion, and aortic and mitral valve disease.\(^ {20}\) The clinical features are

### Table 100.1 Two-Day Risk for Stroke Stratified According to the ABCD2 Score

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>NUMBER OF POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 yr</td>
<td>1</td>
</tr>
<tr>
<td>Initial blood pressure &gt; 140/90 mm Hg</td>
<td>1</td>
</tr>
<tr>
<td>Symptoms of focal motor weakness</td>
<td>2</td>
</tr>
<tr>
<td>Symptoms of speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration &gt; 60 min</td>
<td>2</td>
</tr>
<tr>
<td>Duration 10-59 min</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABCD2 SCORE</th>
<th>2-DAY RISK FOR STROKE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0%</td>
</tr>
<tr>
<td>2-3</td>
<td>1.3%</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
</tr>
<tr>
<td>6-7</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

abrupt in onset, with nonprogressive symptoms that may occur in multiple vascular territories. Cardioemboli affect the anterior circulation in 70% of patients. These patients tend to have more severe symptoms and higher mortality rates; disability is more severe in survivors. Patients with embolic TIA have a lower recurrence rate of 2.5%, 4.6%, 11.9% at 7, 30, and 90 days, respectively. Lacunar strokes represent 20% of all ischemic strokes and are caused by small vessel disease—obstruction of the small vessels that penetrate the brain parenchyma at right angles to major parent arteries and supply the basal ganglia, internal capsule, thalamus, andpons. The vessels most commonly involved are small branches of the middle cerebral and basilar arteries. The most common causes of small vessel disease are microatheroma and lipohyalinosis, which are increased in the setting of older age, hypertension, diabetes, and smoking. Small embolic events rarely cause ischemia in these vessels.

Patients with lacunar TIA and stroke commonly have hypertension and diabetes. Black populations are affected more than white populations, and there does not seem to be a gender preference in patients with lacunar infarcts. These patients have a favorable prognosis with low, short-term recurrence rates of 0%, 2%, and 3.4% at 7, 30, and 90 days, respectively.

Rare causes of stroke account for approximately 2% to 3% of annual cases. Common causes are nonatherosclerotic vasculopathies (acute arterial dissection, vasculitis, polyarteritis, giant cell arteritis, infectious arteritis), hypercoagulable conditions (deficiencies in proteins C and S and antithrombin III, antiphospholipid antibody syndrome/systemic lupus erythematosus, pregnancy, postmenopausal hormone replacement), hematologic disorders (sickle cell disease, polycythemia, myeloproliferative disorders), and other causes of emboli (patent foramen ovale, endocarditis, air).

Cryptogenic stroke is the designation used for stroke without a well-defined etiology despite extensive evaluation. It accounts for 30% to 40% of all strokes in some stroke databases. Patients with cryptogenic stroke have a better 1-year prognosis than those with other subtypes; the 2-year risk for recurrence is 14% to 20%.

Systemic hypoperfusion is an uncommon cause of cerebral ischemia that represents a global decrease in cerebral blood flow. Causes include cardiac arrest and reduced cardiac output as a result of cardiac ischemia, pericardial effusion, arrhythmias, pulmonary emboli, hemorrhage, and medications. Symptoms consist of diffuse brain dysfunction in the setting of unstable vital signs.

### PRESENTING SIGNS AND SYMPTOMS

Patients who have suffered a TIA often have no physical findings but a variety of historical clinical symptoms. Several studies have demonstrated that interobserver disagreement is high when making the diagnosis of TIA. A few basic principles can guide accurate diagnosis of TIA. The symptoms are sudden in onset and vascular in nature. TIAs are commonly brief, lasting less than 1 to 2 hours with many lasting less than 10 to 15 minutes. Symptoms are associated with loss of function such as hemiparesis, hemiparesis, dysarthria, aphasia, monocular vision loss, diplopia, and gait and balance disturbances. Symptoms such as shaking, scotomata, and marching of symptoms to other body parts are more consistent with migraine or seizure.

Approximately 80% of ischemic strokes occur in the distribution of the anterior circulation and give rise to deficits in behavior, sensation, movement, and speech, as well as some elements of visual awareness. The minority of strokes occur in the distribution of the posterior circulation. Common posterior circulation symptoms are limb weakness, gait and limb ataxia, oculomotor palsy, and oropharyngeal dysfunction. In addition, patients often exhibit nausea and vomiting because of brainstem involvement, as well as vertigo and balance disorders related to cerebellar and brainstem injury.

### OPHTHALMIC ARTERY

Transient monocular blindness, known as amaurosis fugax, is caused by transient occlusion of the ophthalmic artery. It is commonly associated with internal carotid artery stenosis and carries a better prognosis than does carotid disease associated with hemispheric TIA.

### MIDDLE CEREBRAL ARTERY

Patients with middle cerebral artery occlusion typically exhibit sensory loss homoplegia, contralateral sensory loss, and contralateral homonymous hemianopia. Patients with dominant hemispheric lesions have aphasia; those with non-dominant hemispheric lesions demonstrate contralateral hemisensory neglect. Subtle findings include gaze preference toward the side of the lesion and contralateral gaze weakness.

