Definitions

Stroke is a sudden neurologic deficit caused by either ischemia (80%) or hemorrhage (20%). Ischemic stroke is characterized by the area of the brain affected and the etiologic mechanism. Hemorrhagic stroke is classified as either subarachnoid (5%) or intracerebral (intraparenchymal) (15%). Transient ischemic attack (TIA) is a sudden vascular-related focal neurologic deficit that resolves completely. TIAs are classically defined as lasting less than 24 hours and generally last less than 1 hour. A TIA should not be considered a separate entity but, rather, as a herald of ischemic stroke and an opportunity to intervene.

Epidemiology

Stroke is the leading cause of disability and the third leading cause of death in the United States. Until 1998, annual stroke incidence was estimated at 550,000, on the basis of studies of homogeneous, predominantly white populations. Results of the Greater Cincinnati/Northern Kentucky Stroke Study suggest that previous reports underestimated stroke incidence by almost 50%. By rigorously counting strokes in all racial and ethnic groups in Cincinnati, the yearly estimate for the United States was revised to 731,100. The explanation for the previous underestimation of stroke incidence is that African Americans have an excess stroke burden relative to non-Hispanic whites. African Americans in Cincinnati had a twofold to fourfold higher incidence of stroke than non-Hispanic whites in Rochester, Minnesota, during the same period. In upper Manhattan, African Americans had a 2.4-fold higher incidence of stroke than non-Hispanic whites.

African Americans also have higher stroke mortality. In Texas, African-American men 45 to 59 years of age had a 306% higher stroke mortality than non-Hispanic whites. At 75 years of age and older, when stroke mortality is at its highest, the excess mortality for African-American men had diminished to 26% above the mortality for non-Hispanic whites. African-American women in the same age groups had a 222% and a 10% greater stroke mortality, respectively, than non-Hispanic whites. The increased burden of stroke among African Americans may be worsening. Between 1992 and 1996, rates of almost all subtypes of stroke had increased among African Americans, and the number of stroke deaths had increased by 8%.

The pathogenesis of stroke in African Americans may also differ somewhat from that in non-Hispanic whites. Extracranial carotid disease and cardioembolism more commonly cause ischemic stroke in non-Hispanic whites, whereas intracranial thromboembolic disease is more common in African Americans. However, the various disease mechanisms can occur in either racial group.

Information on stroke in Hispanic Americans is less readily available. Data from upper Manhattan suggest a twofold higher incidence of stroke in Hispanics than in non-Hispanic whites.

Women have lower stroke rates than men at all age ranges except 75 years and older, when stroke rates are at their highest. In Texas, 61% of all stroke-related deaths occur in women. Stroke and vascular disease have traditionally been seen as male disorders, thus shifting the focus of prevention and acute treatment regimens away from women.

Overall, the decline in stroke-related mortality has inexplicably slowed over the past several decades and almost came to a halt in the 1990s. A lack of emphasis on prevention may have led to an increase in incidence, particularly in some racial and ethnic groups. As people survive other diseases, stroke may become a more common cause of death. Nonetheless, this stabilization of the previous downward trend in stroke mortality is cause for alarm.

Approach to the Acute Stroke Patient

Stroke is the quintessential medical emergency. In 1995, a group of Spanish stroke neurologists published a study that demonstrated that stroke patients who received neurologic care within 6 hours of the onset of symptoms had a 460% greater chance of a good outcome than those treated after this acute period. This observation, which was made before the thrombolytic era, illustrates the crucial link between time and outcome for stroke victims. Patients who receive early treatment to restore cerebral perfusion and to maximize protection of neurons have better outcomes. Physicians can reduce the delay in getting stroke victims to the emergency department by educating at-risk patients and their families about stroke symptoms and encouraging them to call 911 if stroke symptoms occur. Once a stroke patient arrives at the emergency department, triage and treatment are critical in reducing mortality and morbidity.
Several imaging techniques may characterize the acute vasculature, which may demonstrate acute occlusion or an embolus lodged at a vascular bifurcation. The vasculature can also be visualized quickly and noninvasively with CT-angiography (CT-A) and magnetic resonance angiography (MRA). Alternatively, transcranial Doppler ultrasonography can provide indirect evidence of major vascular occlusion and offers the advantage of real-time bedside monitoring in patients who receive thrombolytic therapy.¹⁴

**Medical management of acute ischemic stroke**

Several general medical issues are important for all stroke patients, such as management of airway and oxygenation, blood pressure and hemodynamics, blood glucose, and temperature. Medical complications are also common after stroke, and such complications are associated with poor outcomes. Management of these common issues and complications is critically important. Therefore, it is advisable to treat stroke patients in dedicated stroke units to reduce morbidity, mortality, and disability.¹⁶

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Respiratory function must be evaluated immediately in all stroke patients. Ventilatory drive is usually intact except after medullary or massive hemispheric infarction. The ability to protect the airway from aspiration may also be impaired, particularly in the acute setting. Intubation and mechanical ventilation may be necessary in these patients. Most stroke patients do not require such aggressive maneuvers, but supplemental oxygen should be provided to maintain oxygen saturation above 95%.