### ANTERIOR CEREBRAL ARTERY

Occlusion of branches of the anterior cerebellar artery is more common than stem lesions and is associated with well-recognized clinical findings: contralateral motor weakness and sensory deficit in the lower extremity. Other symptoms include urinary incontinence because of contralateral weakness of the pelvic floor muscles, memory loss or aphasia secondary to occlusion of the orbital or frontopolar branch, dysarthria secondary to compromise of the medial striate artery, and ideomotor apraxia (inability to perform skilled movements) as a result of occlusion of the pericallosal branch.

### SMALL VESSEL DISEASE (LACUNAE)

Patients with lacunar ischemia are commonly hypertensive, diabetic, or both, and they do not have associated cortical dysfunction (speech, calculation, and spatial orientation deficits). Lacunar infarcts result from ischemic events involving small penetrating branches of the middle cerebral, anterior cerebral, posterior cerebral, and basilar and anterior choroidal arteries. These lesions affect the basal ganglia, internal capsule, thalamus, putamen, and internal capsule. Five major lacunar syndromes are recognized: pure motor hemiparesis, ataxic hemiparesis, pure sensory syndrome, mixed sensorimotor syndrome, and dysarthria–clumsy hand syndrome. Pure motor hemiparesis is the most common lacunar syndrome and occurs in 50% of patients with lacunar strokes. Patients have stuttering symptoms that develop over hours, as well as contralateral facial and arm weakness, but do not have sensory or higher cortical dysfunction. The injury involves the corona radiata or internal capsule.

Ataxic hemiparesis syndrome is characterized by weakness and dysmetria (inability to fix the range of movement) on the
same side. The lower extremity is more often affected and the face is least affected. The injury involves the internal capsule, basis pontis, or corona radiata.\textsuperscript{22}

Patients with pure sensory syndrome have contralateral sensory loss in the face, arm, and leg. Symptoms include sensory ataxia, a movement disorder secondary to sensory impairment; a wide-stance gait with gaze directed to the feet; and a walking pattern characterized by a stamping action that maximizes any remaining proprioception. The injury involves the ventral posterior nucleus of the thalamus.\textsuperscript{22}

In mixed sensorimotor syndrome, patients have hemiparesis or hemiplegia associated with sensory loss on the same side. This syndrome is distinguished from the other syndromes by the lack of associated cortical symptoms. The posterolateral thalamus and the posterior limb of the internal capsule are the sites of injury.\textsuperscript{22}

Dysarthria–clumsy hand syndrome is the least common of the lacunar syndromes and affects 6% of patients with lacunar stroke. Patients are typically dysarthric secondary to paresis of the lip, tongue, and jaw musculature and report clumsiness of hand movement. The injury involves fibers descending through the genu of the internal capsule.\textsuperscript{22}

VERTIBROBASILAR ARTERIES
Twenty percent of ischemic events affect brain tissue supplied by the posterior circulation. Patients with posterior circulation ischemia rarely have a single initial sign or symptom. Typical symptoms are dizziness, vertigo, headache, vomiting, double vision, loss of vision, transient interruption of consciousness, numbness, weakness, and ataxia. These patients often have crossed signs that include ipsilateral cranial nerve deficits associated with contralateral motor deficits. The most common signs include contralateral limb weakness, gait and limb ataxia, oculomotor palsy, and oropharyngeal dysfunction.

POSTERIOR CEREBRAL ARTERY
Occlusion of the posterior cerebral artery and its branches leads to a variety of defects in the cerebral cortex, midbrain, thalamus, subthalamic nuclei, and corpus callosum. Stem lesions in the posterior cerebral artery cause isolated contralateral homonymous hemianopia. Midbrain lesions result in crossed symptoms with ipsilateral third nerve palsy accompanied by contralateral motor hemiplegia. Thalamic branch lesions cause contralateral sensory loss accompanied by hemianopia. Injury to the subthalamic nuclei results in ballism of the contralateral arm. Finally, corpus callosum injury results in an inability to transfer written information from right to left, as well as alexia (inability to read written material).\textsuperscript{23}

CEREBELLAR INFARCT
The most common cause of an ischemic injury involving the cerebellum is an embolic infarct in the upper part of the cerebellum. Symptoms include dizziness, vertigo, vomiting, blurred vision, and difficulty walking. Patients may report that they veer to a specific side or are unable to sit upright without assistance. Cerebellar infarcts are distinguished from infarcts in other anatomic locations by the lack of hemiparesis or hemisensory deficits.\textsuperscript{23,28} Hypotonia may be present in the arm on the affected side. This sign is best elicited by having patients hold their arms straight out at 90 degrees from the trunk, quickly lower them, and then abruptly stop the lowering motion. The affected side is detected because the hypotonic arm will overshoot the rapid descent.

LATERAL MEDULLARY SYNDROME (WALLENBERG SYNDROME)
Occlusion or narrowing of the intracranial vertebral artery causes signs and symptoms related to ischemic injury to the lateral medullary tegmentum. Symptoms include ipsilateral facial sensory loss, ataxia, and nystagmus. Patients may also have Horner syndrome, hoarseness, difficulty swallowing, and contralateral hemisensory loss of pain and temperature sense.

DIFFERENTIAL DIAGNOSIS AND MEDICAL DECISION MAKING
Evaluation of patients with suspected ischemic injury is summarized in Box 100.1. The results of these fundamental tests combined with risk stratification can guide the EP in determining whether cerebral injury has occurred, as well as the cause of the ischemia.

Patients with TIA and ischemic stroke require rapid and accurate diagnosis to determine the cause and location of the event and the extent of damage. This knowledge allows the EP to estimate the risks and benefits associated with therapies that will reestablish cerebral blood flow and preserve viable brain tissue.

Rapid diagnosis of acute ischemic stroke begins with public education about recognition of the major warning signs of stroke. Prehospital personnel also play a crucial role in early diagnosis and rapid transport of stroke patients to treatment facilities. Tools such as the Cincinnati Prehospital Stroke Scale and the Los Angeles Prehospital Stroke Screen (LAPSS) are used to evaluate facial droop, arm weakness, and speech abnormalities in patients with suspected stroke. In addition, the LAPSS screens for mimics of stroke such as hypoglycemia, hyperglycemia, and seizure and has high sensitivity (93%) and specificity (97%) for the diagnosis of acute stroke.\textsuperscript{29,30}

EPs caring for patients with acute ischemic stroke are often under enormous time constraints. A systematic method is necessary to distinguish patients with stroke from those with conditions that mimic stroke.\textsuperscript{31} In addition, the EP must combine historical and physical data with the results of
neurologic imaging to exclude hemorrhage and determine the extent of injury. These elements, coupled with basic laboratory tests and an electrocardiogram (ECG), as recommended by the American Heart Association (AHA), are the foundation for accurate diagnosis of an acute ischemic stroke.

The history is the cornerstone of accurate stroke diagnosis. Historical evidence that has been identified as being predictive of a patient having a stroke includes persistent focal neurologic deficits, acute onset during the previous week, and no history of head trauma. Clinical symptoms such as arm and leg weakness and speech impairment are more reliable indicators than subjective isolated sensory symptoms are. The single most important piece of historical information is the time of onset of the symptoms. This is considered to be the last time that the patient was at the previous baseline or symptom-free state. For patients unable to provide this information or awaken with stroke symptoms, onset is defined as time when the patient was last seen to be normal. Other key historical factors include contraindications to thrombolytic therapy, medications being taken by the patient, heart disease, previous stroke, TIA, seizures, vomiting, or headache occurring at the beginning of the patient’s acute symptoms.

EPs must use a reproducible standardized physical examination to assess the severity of injury in stroke patients. Three key physical findings—facial paresis, arm drift, and abnormal speech—are highly predictive of an acute stroke. The National Institutes of Health Stroke Scale (NIHSS) (see the Document box) is a valid, standardized tool that records clinical findings and provides information that is helpful in determining the prognosis and therapeutic options. This 42-point scale evaluates level of consciousness, cranial nerves, motor function, ataxia, sensation, speech, and neglect. It can be used for serial examinations and is a predictor of patient outcome and risk associated with therapy, which can be useful when discussing treatment options with specialists, patients, and family members.

Patients with an NIHSS score lower than 6 have a predicted excellent outcome at 6 months, and 81% are discharged home. Nearly half the patients with an NIHSS score higher than 15 will require transfer to a nursing facility. Patients with an NIHSS score higher than 20 have a 17% risk for intracerebral hemorrhage when treated with recombinant tissue plasminogen activator (rt-PA). Finally, each additional point on the NIHSS decreases the likelihood of an excellent outcome by 17%,33,35

Although the history and physical examination are important elements in making an accurate diagnosis of patients with acute neurovascular events, neuroimaging is the key diagnostic tool. The goals of modern neuroimaging evaluation are to (1) obtain evidence of a vascular origin of the symptoms; (2) exclude an alternative nonischemic origin; (3) ascertain the underlying vascular mechanism of the event, which helps guide therapy; (4) identify prognostic outcome categories; and (5) improve selection of patients to be treated with reperfusion therapies by identifying those with regions of salvageable brain tissue, low risk for hemorrhagic transformation, or occlusion of large arteries that might be amenable to therapy.31 Currently, EPs have a multitude of imaging options that are based on availability of the imaging modality and local expertise in interpretation of the images.