Maintenance of adequate blood pressure is vital for all patients. Cerebral blood flow to ischemic regions is dependent on cerebral perfusion pressure, which in turn is determined by the difference between mean arterial pressure and intracranial pressure. Elevated blood pressure is common at the time of initial stroke presentation, even among patients without chronic hypertension. Rapid lowering of blood pressure may further impair cerebral blood flow and worsen the ischemic injury. Elevated blood pressure will often spontaneously and gradually improve during the first few days after stroke. Antihypertensive therapy is indicated (1) before and during thrombolysis with tissue plasminogen activator (t-PA); (2) after hemorrhagic conversion of the infarction; (3) in the presence of myocardial ischemia or aortic dissection; and (4) in association with hypertensive encephalopathy. Candidates for thrombolysis should be treated only with modest measures (topical nitropaste or small

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**Figure 2**  (a) Early computed tomographic findings in acute ischemic stroke. Three hours after onset of left hemiparesis and neglect, this noncontrast CT scan reveals extensive early findings in the right hemisphere, including obscuration of the gray-white junction and the basal ganglia and effacement of the cortical sulci. (b) Detail of CT findings in panel a. (c) Noncontrast head CT scan of a right putaminal intracerebral hemorrhage. (d) Noncontrast head CT scan of a subarachnoid hemorrhage manifesting the classic star-shaped area of hyperdensity in the basal cisterns. (C—caudate nucleus; P—putamen; T—thalamus; V—ventricles)
in acute stroke. Hypothermia may mitigate neurotransmitter toxic effects that typically peak at 2 to 5 days. In large hemispheric stroke, malignant middle cerebral artery (MCA) syndrome may occur, in which the edematous infarcted tissue causes compression of the anterior and posterior cerebral arteries, resulting in secondary infarctions. Similarly, infarction of the cerebellum may lead to basilar artery compression and brain stem ischemia. Mortality in both MCA and infarction of the cerebellum approaches 80% [see Intracerebral Hemorrhage, below]. Surgical decompression has a potential role in a minority of stroke patients. In acute cerebellar stroke, craniotomy with cerebellar resection is a lifesaving intervention that has become widely accepted. Surgery removes the mass effect and prevents secondary brainstem and vascular compression. Malignant MCA syndrome may be similarly amenable to hemicraniectomy; this controversial approach is under investigation.

Prophylaxis for deep vein thrombosis should be instituted early with heparin (5,000 units given subcutaneously every 12 hours). For patients who cannot receive heparin (e.g., patients with acute hemorrhage), pneumatic compression stockings are employed. Similarly, prevention of aspiration pneumonia should be a priority from the beginning of hospital presentation. Early intervention with physical therapy, occupational therapy, and speech therapy is important in recovery and prevention of complications.

**Ischemic Stroke**

Patients presenting with the sudden onset of neurologic dysfunction or reporting neurologic signs and symptoms evolving over a few minutes to a few hours are most likely victims of stroke. Most of these patients will have ischemic rather than hemorrhagic stroke [see Table 1].

**Lesion Localization**

Two pairs of vessels supply blood to the brain: the internal carotid arteries and the vertebral arteries. These vessels, which deliver 20% of the cardiac output, join on the ventral surface of the brain to form the intracranial vessels and the circle of Willis [see Figure 4]. The anterior cerebral artery supplies blood to the medial frontal and deep structures. Occlusion of the anterior cerebral artery is characterized by contralateral leg weakness [see
Table 2, but isolated infarction of the anterior cerebral artery is uncommon. The middle cerebral artery divides into two major trunks, and each trunk divides into five to seven branches that supply blood to the lateral hemisphere. Because of its large territory, middle cerebral artery occlusion causes a clinical syndrome that includes contralateral hemiparesis and hemisensory deficit (face + arm > leg), aphasia (dominant hemisphere) or neglect (nondominant hemisphere), contralateral visual-field defect, deviation of gaze, dysarthria, and other cortical symptoms.

The two major branches of the vertebral arteries are arteries to the spinal cord and the posterior inferior cerebellar artery to the inferior cerebellum and lateral medulla. The two vertebral arteries then unite to form the basilar artery. The major branches of the basilar artery are the anterior inferior cerebellar artery and the superior cerebellar artery, which supply parts of the pons and cerebellum. Occlusion of the vertebral arteries or basilar artery leads to a combination of signs and symptoms that depend on the level and extent of infarction. These signs and symptoms include so-called crossed facial sensory and body motor signs, diplopia, facial numbness and weakness, vertigo, nausea and vomiting, tinnitus, hearing loss, ataxia, gait abnormality, hemiparesis, dysphagia, and dysarthria. The basilar artery terminates by dividing into two posterior cerebral arteries that supply the medial temporal lobe, the occipital lobe, and parts of the thalamus. Occlusion of the posterior cerebral artery results in occipital infarction and therefore contralateral visual-field loss. Such occlusion may also cause contralateral hemiparesis and behavioral changes.

After the circle of Willis, the vessels branch repeatedly and ultimately become end arteries. Occlusion of these penetrating vessels can cause typical clinical syndromes, such as pure motor hemiparesis, pure sensory stroke, clumsy hand–dysarthria syndrome, and ataxic hemiparesis.

Table 1  Differential Diagnosis of Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Possible Cause</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs or other toxins</td>
<td>Unlikely to cause focal neurologic symptoms; exclude by history and CT scan</td>
</tr>
<tr>
<td>Seizure</td>
<td>Can mimic focal neurologic signs; exclude by history</td>
</tr>
<tr>
<td>Metabolic derangements</td>
<td>Abnormalities of glucose, calcium, ( P_{CO_2}, P_{O_2} ), and electrolytes and liver and kidney dysfunction can cause neurologic abnormalities; hypoglycemia and hyperglycemia are notorious for causing focal signs; exclude by laboratory tests</td>
</tr>
<tr>
<td>Migraine</td>
<td>Although migraine is a diagnosis of exclusion, it must be considered in patients with stroke; headache can be a prominent component of both ischemic and hemorrhagic stroke; exclude by history and physical examination</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>Unlikely to present acutely; exclude by history and CT scan</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Subdural, epidural, subarachnoid, and intracerebral hemorrhage can all mimic ischemic stroke; exclude by CT scan</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>Conversion disorder and malingering can usually be discovered by a careful physical examination and history</td>
</tr>
</tbody>
</table>

CT—computed tomography  \( P_{CO_2} \)—carbon dioxide tension  \( P_{O_2} \)—oxygen tension