Non–contrast-enhanced CT remains the standard imaging technique for evaluating patients with acute stroke. It can be performed in the majority of hospitals, images are acquired rapidly, and it is sensitive in detecting acute hemorrhage. For patients with TIA, CT has been shown to provide an alternative diagnosis in 1% of all cases, and a new infarct has been found within 48 hours in 4% of patients with TIA. Of these patients, 38% eventually experienced a new ischemic stroke in the next 90 days.36 CT findings not associated with an increased short-term risk for stroke include old infarction, periventricular white matter disease, cerebral atrophy, and vascular calcification.30 Unfortunately, CT scans are frequently negative in the first hours after an ischemic stroke, are limited in defining posterior fossa structures and discriminating between infarct and viable at-risk tissue (penumbra), and provide no information on the presence or location of vascular pathology.32

Subtle clues found on CT scanning are cortical hypodensity, hyperdense middle cerebral artery, middle cerebral artery dot sign, sulcal effacement, hypointensity of the insular ribbon, and obscuration of the lentiform nucleus. The Alberta Stroke Program Early CT Score (ASPECTS) organized these early subtle clues into a semiquantitative 10-point grading system for early ischemic changes in the middle cerebral artery territory found on CT scans. Patients with an ASPECTS higher than 7 were found to have a much higher incidence of parenchymal hematoma after receiving rt-PA therapy.37

Perfusion CT is an advanced neuroimaging technique that uses intravenous (IV) contrast material to provide semiquantitative information on cerebral blood flow and cerebral blood volume. Other useful calculations include the mean transit time of the contrast agent from the arterial to the venous circulation and time to peak, which measures the time between the first arrival of contrast agent in the artery and the peak of the bolus within the brain tissue.38 Studies suggest that a CT battery that includes non–contrast-enhanced CT, CT angiography, and CT perfusion can be performed quickly in patients with acute stroke and can provide comprehensive

**DOCUMENTATION**

- Time of onset of symptoms or the last time that patient was seen to be normal
- Initial National Institutes of Health Stroke Scale (NIHSS) score
- Resolution of symptoms and NIHSS score of 0 for patients with a transient ischemic attack (TIA)
- Single or multiple events
- History of stroke risk factors
- Current medications, including antplatelet drugs and anticoagulants
- Results of cerebral imaging
- ABCD2 score for patients with TIA
- Suspected cause and initiation of preventive or thrombolytic therapy
- Specialist consultation and early (within 48 hours) follow-up for low-risk patients with TIA discharged from the emergency department
- Specialist consultation and admission to a stroke unit for patients with stroke
The goal of management of patients with TIA is the introduction of therapy that will prevent stroke and thus avoid permanent disability and untimely death. Three types of medical therapy to achieve this goal are available: antiplatelet therapy, anticoagulation therapy, and surgical or endovascular therapy. In addition, patients should be instructed about measures that modify risk factors for stroke.

ED management of patients with acute ischemic stroke requires a team approach that is organized, time sensitive, and goal directed. The goal of ED care is to ensure medical stability, identify the cause of the ischemic event, determine the extent of injury, and create a therapeutic plan that reestablishes cerebral function and prevents or limits further injury. Four time goals for therapy have been established (see the Priority Actions box).

**TREATMENT**

The use of antiplatelet agents rather than oral anticoagulation is the treatment of choice for the prevention of stroke in patients with TIA secondary to atherothrombic disease (Box 100.2). Aspirin is the most widely used and the most economical drug available for prevention of stroke. Currently,
clopidogrel, ticlopidine, and combined dipyridamole-aspirin (DPA) are antiplatelet agents that are effective alternatives to aspirin. Unfortunately, despite being the standard of care in the AHA guidelines, these agents are often underused, with only 18% of TIA patients encountered in the ED receiving aspirin, 7% receiving other antiplatelet agents, and 42% receiving no treatment.

Aspirin is a mainstay of antiplatelet therapy for prevention of atherothrombotic stroke in TIA patients. It achieves this benefit though irreversible block of the enzyme cyclooxygenase, which in turn prevents the metabolism of arachidonic acid to the potent vasoconstrictor and platelet aggregator thromboxane A₂. The effective dose of aspirin is 50 to 325 mg. It is associated with an overall reduction of 15% to 18% in the combined end points of stroke, myocardial infarction, and death. It is well tolerated and inexpensive; however, gastrointestinal bleeding is a documented major side effect.

Clopidogrel (75 mg daily) and ticlopidine (250 mg twice daily) are adenosine diphosphate receptor antagonists that prevent platelet aggregation. Clopidogrel has the advantages of once-daily dosing, less neutropenia, and fewer gastrointestinal side effects. It must be noted that clopidogrel has been reported to induce thrombotic thrombocytopenic purpura in a very small percentage of patients. In addition, clopidogrel has not been compared with placebo for secondary stroke prevention.

Large, multicenter randomized controlled trials have compared clopidogrel with aspirin and combined clopidogrel-aspirin with clopidogrel alone in the prevention of stroke, myocardial infarction, and death. Subgroup analysis failed to find a statistically significant reduction in ischemic stroke in favor of clopidogrel or the combined drugs. In addition, no increase in reduction of the risk for stroke was achieved by giving aspirin to symptomatic patients currently taking clopidogrel; in fact, major bleeding increased with the combination of the two drugs. Clopidogrel remains a viable option for patients who are aspirin sensitive, and it has been shown to be beneficial in patients who have concomitant cerebral vascular and coronary disease or recent stent placement.

Dipyridamole is a cyclic nucleotide phosphodiesterase inhibitor that inhibits platelet aggregation by increasing levels of cyclic adenosine monophosphate. Extended-release dipyridamole in combination with aspirin has been shown to reduce the risk for stroke by 37% when compared with placebo and to reduce risk by 23% when compared with aspirin alone. Studies comparing extended-release DPA and clopidogrel have demonstrated that they are not different in their efficacy. Common side effects include headache and gastrointestinal disturbances.

**ANTICOAGULATION**

Atrial fibrillation (AF) is responsible for 50% of all cardioembolic events. Patients with a TIA or ischemic stroke and paroxysmal or sustained AF should receive warfarin as the therapy of choice for the prevention of stroke. These patients have a target INR of 2.5 (range, 2.0 to 3.0). Risk factors for stroke in patients with AF include congestive heart failure, hypertension, age older than 75 years, diabetes, and previous stroke or TIA. For these high-risk patients who require temporary interruption of oral anticoagulation, bridging therapy with low-molecular-weight heparin administered subcutaneously is reasonable.

Other cardiac risk factors include left ventricular thrombus in the setting of acute myocardial infarction, native valvular heart disease, and prosthetic heart valves. Warfarin is a reasonable option for all these conditions with slight variations. With a left ventricular thrombus, oral anticoagulation with a target INR of 2.5 (range, 2.0 to 3.0) should be continued for at least 3 months. In the setting of rheumatic mitral valve disease, oral anticoagulation with a similar target is also reasonable. Because of the increased risk for stroke in patients with mechanical prosthetic heart valves, the target range for anticoagulation is increased and the target INR should be 3.0 (range, 2.5 to 3.5). Patients with bioprosthetic valves can be maintained at an INR of 2.5 (range, 2.0 to 3.0). In general, to avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin unless a patient with a prosthetic heart valve has an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants and is not at high risk for bleeding. Warfarin has not been shown to be superior to aspirin in the prevention of noncardioembolic forms of stroke.

**SURGICAL MANAGEMENT**

Carotid endarterectomy (CEA) performed in patients with symptomatic severe carotid stenosis greater than 70% to 99% results in a long-term benefit in preventing strokes. Patients with symptomatic stenosis of 50% to 69% may also benefit from CEA, depending on age, sex, and comorbid conditions, if their perioperative risk for morbidity and mortality is estimated to be less than 6%. Finally, CEA is not beneficial or is harmful in symptomatic patients with stenosis of less than 50% (Box 100.3). When performed within 2 weeks, surgery is reasonable in patients with no contraindications to early revascularization.

Recently, carotid angioplasty plus stenting (CAS) has been deemed a possible alternative to surgical carotid therapy and has been shown to have outcomes comparable with those achieved with CEA. The AHA now recommends CAS as
an alternative to CEA for symptomatic patients at average or low risk for complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is found to be reduced by more than 70% by noninvasive imaging or by more than 50% by catheter angiography, and CAS can be used in patients with greater than 70% stenosis if the stenosis is difficult to access surgically or if they are deemed to be poor surgical candidates.

**RISK FACTOR REDUCTION**

Several factors portend an increased risk for stroke in patients who have experienced a TIA. Modifiable risk factors include hypertension, diabetes, hyperlipidemia, cigarette smoking, and heavy alcohol consumption. The AHA recommends that blood pressure be reduced in all patients with TIA beyond the first 24 hours of symptoms, with an average reduction of approximately 10/5 mm Hg and an ultimate goal of less than 120/80 mm Hg. Reduction of blood pressure can be attained through lifestyle modification and antihypertensive therapy.

In diabetic patients, diet, exercise, oral hypoglycemic drugs, and insulin are recommended to gain glycemic control.

Elevations in total cholesterol or low-density lipoprotein cholesterol (LDL-C) and low levels of high-density lipoprotein cholesterol (HDL-C) are modest risk factors for stroke. A metaanalysis of statin trials showed that the larger the reduction in LDL-C, the greater the reduction in risk for stroke. Therefore, the AHA recommends statin therapy with intensive lipid-lowering effects in patients with TIA who have evidence of atherosclerosis and an LDL-C level higher than 100 mg/dL. It is reasonable to target a reduction of at least 50% or levels of less than 70 mg/dL. For patients with TIA and low HDL-C, treatment with niacin or gemfibrozil can be considered.

Additional lifestyle risk factor reduction includes providing TIA patients with smoking cessation counseling and advising patients to avoid environmental (passive) tobacco smoke. Patients who are heavy drinkers should eliminate or reduce their consumption of alcohol to no more than two drinks per day for men and one drink per day for women who are not pregnant.