Figure 4  Cerebrovascular anatomy and common sites of atherosclerosis are shown. The internal carotid artery (ICA) enters the skull, and its first major branch is the ophthalmic artery to the eye. Next are the anterior choroidal artery and the posterior communicating artery (PCommA). The PCommA connects the anterior circulation to the posterior circulation. The ICA then terminates as it divides into the anterior cerebral artery (ACA) and the middle cerebral artery (MCA). The vertebral arteries (VA) enter the skull and merge at the inferior border of the pons to form the basilar artery (BA). The BA then terminates as it divides into the two posterior cerebral arteries (PCA).

etiology

Common Causes

Ischemic stroke is classically labeled as either thrombotic or embolic, but these two mechanisms may be impossible to distinguish clinically. Ischemic stroke mechanisms are more reliably categorized as cardioembolism, large vessel atherosclerosis, small vessel occlusive disease, other identified mechanisms, or cryptogenic. 5

Cardioembolism most commonly results from atrial fibrillation, mural thrombus, ventricular akinesis after myocardial infarction, dilated cardiomyopathy, and valvular disease [see Figure 5]. In each of these disorders, thrombus develops within the heart and embolizes to the brain. Ischemic events may be multiple and may occur in any major vessel. Therefore, cardioembolism must be considered in nearly every ischemic stroke patient.
artery embolic stroke, or focal hypoperfusion causing acute occlusion of the parent vessel, distal artery-to-arterial narrowing of the major extracranial or intracranial arteries, should also be considered.

In general, atherosclerosis occurs at major arterial branch points (e.g., the carotid bifurcation in the neck or intracranial branch points) and at vessel origins (the origin of the vertebral artery from the subclavian artery).

Small vessel occlusive disease is often synonymous with so-called lacunar infarction. Small vessels are tiny terminal branch-lesions of larger vessels, such as those in the internal capsule, corona radiata, thalamus, and pons. The mechanism of the occlusive process is uncertain, but lipohyalinosis, local atherosclerosis, and microthrombosis are possible. The process is most common in patients with long-standing diabetes or hypertension and is characterized by several specific clinical syndromes [see Lesion Localization, above]. The diagnosis of small vessel disease rests on the clinical syndrome and absence of an alternative etiology.

diagnostic evaluation

The highest risk of recurrent stroke occurs within the first month after initial stroke symptoms, so an expeditious evaluation of patients presenting with TIA or suspected stroke should be undertaken and prophylactic therapy begun immediately at presentation [see Figure 6]. In a patient with ischemic stroke, the first step is to localize the lesion [see Lesion Localization, above]. Patients with anterior circulation strokes need an evaluation of the heart, extracranial carotid arteries, and intracranial anterior circulation. Cardiac evaluation [see Figure 5] begins with an electrocardiogram, a cardiac examination and history, and a transthoracic echocardiogram (TTE). If an absolute diagnosis is not made but these evaluations lead to suspicion of mural thrombus, valvular disease, or patent foramen ovale, then a transesophageal echocardiogram (TEE) is ordered. A TEE allows visualization of structures not seen on a TTE, including clotting in the left atrial appendage and aortic arch. The extracranial carotid circulation and intracranial anterior circulation can be visualized by MRA or CT-A. In places where these diagnostic tools are either not available or of poor quality, carotid ultrasonography should be performed. Transcranial Doppler imaging can help detect intracranial stenosis. The gold standard remains conventional cerebral angiography. Because this invasive test has possible complications (1% risk of stroke in most series) and is expensive, it should be reserved for cases in which treatment decisions would be changed. Posterior circulation evaluation involves the same cardiac evaluation. The posterior circulation is visualized by MRA, CT-A, or conventional angiography.

Lacunae greater than 1.5 cm are likely thromboembolic in nature and should be evaluated as described, depending on anterior or posterior location.

Laboratory investigations for all patients include fasting lipids within 48 hours of symptom onset, homocysteine level, complete blood count, prothrombin time, partial thromboplastin time, and chemistry panel. If the patient is younger than 45 years or has no stroke risk factors, the following tests should be ordered: anticardiolipin antibody, lupus anticoagulant, sedimentation rate, factor V Leiden, rapid plasmin reagin, and antinuclear antibody. Tests for rarer causes of ischemic stroke should include protein C and S, antithrombin III, HIV, and lactate (for mitochondrial disease). In young patients and patients without risk factors, a lumbar puncture, TEE, and cerebral angiography should also be considered.

treatment of acute ischemic stroke

Antiplatelet and Antithrombotic Treatment in Acute Ischemic Stroke

Aspirin (160 to 325 mg daily) administered within 48 hours of stroke onset was shown to significantly reduce the risk of recurrent stroke during the first 2 weeks and, possibly, improve outcome at 6 months. Therefore, aspirin is recommended as initial therapy for most acute stroke patients.

Anticoagulation is commonly used in the acute setting to prevent progressive or recurrent thromboembolic events. Despite its long-standing use in neurologic practice, the efficacy and safety of anticoagulation are not well established, and its role in clinical stroke management is controversial. Many neurologists use heparin, although studies have suggested that it offers no appreciable benefit for most patients. The International Stroke Trial was a multicenter clinical trial that randomized 19,436 patients within 48 hours of stroke onset to receive 12,500 units of subcutaneous heparin twice daily, 5,000 units twice daily, or no heparin for 14 days. Patients were independently randomized to receive either 300 mg of aspirin daily or no aspirin. The rate of recurrent stroke or death at 14 days was 11.7% in the heparin groups (either dose) and 12.0% in the nonheparin group, an insignificant difference, and there was no improvement in outcome at 6 months. The reduction in ischemic strokes by heparin was completely counterbalanced by an increase in hemorrhagic strokes. Similarly, low-molecular-weight heparins (LMWHs) were studied in randomized clinical trials with no reduction in recurrent stroke or improvement in outcomes. Therefore, most patients with ischemic stroke should not be treated with anticoagulation. However, carefully selected patients, such as those with acute basilar thrombosis, are believed to benefit.