**THROMBOLYSIS**

The only treatment of acute ischemic stroke approved by the Food and Drug Administration (FDA) is IV rt-PA therapy, which has traditionally been recommended for carefully selected patients older than 18 years who are seen within 3 hours of the onset of an acute ischemic stroke. There have been some recent updates to recommendations for the use of IV rt-PA outside the traditional 3-hour time window, as well as the use of intraarterial thrombolysis for patients initially seen between 3 and 6 hours after the onset of symptoms.

Adjuncts to intraarterial thrombolysis include angioplasty, stenting, and clot retrieval devices. Other therapies include prevention of hypoxemia and dehydration, administration of antiplatelet and anticoagulation agents, normalization of glucose, and temperature control.

The era of emergency intravenous thrombolysis for acute ischemic stroke began in 1995 with the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA trial. This study was a single randomized controlled trial that compared patients with ischemic stroke treated with IV rt-PA versus placebo (given at 0 to 90, 90 to 180, and 0 to 180 minutes). Despite no difference in the NIHSS score at 24 hours, the main outcome of the trial was a 30% decrease in disability at 3 months in patients treated with IV rt-PA versus 20% in those treated with placebo. This benefit was similar 1 year after stroke. Adverse events included a 10-fold increase in the rate of intracerebral hemorrhage 36 hours after treatment with rt-PA (6% versus 0.6%); however, the death rate in the two treatment groups was similar at 3 months (17% versus 20%) and at 1 year (24% versus 28%).

Concern over data that support the use of thrombolitics for acute ischemic stroke and external validity in community hospitals has been raised by some EPs. Some community hospital groups have reported high rates of intracranial hemorrhage and fewer favorable outcomes. In these studies the risk for hemorrhage is proportional to the degree to which the NINDS protocol is not followed. Critics also observed that the relative predominance of mild strokes (NIHSS score < 5) with a probably good outcome in the rt-PA group may explain the entire benefit reported in patients treated between 91 and 180 minutes. Neither reanalysis of the data by the NINDS study group nor a separate analysis by an independent group could demonstrate that the effect of the imbalance in severity influenced the overall result that rt-PA therapy positively influenced outcome. Several recent studies also demonstrated improved neurologic outcomes and similar hemorrhage rates as the original NINDS data.

The effectiveness of thrombolysis is determined by several variables. Time until treatment is extremely important: 75% of patients in one pooled analysis who were treated within 60 minutes of the onset of stroke in the initial pooled analysis...
had the best chance of achieving complete or partial reopening of the occluded artery.\textsuperscript{78} Patients with mild to moderate strokes (NIHSS score < 20) and patients younger than 75 years had the greatest potential for a favorable response to treatment.\textsuperscript{80} Predictors of a poor postthrombolysis prognosis include older patient age, higher stroke severity (NIHSS score > 22), systemic hypertension or hypotension, hyperglycemia, and fever.

Despite its effectiveness in improving neurologic outcomes, the majority of patients with ischemic stroke are not treated with rt-PA, largely because they arrive after the 3-hour window for treatment. One potential solution would be to designate a longer time window for treatment. A pooled analysis of previous large trials suggested that the upper limit of the treatment window may be as late as 5 to 6 hours.\textsuperscript{78} The ECASS-3 trial enrolled patients to either rt-PA or placebo by using the current guideline protocols of between 3 and 4.5 hours after the onset of symptoms. It excluded patients older than 80 years, those taking oral anticoagulants, those with a history of both previous stroke and diabetes, and patients with a baseline NIHSS score higher than 25. The rate of symptomatic intracranial hemorrhage (as defined by NINDS criteria) was 7.9\% for the treatment group and 3.5\% for the placebo group, neurologic improvement was significantly higher in the rt-PA group than in the placebo group, and mortality in the two treatment groups did not differ significantly.\textsuperscript{66} These findings are consistent with the results in this time window from pooled analyses of previous trials.\textsuperscript{78} Subsequently, the AHA made recommendations regarding expansion of the time window for the treatment of ischemic stroke with IV rt-PA (Box 100.4).\textsuperscript{81}

Centers that care for stroke patients must develop guidelines for the appropriate selection of patients and develop systems to rapidly deliver thrombolysis therapy to these patients. Candidates for IV thrombolysis must have a clearly defined time of symptom onset of less than 270 minutes, must be older than 18 years, and must have no contraindications to thrombolytic therapy (Box 100.5).\textsuperscript{32} The dosing regimen is 0.9 mg/kg (maximum of 90 mg) of rt-PA, with 10\% (maximum of 9 mg) given as a bolus over a 1- to 2-minute period, followed by the remaining dose (maximum of 81 mg) infused by pump over a 1-hour period. Any indwelling catheters should be placed before the administration of thrombolytics. The patient should be admitted to an intensive care or stroke unit for frequent neurologic examination and blood pressure checks, with the goal of maintaining blood pressure lower than 180/105 mm Hg. If severe headache, acute hypertension, nausea, or vomiting develops, the infusion should be discontinued and an emergency non–contrast-enhanced head CT scan should be obtained. The institution must have a protocol for the management of thrombolytic-induced intracerebral hemorrhage. The patient should not receive aspirin or heparin during the first 24 hours after thrombolytic therapy. A follow-up non–contrast-enhanced head CT scan should be done at 24 hours and before starting anticoagulant or antiplatelet therapy.\textsuperscript{32}

### ENDOVASCULAR PROCEDURES

Procedures such as intraarterial thrombolysis with or without mechanical embolectomy, angioplasty, and carotid stenting are considered experimental therapies that may benefit patients with ischemic stroke.

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**BOX 100.4 Recommendations of the American Heart Association Regarding Extension of the Time Window for Administration of Recombinant Tissue Plasminogen Activator in Patients with Ischemic Stroke**

Recombinant tissue plasminogen activator should be administered to eligible patients who can be treated in the 3- to 4.5-hour period after the onset of stroke. Exclusion criteria for the extended treatment window include:

- Patients older than 80 years
- Baseline National Institutes of Health Stroke Scale score higher than 25
- Patients with a history of both stroke and diabetes
- All patients receiving oral anticoagulants regardless of their international normalized ratio
- Delays in evaluation and initiation of therapy should be avoided because of the opportunity for greater neurologic improvement with earlier treatment.

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**BOX 100.5 Contraindications to Administration of Recombinant Tissue Plasminogen Activator**

- Head trauma or stroke in the previous 3 months
- Myocardial infarction in the previous 3 months
- Gastrointestinal or urinary tract hemorrhage in the previous 3 weeks
- Major surgery in the past 2 weeks
- Arterial puncture at a noncompressible site in the previous 7 days
- History of previous intracranial hemorrhage
- Systolic blood pressure higher than 185 mm Hg, diastolic blood pressure higher than 110 mm Hg
- Evidence of active bleeding or acute trauma (fracture) on examination
- Oral anticoagulation with an international normalized ratio higher than 1.7
- Receiving heparin in the previous 48 hours with an abnormal activated partial thromboplastin time
- Platelet count lower than 100,000/mm\(^3\)
- Blood glucose level lower than 50 mg/dL
- Seizure with postictal residual neurologic impairments
- Computed tomography scan demonstrating multilobar infarction (hypodensity in more than a third of the cerebral hemisphere)

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specific patient groups who are seen outside the 3-hour window or have contraindications to IV thrombolysis, such as recent surgery. Benefits of this therapy include a lower dose of thrombolytic, direct visualization of the occluded vessel, and higher recanalization rates. The FDA has approved use of the MERCI (Mechanical Embolus Removal in Cerebral Embolism) devise. Treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists.

**ADJUVANT THERAPIES**

**Blood Pressure Management**

Management of blood pressure in an acute stroke patient is controversial. In an ED study of patients with acute ischemic stroke, systolic blood pressure outside the range of 155 to 220 mm Hg and diastolic blood pressure outside the range of 71 to 105 mm Hg were associated with increased 90-day mortality. These findings demonstrate the harmful effects of both hypertension and hypotension and indicate that there is an optimal range of blood pressure required to perfuse at-risk tissue in these patients. Current American Stroke Association and European Stroke Initiative guidelines recommend withholding antihypertensive therapy in patients with acute ischemic stroke unless they are thrombolysis candidates or show evidence of end-organ dysfunction (acute myocardial infarction, aortic dissection, pulmonary edema, and renal failure). Short-acting IV medications with reliable dose response and safety profiles should be used. Medications that meet these requirements include labetalol, nicardipine, and esmolol. Despite concern that lowering blood pressure in the acute stroke setting might be harmful, pilot data from the CHHIPS trial demonstrated that labetalol and lisinopril are effective antihypertensive drugs for patients with acute stroke and do not increase serious adverse events. Early lowering of blood pressure also resulted in a reduction in mortality. However, in view of the small sample size, care must be taken when these results are interpreted, and further evaluation in larger trials is needed. Conversely, small clinical studies suggest that drug-induced hypertension could be used in the management of some patients with acute ischemic stroke to improve cerebral blood flow, but data from large clinical trials are lacking. The AHA recommends using this method only in exceptional cases or within the setting of clinical trials.

**Glucose Management**

Hyperglycemia (glucose > 185 mg/dL) and hypoglycemia (glucose < 60 mg/dL) are associated with worsening of clinical and tissue outcome in patients with acute ischemic stroke. Hyperglycemia can accelerate the course of ischemic injury, actively convert penumbra to infarcted tissue, and increase the risk for hemorrhagic events and poor outcome in patients receiving rt-PA therapy. Glycemic control with rapidly acting insulin should be instituted to maintain blood glucose between the suggested levels of 140 to 185 mg/dL while taking care to avoid hypoglycemia.

**Temperature Management**

Hyperpyrexia (temperature > 38.0° C) is associated with increased morbidity and mortality. The pathologic effects stem from increased neurotransmitter and free radical production and adverse effects on the blood-brain barrier, which seem to be most pronounced at the border zone or penumbra of the infarct and lead to loss of potentially viable tissue. Therefore, the source of the fever should be actively sought and treated with acetaminophen.