Intravenous Recombinant Tissue Plasminogen Activator

Intravenous recombinant t-PA (rt-PA) for acute ischemic stroke was approved by the Food and Drug Administration in June 1996, and consensus statements from the American Academy of Neurology and the American Heart Association support its use. Although the FDA has approved the use of intravenous
rt-PA for acute ischemic stroke within 3 hours of onset of symptoms, physicians should strive to treat patients as quickly as possible [see Table 3].

The major trials that led to approval were the two National Institute of Neurological Disorders and Stroke (NINDS) rt-PA acute stroke studies. The final outcome measure was return to independent function (no disability) at 3 months after onset of stroke. These studies together enrolled 624 patients at eight centers across the United States. Intravenous rt-PA (0.9 mg/kg; maximum dose, 90 mg) was compared with placebo for patients presenting within 3 hours of onset of symptoms. The symptomatic intracranial hemorrhage rate at 36 hours after administration of intravenous rt-PA was 6.5%, compared with 0.6% in the control group. Mortality from intracranial hemorrhage was 2.9% in the rt-PA group, compared with 0.3% in the placebo group.
Including the risk of intracranial hemorrhage, disability was significantly reduced when measured at 3 months, 6 months, and 1 year. The rt-PA-treated patients were at least 30% more likely to recover to independent function than the placebo-treated patients. Mortality at 1 year was 24% in the rt-PA group and 28% in the placebo group. This benefit was seen in all stroke subtypes regardless of age or patient risk factors. Patients with large strokes were more likely to have intracranial hemorrhage after intravenous rt-PA, but this group was also more likely to have severe disability or die if left untreated. Recent reports confirm...
Table 3  Indications and Contraindications for Intravenous rt-PA Treatment in Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Indications</th>
<th>Absolute and Relative Contraindications</th>
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<tbody>
<tr>
<td>Clinical diagnosis of disabling stroke firmly established</td>
<td>Onset &gt; 3 hr ago or patient not seen normal within previous 3 hr (absolute)</td>
</tr>
<tr>
<td>Patients &gt; 17 yr of age</td>
<td>Intracranial mass lesion or hemorrhage on noncontrast head CT (absolute)</td>
</tr>
<tr>
<td>Onset of symptoms or last time seen normal &lt; 3 hr ago</td>
<td>Glucose &lt; 50 or &lt; 400 mg/dl (relative)</td>
</tr>
<tr>
<td>Previously independent functional status</td>
<td>Previous stroke or severe head trauma within previous 3 mo (absolute)</td>
</tr>
<tr>
<td></td>
<td>Any history of intracranial hemorrhage (absolute)</td>
</tr>
<tr>
<td></td>
<td>Current use of anticoagulants with PT &gt; 15 sec or use of heparin within the past 48 hr (absolute)*</td>
</tr>
<tr>
<td></td>
<td>Seizure at stroke onset (relative)</td>
</tr>
<tr>
<td></td>
<td>Major surgery within 14 days (relative)</td>
</tr>
<tr>
<td></td>
<td>Arterial puncture at a noncompressible site or LP within 1 wk (relative)</td>
</tr>
<tr>
<td></td>
<td>Platelets &lt; 100,000 (absolute)</td>
</tr>
<tr>
<td></td>
<td>Rapidly improving symptoms suggestive of TIA (relative)</td>
</tr>
<tr>
<td></td>
<td>GI or GU hemorrhage within 21 days (relative)</td>
</tr>
<tr>
<td></td>
<td>Presenting symptoms suggestive of subarachnoid hemorrhage (worst headache of patient’s life) (absolute)</td>
</tr>
<tr>
<td></td>
<td>Blood pressure &gt; 185/110 mm Hg unless minimal doses of a smooth-acting I.V. agent such as labetalol were sufficient to lower below this range (absolute)*</td>
</tr>
<tr>
<td></td>
<td>Previously known cerebral aneurysm or arteriovenous malformation (absolute)</td>
</tr>
</tbody>
</table>

*PTT and PT results are not needed before therapy unless patient is on anticoagulants.  
*Caution: Do not lower blood pressure acutely by more than 10%–15% and avoid agents that precipitously lower blood pressure. A patient who requires multiple doses should be excluded. After I.V. rt-PA is administered, blood pressure must be kept below 185/110 mm Hg for at least 24 hours.  
CT=computed tomography GI=gastrointestinal GU=genitourinary  
LP=lumbar puncture PT=prothrombin time rt-PA=recombinant tissue-plasminogen activator TIA=transient ischemic attack

what is known from animal stroke studies: the earlier patients are treated, the better the long-term outcome. If treatment with rt-PA is suspected of inducing intracranial hemorrhage, use of rt-PA should be suspended.

Intra-arterial Thrombolysis

Direct infusion of thrombolytic agents into occluded blood vessels is a potential alternative or adjunctive therapy to intravenous rt-PA [see Figure 7]. Prourokinase (Prolyse) is the highly clot-specific precursor to urokinase. The Prolyse in Acute Cerebral Thromboembolism Trial (ProACT)41 enrolled patients with ischemic stroke caused by MCA occlusion within 6 hours of onset. Eligibility criteria were similar to those for intravenous rt-PA treatment. Patients underwent emergent angiography, and if MCA occlusion was confirmed, either intra-arterial prourokinase (9 mg) or placebo was infused for 2 hours. All patients received concomitant intravenous heparin. Prourokinase effectively opened 67% of arterial occlusions, compared with only 18% in patients given placebo. Three months after stroke, 40% of treated patients were functionally independent, compared with 25% of those given placebo (P = 0.04). The drug seemed particularly effective for moderately severe strokes. Symptomatic intracerebral hemorrhage occurred in 10.2% of treated patients, compared with 1.8% of those given placebo.

Because prourokinase is not commercially available, many centers with the ability to perform intra-arterial thrombolysis are using rt-PA, although it is not approved for this purpose. The intra-arterial rt-PA dose is 0.2 mg/kg (maximum, 20 mg), and all other aspects of the ProACT protocol may be followed.

The role of intra-arterial thrombolysis in other cerebral vessels remains uncertain. Cases of spectacular responses to thrombolytics have been reported in patients with basilar occlusion, even well beyond 6 hours. Although it is claimed that the brain stem may be relatively more tolerant of ischemia and less susceptible to hemorrhage, this hypothesis remains to be proved.

Neuroprotection

Neuroprotective strategies involve interfering with the ischemic cascade, thereby prolonging and substantially reducing stroke size. Regrettably, a number of different compounds that seemed effective in animal studies have failed in human clinical trials.6 While several agents are being developed, researchers are attempting to determine how to best simulate stroke in animals so that animal data will be more generalizable to humans.

Prognosis and recovery

Despite advances in treatment of acute stroke, the majority of stroke survivors will have residual neurologic dysfunction. Most patients will have some improvement, but it is rarely complete. The initial stroke severity is one of the strongest predictors of outcome,24 and early evidence of improvement is a good prognostic sign.4 Recovery also depends on the size and location of the infarction or hemorrhage. Small infarctions, particularly subcortical lacunar strokes, may result in little chronic deficit, whereas large cortical infarctions may cause severe and permanent disability. Comorbid diseases, such as hypertension and diabetes, do not appear to affect recovery, but younger patients have a better prognosis than older patients.6 Despite these predictors, there remains marked variability among patients that makes early prognostication difficult. In general, recovery is greatest in the first 3 months after stroke.

The mechanisms of recovery after stroke remain poorly understood. Infarcted brain tissue is irreparable, so recovery of function has long been presumed to occur by recruiting other neurons to serve new or additional roles. In rodents, neurons may be influenced to create new synapses after stroke.6 Electrical brain mapping in monkeys has demonstrated that the cerebral cortex can be functionally reorganized during recovery after an infarction.6 Similarly, functional MRI in humans has shown increased activity in both hemispheres as patients improve, suggesting recruitment of neighboring cortex as well as the corresponding area of the contralateral cortex.6

Recovery may be improved by inducing these restorative mechanisms. Physical, occupational, and speech therapy are widely used, but no consensus exists regarding the optimal approach or timing of intervention. Neurotrophic growth factors and amphetamines may stimulate neuronal sprouting and also accelerate recovery by increasing the activity of uninjured neurons.4 However, the pharmacologic approaches require extensive research before they can be advocated for routine use in stroke rehabilitation.

Ischemic stroke prevention

Reduction of Risk Factors

Numerous risk factors for stroke are modifiable. Reduction of factors such as alcohol consumption, tobacco use, hypertension,
diabetes, lipid levels, and homocysteine levels contributes to stroke prevention [see Table 4].

**Hypertension** Hypertension has the highest population-attributable risk of any of the modifiable risk factors for stroke, and reduction in blood pressure has been shown to dramatically reduce stroke risk. The reduction in risk of first stroke for those treated with antihypertensive agents is 25% to 47%. Both diastolic and systolic hypertension has been linked to excess risk of stroke. Reducing isolated systolic hypertension even in the elderly has been shown to markedly lower stroke rates. Patients who are undertreated with antihypertensive agents still have a higher stroke rate than those who are adequately treated. Recommended actions to reduce the risk of stroke include (1) maintaining blood pressure below 140/90 mm Hg; (2) frequent checking of patients’ blood pressure by physicians; and (3) at-home monitoring of blood pressure by patients. Awareness of the fact that lowering diastolic blood pressure by 5 to 6 mm Hg can reduce stroke risk by 42% should motivate the primary care physician to assiduously diagnose and treat hypertension.

Although many antihypertensive agents can effectively reduce blood pressure, angiotensin-converting enzyme (ACE) inhibitors appear to have a unique role in stroke prevention. Two major studies demonstrated that ramipril alone or perindopril combined with the diuretic indapamide reduces the risk of recurrent stroke by about 30%. These drugs appeared to decrease the risk of stroke more than would be expected by their relatively modest lowering of blood pressure, which suggests the possibility of an additional beneficial action via an uncertain mechanism.

**Tobacco use** Daily cigarette smoking has been shown to increase the risk of stroke by 250%. A dose-effect response is seen in most studies. For those who smoke less than one pack a day, quitting reduces their risk to baseline within 5 years. For heavy smokers, the risk is greatly reduced but remains higher than that in individuals who never smoked. Switching from cigarettes to a pipe or cigars does not reduce stroke risk.

**Hyperlipidemia** Evidence has emerged implicating hyperlipidemia as an independent risk factor for stroke, and studies have demonstrated impressive stroke risk reductions with statin agents. The Medical Research Council/British Heart Foundation Heart Protection Study (HPS), which included over 20,500 persons at high risk for coronary artery disease but with characteristics that excluded them from previous statin studies, showed that long-term treatment with simvastatin (40 mg daily for more than 5 years) reduced all strokes by 27%. Benefits were apparent even in patients with total cholesterol levels below 200 mg/dl.

In an older study of patients with previous myocardial infarction and cholesterol levels lower than 240 mg/dl, patients given pravastatin had a 31% reduced risk of stroke, compared with patients given placebo. In a study involving patients with a median cholesterol level of 218 mg/dl who received pravastatin, the relative risk reduction of stroke was 19%. Meta-analyses also suggest that the use of statins reduces the risk of first stroke by 24%–31%.

**Risk Factor** | **Prevention** | **Risk-Reduction Potential** | **Clinical Trial Evidence?**
---|---|---|---
Hypertension | P; S | 25%-47% | Yes
Tobacco | P; S | ? | No
Hyperlipidemia | P; S | 24%-31% | Yes
Diabetes | P | ? | No
Alcohol | P | 50% | No
Exercise | P; S | ? | No
Homocystine or homocysteine | P; S | ? | No
Infection | P | ? | No
Atrial fibrillation | P; S | 68% | Yes
Symptomatic carotid stenosis > 70%* | S | 65% | Yes
Asymptomatic carotid stenosis > 60%† | S | 53% | Yes

*Two-year absolute risk reduction of 17%.
†Five-year absolute risk reduction of 6%.
P—primary S—secondary

Figure 7  Intra-arterial thrombolysis for acute ischemic stroke. Four hours after onset of left hemiparesis and neglect, conventional angiography (lateral view shown) revealed acute occlusion of the middle cerebral artery (MCA) (a). After treatment with intra-arterial thrombolysis, the MCA recanalized (b) and the patient had near-complete recovery of the deficit.
shown to be an independent risk factor for stroke.66 Studying whether high doses of vitamins B6, B12, and folic acid have a higher incidence of stroke. Although this increase may be related to contributing factors, there appears to be a J-shaped relation between alcohol intake and risk. In one report, those who consumed more than six drinks a day were at increased risk for stroke; those who consumed one to two drinks a day appeared to benefit from a protective effect of alcohol that reduced the risk of stroke by almost 50%.62 There did not appear to be a difference associated with the type of alcoholic beverage consumed (i.e., wine, beer, or liquor). In another report, drinking as little as one alcoholic drink a week reduced the risk of stroke by 22%, compared with drinking no alcohol.63

Homocysteine level Elevated homocysteine levels are an independent risk factor for stroke.64 Currently, there is a trial studying whether high doses of vitamins B6, B12, and folic acid can suppress the elevated homocysteine levels and reduce stroke risk. Because vitamin supplementation is inexpensive and commercially available, some clinicians have already begun this therapy. However, studies are needed to determine whether these high doses are safe and effective.

Exercise Data from the Physician Health Study, a prospective cohort study of 21,823 men, demonstrated that exercise significantly reduced the risk of stroke, most likely by reducing other risk factors, including hypertension, lipid levels, and diabetes.65

Infection Infection and inflammation may be the single most important area of stroke research in the next decade. There have been several observations linking infection and inflammation with stroke. People with poor dentition seem to have a higher incidence of stroke. Although this increase may be related to other risk factors and access to care, it may also be related to oral infections. Chlamydia pneumoniae titers have been shown to be an independent risk factor for stroke.66 Chlamydia seems to promote thrombosis through effects on fibrinogen and vascular endothelium.

Therapeutic Measures to Prevent Ischemic Stroke

Management of risk of cardioembolism Disorders in many regions of the heart can potentially lead to stroke [see Figure 5]. Cardiac valves affected by bacterial endocarditis can give rise to septic emboli. The therapy for this condition is aggressive administration of antibiotics. Akinetic ventricular segments can cause mural thrombi that in turn act as cardiac emboli. The treatment for this disorder is anticoagulation with warfarin (international normalized ratio [INR], 2.0 to 3.0). Similarly, anticoagulation after myocardial infarction is beneficial for patients with concomitant atrial fibrillation, decreased left ventricular function, or left ventricular thrombus. Long-term warfarin therapy is necessary for patients with mechanical prosthetic valves. However, bioprosthetic valves require only brief anticoagulation, followed by antiplatelet treatment. Other conditions, such as patent foramen ovale, septic emboli, and aortic arch atheroma, are more of a therapeutic dilemma. Although these conditions are known to be related to increased stroke risk, there is still uncertainty as to whether antiplatelet or antithrombotic treatment is superior for stroke prevention. Indications for surgical intervention are also uncertain.

The most rigorously studied cardiac condition in terms of stroke prevention is atrial fibrillation [see Table 4]. Nonvalvular atrial fibrillation is a common and readily preventable cause of stroke in the elderly.67 Lack of treatment of at-risk patients remains a significant public health challenge. The groups at highest risk for stroke include those with a history of hypertension, diabetes mellitus, previous TIA or stroke, poor left ventricular function, and women older than 75 years. These patients should be treated with warfarin if they are appropriate candidates. For patients without risk factors and for those younger than 65 years, the risk of stroke is 1% a year without therapy. Thus, warfarin treatment is not necessary. For those individuals 65 to 75 years of age without risk factors, the yearly risk of stroke is 1.1% with warfarin therapy and 1.4% with aspirin therapy. It is critical to monitor patients’ INR to keep them in the 2.0 to 3.0 range and minimize the risk of ischemic stroke or hemorrhage from undertreatment or overtreatment.68

Management of risk of carotid artery disease Surgical treatment of symptomatic carotid stenosis greatly reduces stroke risk. Patients with diameter stenosis greater than 70% who are good surgical candidates dramatically reduce their 2-year risk of stroke, from 26% to 9%.69 For patients with 50% to 70% stenosis, the benefit is not as great. In this moderate-stenosis group, the risk of stroke over 5 years decreases from 22% to 16%. This benefit is seen mostly in men, in those with recent stroke symptoms, and in those with hemispheric rather than ocular symptoms.70

Patients with less than 60% asymptomatic carotid diameter stenosis also benefit from surgery, but the risk and the results from surgery are more modest. In the Asymptomatic Carotid Atherosclerosis Study, stroke risk was reduced at 5 years from 26% to 9%.71 Patients with 50% to 70% stenosis, the benefit is not as great. In this moderate-stenosis group, the risk of stroke over 5 years decreases from 22% to 16%. This benefit is seen mostly in men, in those with recent stroke symptoms, and in those with hemispheric rather than ocular symptoms.70

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Angioplasty and stenting of the carotid artery is being evaluated as an alternative to carotid endarterectomy. Although some case series have been performed, there are no data from randomized clinical trials to support angioplasty and stenting except as part of a research protocol with appropriate informed consent from the patient.

**Antiplatelet and antithrombotic treatment** Inhibition of platelet activation can be achieved with several available agents, including aspirin, dipyridamole, ticlopidine, and clopidogrel [see Table 5]. The role of aspirin in the primary prevention of stroke is uncertain, although it prevents myocardial infarction in high-risk patients. However, aspirin is clearly indicated for secondary prevention of stroke (for patients already with TIA or stroke). Numerous trials of antiplatelet therapy demonstrated that aspirin reduced the risk of nonfatal stroke by about 30%. The ideal aspirin dose is controversial, and there is significant variability among patient responses. For the majority of patients, 50 to 325 mg a day, the dose recommended by the FDA, appears to maximize the prophylactic effect and minimize the bleeding risk.

Other antiplatelet drugs offer modest additional preventive benefit compared with aspirin but at a greater cost and with more potential adverse effects. These medications are recommended for patients who are unable to tolerate aspirin or who have recurrent vascular events while on aspirin. Ticlopidine and clopidogrel reduce the risk of stroke by approximately 21% and 7.3%, respectively, compared with aspirin. Ticlopidine may cause significant neutropenia and thrombocytopenia and therefore requires complete blood count monitoring every 2 weeks for the first 3 months. Clopidogrel is associated with a lower frequency of neutropenia than ticlopidine, but thrombotic thrombocytopenic purpura has been reported, and monitoring of platelet counts has been recommended in patients receiving clopidogrel. Dipyridamole inhibits platelet phosphodiesterase activity and increases the availability of adenosine. Although early trials failed to demonstrate any benefit of dipyridamole, the European Stroke Prevention Study–2 compared regimens consisting of aspirin (50 mg), dipyridamole (extended release, 200 mg), both drugs in combination, and placebo and found a relative risk reduction with the combination of aspirin and dipyridamole of 23% when compared with aspirin alone.

Oral anticoagulation with warfarin is used to inhibit the coagulation cascade and the formation of red blood cell thrombi. Warfarin may also have a role in prevention of stroke caused by some noncardiac mechanisms. Retrospective data support warfarin therapy for intracranial and vertebrobasilar stenosis, and many stroke neurologists also recommend warfarin for internal carotid artery occlusion and arterial dissection, although controlled trials are lacking. Warfarin is sometimes used empirically for patients with recurrent cerebrovascular events while on antiplatelet therapy, but in this setting warfarin may not be warranted. The Warfarin Aspirin Recurrent Stroke Study (WARSS) compared warfarin with aspirin in 2,000 patients with noncardioembolic strokes, most of them lacunar strokes. The risk of recurrent stroke was the same in the two treatment arms, whereas the risk of hemorrhage tended to be slightly higher in the warfarin group. Consequently, the role of warfarin in noncardioembolic strokes has become somewhat dubious.

Contraindications to warfarin include pregnancy, poor compliance, alcohol abuse, and risk of falling. The long-term risk of chronic anticoagulation is major hemorrhage, occurring at a rate of 1% to 3% a year.

### Uncommon Causes

Unusual causes account for a minority of all strokes, but they have specific diagnostic and therapeutic implications. Moreover, they are disproportionately represented in young stroke victims, accounting for nearly one third of strokes in victims younger than 45 years.

The extracranial and intracranial arteries are commonly affected by atherosclerosis, but several nonatherosclerotic disorders may also cause stroke. These disorders include inflammatory arteriopathies such as collagen vascular diseases, Takayasu disease, and neurovascular syphilis, as well as noninflammatory arteriopathies such as arterial dissection, fibromuscular dysplasia, moyamoya disease, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), radiation vasculopathy, and vasospasm after subarachnoid hemorrhage (SAH).

**Arterial Dissection**

Dissection of the internal carotid artery and vertebral artery can occur after head and neck trauma but may also occur spontaneously. Some connective tissue disorders may be risk factors, including fibromuscular dysplasia, Marfan syndrome, and Ehlers-Danlos syndrome. Arterial wall dissection causes vascular stenosis, occlusion, or a dissecting aneurysm. Clinical features include neck pain, headache, Horner syndrome, TIA or ischemic stroke, and tinnitus or audible bruits. Conventional angiography is the diagnostic gold standard and reveals string sign, tapered stenosis or occlusion, dissecting aneurysm, intimal flap, distal pouch formation, and an underlying arteriopathy. Dissection may be diagnosed noninvasively with ultrasonography, CT-A, MRI, or MRA, but each has potential limitations.

Prevention of stroke secondary to extracranial arterial dissection consists primarily of antithrombotic therapy. Heparin should be considered early because stroke risk is greatest in the first few days after the initial vascular injury. If anticoagulation is contraindicated, aspirin is recommended. Patients receive antithrombotic therapy until serial imaging demonstrates recanalization or stabilization of the dissected vessel.

**Inflammatory Arteriopathy**

Inflammatory arteriopathies, or vasculitides, are a heterogeneous group of disorders in which vascular inflammation results in cerebral ischemia. Vasculitis may be primary (isolated to
angiitis of the central nervous system) or secondary to infections (syphilis, tuberculosis, or varicella-zoster virus), toxins (cocaine, amphetamines, or LSD), neoplasms, or systemic inflammatory disorders (polyarteritis nodosa, Churg-Strauss angiitis, Wegener granulomatosis, giant cell arteritis, systemic lupus erythematosus, or rheumatoid arthritis). Symptoms may include headache, seizures, focal neurologic deficits, and multifocal encephalopathy. Clinical and serologic features of the vasculitides vary, but angiographic findings tend to be similar and nonspecific, showing segmental narrowing and dilatation (beading). Brain biopsy may confirm the diagnosis. Treatment should be directed at any underlying systemic disorder. Immunosuppressive regimens with corticosteroids and other agents are often used empirically.

**Hereditary Causes**

Ischemic stroke may be associated with hereditary and acquired prothrombotic states, including abnormalities of red cell or platelet function, coagulation factors, or endogenous fibrinolysis. These disorders are uncommon but should be considered when no alternative etiology is identified.84.88

**Cerebral Venous Thrombosis**

Cerebral venous thrombosis (CVT) is a rare but important cause of stroke that is often missed or discovered late in diagnosis. Infection is the common cause of CVT in children, whereas in adults, most cases are associated with pregnancy. Infrequent etiologies include severe dehydration, sickle cell anemia, malignancy, and hypercoagulable states. Oral contraceptive agents have also been implicated. Severe headache, nausea, and vomiting are nonspecific but common symptoms, and papilledema, if present, may be the only abnormality on initial examination. Fluctuating focal neurologic deficits, such as unilateral weakness, numbness, or seizures, may appear. Lumbar puncture may demonstrate elevated protein, red cells, or xanthochromia. Noncontrast CT can determine whether acute hemorrhage or mass effect is present. Contrast CT may demonstrate a so-called empty delta sign in the sagittal sinus. MRI and MR venogram (MRV) have better sensitivity for detection of CVT, and conventional cerebral angiography remains the diagnostic gold standard. A small randomized trial demonstrated safety and efficacy of intravenous heparin in acute hemorrhage or mass effect is present. Contrast CT may be considered when no alternative etiology is identified.

### Hemorrhagic Stroke

#### Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) accounts for 11% of stroke deaths and notably affects African Americans.92 ICH cannot be reliably distinguished from ischemic stroke by clinical criteria alone. Noncontrast CT imaging is required to detect the presence of blood. Volume of ICH and level of consciousness are the two most powerful predictors of outcome. Specific therapy for ICH remains largely an enigma. Patients with ICH frequently deteriorate as edema worsens over the first 24 to 48 hours. Late hematoma evacuation is ineffective in reducing mortality or improving outcome. Early surgical evacuation remains controversial. Theoretically, early hematoma evacuation may reduce surrounding ischemic injury and prevent edema formation and consequent herniation. Pilot studies of surgery within 12 hours and 24 hours suggest early surgery is feasible and may be beneficial.

### Table 6 Management Strategies for Intracranial Pressure

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Ventricular drainage</td>
<td>Most useful in hydrocephalus</td>
</tr>
<tr>
<td>Osmotic diuresis</td>
<td>Mannitol load, 0.5–1.0 g/kg IV; maintenance dose, 0.25–1.0 g q. 6 hr; titrate to keep serum osmolality 300 to 310 mOsm/kg H2O</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Titrate to keep Pco2 30–35 mm Hg; wean slowly</td>
</tr>
<tr>
<td>Sedation</td>
<td>Consider propofol or other benzodiazepine drip</td>
</tr>
<tr>
<td>Neuromuscular blockade</td>
<td>Always combine with sedation</td>
</tr>
<tr>
<td>Barbital coma</td>
<td>Rarely indicated</td>
</tr>
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Spontaneous subarachnoid hemorrhage most commonly results from aneurysms of the circle of Willis [see Figure 2]. The anterior and posterior communicating arteries are most frequently responsible. Hypertension and cigarette smoking are clear risk factors for aneurysmal rupture. Family history in first-degree relatives of patients with SAH is also a risk factor for unruptured aneurysm detection (about 4%), but routine screening is not recommended. The risk of rupture depends on aneurysm size. For patients with no history of SAH, the risk of rupture of aneurysms less than 10 mm in diameter is 0.05% a year. For aneurysms greater than 10 mm in diameter, the risk is slightly less than 1% a year. For aneurysms at least 25 mm in diameter, the risk jumps to 6% in the first year.

Diagnosis
Up to 50% of patients with SAH present with a so-called warning leak or sentinel hemorrhage. Establishing the diagnosis early and consequent prompt aneurysm clipping can reduce long-term morbidity and mortality. Modern head CT imaging [see Figure 2] can establish the diagnosis in 97% of cases of patients presenting to the emergency department with “the worst headache of my life.” In the remaining few percent, lumbar puncture and examination of the cerebrospinal fluid for xanthochromia are necessary. In addition to severe headache, the following all suggest SAH and should prompt a thorough evaluation: rapid onset, photophobia, stiff neck, decreased level of consciousness, and focal neurologic signs.

Treatment
The treatment of SAH involves localizing the aneurysm with cerebral angiography and surgical clipping within 72 hours of onset. In patients with severe symptoms (coma), surgery is often delayed and other options, including interventional radiologic procedures, are frequently employed. Before aneurysm clipping, patients are kept mildly sedated in a quiet room and given stool softeners to reduce the risk of rebleeding. Anticonvulsants ( fosphenytoin) should be given at the first sign of any seizure activity. Blood pressure is gently controlled. Although hypertension is related to rebleeding, some investigators believe that blood pressure works to tamponade the bleeding, and drastic reductions in blood pressure should be avoided.

Hydrocephalus is common after SAH and is very treatable with ventricular drainage. Any change in mental status should prompt the performance of an emergency CT to look for signs of hydrocephalus. Because it has been shown to improve outcome, nimodipine, a calcium channel blocker, is begun on the first day and continued for 21 days. After aneurysm clipping, the goal is to prevent vasospasm. Daily transcranial Doppler examinations are warranted. Patients should be well hydrated, and blood pressure should be slightly high. At the first clinical or transcranial Doppler sign of vasospasm, triple H (hypertensive, hyperemic, and hemodilution) therapy should be initiated. Both colloidal and crystalloid therapy are employed, and frequently, pressor support is needed.

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