**Anticoagulation**

Currently, early administration of heparin is not recommended for any type of acute ischemic stroke because of the increased risk for secondary hemorrhagic conversion; furthermore, clinical trial data have shown no reduction in stroke recurrence or improvement in patient outcome. Additionally, initiation of anticoagulant therapy within 24 hours of treatment with IV rt-PA is not recommended.

**Antiplatelet Therapy**

The goals of antiplatelet therapy in patients with stroke are a reduction in stroke recurrence and stroke-related morbidity and mortality. Aspirin (50 to 325 mg/day) therapy resulted in a significant reduction in death and disability when given within 48 hours of ischemic stroke. It reduced the risk for early recurrent stroke in all stroke subtypes. Therefore, patients who are not aspirin sensitive or at risk for aspiration and are not being administered t-PA should receive aspirin within 48 hours of ischemic stroke. Other oral antiplatelet agents, including clopidogrel, ticlopidine, and combination drugs such as DPA, have not been proved to be safer or more cost-effective than aspirin alone. Clopidogrel is recommended for aspirin-sensitive patients who require emergency antiplatelet therapy in the ED. The use of IV antiplatelet agents such as glycoprotein IIb/IIIa inhibitors is still investigational and is not recommended for use outside the setting of clinical trials.

**FOLLOW-UP, NEXT STEPS IN CARE, AND PATIENT EDUCATION**

The areas that should be emphasized when making decisions regarding admission or discharge are the completeness of the evaluation, the source of the event, and resolution of the symptoms. These issues, coupled with proper risk stratification and cerebral vascular imaging, represent a logical approach to achieving safe and proper disposition of the patient. A thorough diagnostic evaluation that determines the cause of the TIA plays a crucial role in the decision to hospitalize or discharge patients from the ED. Patients who are at high risk for recurrent events and are unable to undergo appropriate cerebral and vascular imaging should be hospitalized to expedite the evaluation and allow observation for recurrent events in the period of vulnerability (hours or days) after the event. Diagnostic benefits of hospital admission include rapid evaluation, monitoring for acute neurologic deterioration, and cardiac telemetry monitoring. Therapeutic benefits include the ability to deliver thrombolytic therapy, rapid institution of antiplatelet and anticoagulation therapy, and early consideration for carotid surgery.

The AHA has recently recommended hospital admission for patients initially seen with TIA within 72 hours of the event and when any of the following criteria are present: (1) ABCD2 score higher than 3, (2) ABCD2 score of 0 to 2 and...
uncertainty that diagnostic work-up can be completed within 2 days as an outpatient, and (3) ABCD2 score of 0 to 2 and other evidence indicating that the patient’s event was caused by focal ischemia.1

Patients deemed to be at low risk after a complete evaluation and those who have a clear cause and are receiving preventive therapy can be discharged after appropriate consultation with a neurologist, cardiologist, or vascular surgeon. It should be emphasized to all patients that a TIA is a high-risk event and that the risk for stroke is highest in the next 2 to 90 days (see the Patient Teaching Tips box). All patients discharged from the ED should be scheduled for follow-up during the next 2 days, which is the most critical period for recurrent events. Preventive therapy, especially antiplatelet therapy, should be initiated before discharge.1

Unlike TIA, all patients with acute ischemic stroke require admission to the hospital to be observed for changes in their condition, facilitate medical or surgical procedures, receive preventive therapy, and recover neurologic function with rehabilitative services. Optimal disposition is dependent on local hospital expertise, severity of the stroke, and intensity of therapy. Following early therapy initiated at a community hospital, patients may be transferred to a stroke center for more comprehensive care, which is often coordinated by stroke teams in hospitals throughout the United States. Patients undergoing thrombolysis should have access to the intensive care unit, neurology and neurosurgery consultation, and blood bank services.

Admission to a stroke unit has been validated in clinical trials as being statistically significant in decreasing disability and mortality while increasing the probability that the patient will return home and resume daily living activities.96 These effects are independent of age, sex, and severity of stroke and are reproducible in a community setting.

Intensive monitoring in a stroke unit allows early detection and treatment of fever, hypoxemia, hyperglycemia, and cardiac rhythm disturbances and permits early mobilization coupled with physical and occupation therapy. Stroke units have been found to be effective for patients with large artery–associated stroke and more costly but equally efficacious as medical ward care for patients with small vessel–associated stroke.97 Hospitals without stroke units should have comprehensive protocols and quality assurance programs that actively manage the variables shown to affect outcome and ensure optimal care for all patients.

Patients who require intensive care unit admission are those with severe stroke and the potential for decompensation. High-risk populations include patients treated with IV or intraarterial thrombolysis or catheter-based therapies, patients with an NIHSS score higher than 17, and patients with large strokes in the cerebellar or middle cerebral artery distribution who are at risk for the development of cerebral edema.

### SUGGESTED READINGS


### REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES


