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438 Ischemic Stroke

some centers combine both CTA and CT perfusion imaging together with the noncontrast CT scan. CT perfusion imaging increases the sen sitivity for detecting ischemia and can measure the ischemic penumbra (Fig. 437-12). Alternatively, MR perfusion can be combined with MR diffusion imaging to identify the ischemic penumbra as the mismatch between these two imaging sequences. ■ ■FURTHER READING Blumenfeld H: Neuroanatomy Through Clinical Cases, 3rd ed. New York, Sinauer Associates, 2020. Tsao CW: Heart disease and stroke statistics-2023 update: A report from the American Heart Association. Circulation 147:e93, 2023. Wade S. Smith, Anthony S. Kim,

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Ischemic Stroke The clinical diagnosis of stroke is discussed in Chap. 437. Once this diagnosis is made and either a noncontrast computed tomography (CT) scan or magnetic resonance imaging (MRI) scan has been per formed, rapid reversal of ischemia is paramount. This chapter will focus on the stroke treatment timeline and subsequent secondary stroke prevention. ■ ■PATHOPHYSIOLOGY OF ISCHEMIC STROKE Acute occlusion of an intracranial vessel causes reduction in blood flow to the brain region it supplies (Fig. 438-1). The magnitude of flow reduction is a function of collateral blood flow, and this depends on an individual’s vascular anatomy (which may be altered by disease), the site of occlusion, and systemic blood pressure. A decrease in cerebral blood flow to zero causes death of brain tissue (neuron cell bodies, dendrites, axons, and glial cells) within 4–10 min; values <16–18 mL/100 g tissue Ischemic energy failure Glutamate release Spreading depression Glutamate receptors Ca2+/Na+ influx Proteolysis Membrane and cytoskeletal breakdown Cell death FIGURE 438-1 Major steps in the cascade of cerebral ischemia. See text for details. iNOS, inducible nitric oxide synthase; PARP, poly-A ribose polymerase.

per minute cause infarction within an hour; and values <20 mL/100 g tissue per minute cause ischemia without infarction unless prolonged for several hours or days. If blood flow is restored to ischemic tissue before significant infarction develops, the patient may experience only transient symptoms, and the clinical syndrome is called a transient ischemic attack (TIA). Another important concept is the ischemic penumbra, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction. The penumbra can be imaged by perfusion imaging using MRI or CT (see Fig. 438-3 and Figs. 437-12 and 437-13). The ischemic penumbra will eventually progress to infarction if no change in flow occurs, and hence, saving the ischemic penumbra is the goal of revascularization therapy. Restoration of blood flow provides oxygen and glucose to the penumbral tissue, preventing infarction not only by supplying fuel for metabolism but by reversing tissue acidosis, clearing glutamate and toxic oxygen species, and halting waves of corti cal

spreading depression emanating from the ischemic core that add metabolic stress to the tissue.

CHAPTER 438 Ischemia causes a reduction in glucose and oxygen delivery, which in turn results in reduced capacity of cells to generate ATP. Without ATP, membrane ion pumps stop functioning and cells depolarize, allowing intracellular sodium and calcium to rise. Cellular depolar ization also causes glutamate release from synaptic terminals and a failure of glutamate uptake by glial cells. The resulting sustained elevation in extracellular glutamate produces neurotoxicity by activat ing postsynaptic glutamate receptors that increase neuronal calcium influx and the production of reactive oxygen species. Reactive oxygen species damage DNA, lipid membranes, and likely other vital func tions of cells. An innate immune response becomes apparent within a few hours after stroke, consisting of activation of proinflamma tory microglia (the resident immune cells in brain) and infiltration of immune cells from the circulation. While important in repairing stroke damage, this acute inflammatory response may also contribute to tissue injury after stroke by release of proteases and reactive oxygen species. Ischemia and the postischemic inflammatory response also injure or destroy axons and dendrites at some distance from the infarct itself. Fever dramatically worsens brain injury during ischemia, as does hyperglycemia (glucose >11.1 mmol/L [200 mg/dL]), so it is reason able to suppress fever and prevent hyperglycemia during and after brain ischemia. The value of induced mild hypothermia to improve stroke outcomes has not been clearly demonstrated and remains the subject of continuing clinical research. Ischemic Stroke Arterial occlusion Thrombolysis and thrombectomy Mitochondrial damage PARP Reperfusion Inflammatory response INOS Free oxygen species Leukocyte adhesion Lipolysis Arachidonic acid production Phospholipase

TREATMENT Acute Ischemic Stroke (Fig. 438-2) After the clinical diagnosis of stroke is made (Chap. 437), an orderly and prompt process of evaluation and treatment should follow. The first goal is to prevent or reverse brain injury. Attend to the patient’s airway, breathing, and circulation (ABCs), and treat hypoglycemia or hyperglycemia if identified by finger stick testing. Perform an emergency noncontrast head CT scan to differentiate between ischemic stroke and hemorrhagic stroke (Chap. 439); there are no reliable clinical findings that conclusively separate ischemia from hemorrhage, although a more depressed level of con sciousness, higher initial blood pressure, or worsening of symptoms after onset favor hemorrhage, and a deficit that is maximal at onset, or remits, suggests ischemia. Treatments designed to reverse or lessen the amount of tissue infarction and improve clinical outcome fall within six categories: (1) medical support, (2) IV thrombolysis, (3) endovascular revascularization, (4) antithrombotic treatment, (5) neuroprotection, and (6) stroke centers and rehabilitation. MEDICAL SUPPORT When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra. Atten tion is also directed toward preventing the common complications of bedridden patients—infections (pneumonia, urinary, and skin) PART 13 Neurologic Disorders Suspected acute stroke Prehospital call ahead Code stroke activation Onset <6 h Onset 6–24 h CT no hemorrhage No Yes IV PA eligible? Favorable perfusion? Give IV PA No Yes ICA/M1-2 or BA occlusion? Thrombectomy Inpatient management Perform CTA FIGURE 438-2 Management of acute stroke (pathway followed by the authors). For suspected stroke identified by prehospital professionals, we encourage calling ahead to the destination hospital. This allows early “stroke code” activation to prepare for an emergent computed tomography (CT) on arrival. For patients with onset <6 h from last time seen normal, we expedite a noncontrast head CT scan, and if free of hemorrhage and the patient is IV thrombolysis eligible (typically <4.5 h of last seen well time), this is administered in

the CT scanner. (For IV tissue PA [tPA], the bolus is given and infusion initiated; for tenecteplase, the full dose is given as a bolus.) Then CT angiography (CTA) from left atrium to skull vertex is performed to identify an eligible target lesion for thrombectomy. For a patient presenting in the 6- to 24-h time window, thrombolysis is not considered, and the decision to perform thrombectomy is based on perfusion imaging. Priorities of Acute Stroke Consultation: Once stroke is suspected, the first priorities are to assess airway and blood pressure, followed by establishing the time last seen normal. Patients with disabling neurologic deficits (particularly with National Institutes of Health Stroke Scale >5) may be eligible for thrombolytic and/or endovascular therapy. Based on the onset time, we follow the protocol shown in the figure. Following acute treatments, if any, we proceed with establishing the cause of the ischemic stroke. If atrial fibrillation is established or newly discovered, we favor use of apixaban 5 mg twice daily (or a reduced dose of 2.5 mg twice daily for impaired glomerular filtration rate) lifelong. If atrial fibrillation is not detected during the hospital encounter, we obtain an ambulatory electrocardiogram monitor to surveil for intermittent atrial fibrillation while treating with antiplatelet agents, then convert to oral anticoagulation if intermittent atrial fibrillation is detected. If we identify significant internal carotid stenosis, we refer for carotid endarterectomy during the same hospitalization regardless of infarct size. For all else, we use the dual antiplatelet agents aspirin (81 mg) and either clopidogrel (600 mg-load, followed by 75 mg daily) or ticagrelor (180-mg load, followed by 90 mg twice daily) daily for 21–30 days then continue aspirin at 81 mg daily. Ticagrelor has the advantage of not being affected by common polymorphisms of CYP2C19 that limit efficacy of clopidogrel in significant proportions of patients, particularly those of Asian descent. If the CTA revealed significant intracranial atherosclerosis or other precranial vessel stenosis within the vascular territory of the infarct (lumen caliber reduced by >50%), we continue dual antiplatelet agents for at least 3 months and then convert to a single agent. Unless contraindicated, all patients receive a highintensity statin such as atorvastatin 80 mg or rosuvastatin 40 mg, with goal low-density lipoprotein level of <70 mg/dL unless the stroke has a nonatherothrombotic cause. Patients who are statin intolerant can receive PCSK9 inhibitors. Blood pressure control should target systolic blood pressure <120 mmHg long term, but we allow permissive hypertension for the first few days or weeks to help with collateral flow to the brain. BA, basilar artery; CTP, computed tomography perfusion; ICA, internal carotid artery; IV, intravenous; M1, middle cerebral artery first division; M2, middle cerebral artery second division; PA, plasminogen activator (tissue plasminogen activator or tenecteplase).

and deep-venous thrombosis (DVT) with pulmonary embolism. Subcutaneous heparin (unfractionated and low-molecular-weight) is safe and can be used concomitantly. Use of pneumatic compres sion stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin. Because collateral blood flow within the ischemic brain may be blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely. Blood pressure should be reduced if it exceeds 220/120 mmHg, if there is malignant hypertension (Chap. 288) or concomitant myocardial ischemia, or if blood pressure is >185/110 mmHg and thrombolytic therapy is anticipated. When faced with the competing demands of myo cardium and brain, lowering the heart rate with a β1-adrenergic blocker (such as esmolol) can be a first step to decrease cardiac work and maintain blood pressure. Routine lowering of blood pres sure below the limits listed above has the potential to worsen out comes. Fever is detrimental and should be treated with antipyretics and surface cooling. Serum glucose should be monitored and kept <10.0 mmol/L (180 mg/dL), and above at least 3.3 mmol/L (60 mg/dL); a more intensive glucose control strategy does not improve outcome. Between 5 and 10% of patients develop enough cerebral

edema to cause obtundation and brain herniation. Edema peaks on the second or third day but can cause mass effect for ~10 days. The larger the infarct, the greater the likelihood that clinically sig nificant edema will develop. Water restriction and IV mannitol CT no hemorrhage CTA/CTP Yes No

or hypertonic saline may be used to raise the serum osmolarity, but hypovolemia should be avoided because this may contribute to hypotension and worsening infarction. Combined analysis of three randomized European trials of hemicraniectomy (craniotomy and temporary removal of part of the skull) shows that hemicra niectomy reduces mortality by 50%, and the clinical outcomes of survivors are significantly improved. Older patients (age >60 years) benefit less but still significantly. The size of the diffusion-weighted imaging volume of brain infarction during the acute stroke is a pre dictor of future deterioration requiring hemicraniectomy. Special vigilance is warranted for patients with cerebellar infarc tion. These strokes may mimic labyrinthitis because of prominent vertigo and vomiting; the presence of head or neck pain should alert the physician to consider cerebellar stroke due to vertebral artery dissection. Even small amounts of cerebellar edema can acutely increase intracranial pressure (ICP) by obstructing cerebrospinal fluid (CSF) flow leading to hydrocephalus or by directly compress ing the brainstem. The resulting brainstem compression can mani fest as coma and respiratory arrest and require emergency surgical decompression. Suboccipital decompression is recommended in patients with cerebellar infarcts who demonstrate neurologic dete rioration and should be performed before significant brainstem compression occurs. INTRAVENOUS THROMBOLYSIS The National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator (rtPA) Stroke Study showed a clear benefit for IV rtPA in selected patients with acute stroke. The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg maxi mum; 10% as a bolus, then the remainder over 60 min) versus pla cebo in ischemic stroke within 3 h of onset. One-half of the patients were treated within 90 min. Symptomatic intracranial hemorrhage occurred in 6.4% of patients on rtPA and 0.6% on placebo. In the rtPA group, there was a significant 12% absolute increase in the number of patients with only minimal disability (32% on placebo and 44% on rtPA) and a nonsignificant 4% reduction in mortality (21% on placebo and 17% on rtPA). Thus, despite an increased incidence of symptomatic intracranial hemorrhage, treatment with IV rtPA within 3 h of the onset of ischemic stroke improved clinical outcome. Three subsequent trials of IV rtPA did not confirm this benefit, perhaps because of the dose of rtPA used, the timing of its delivery, and small sample size. When data from all randomized IV rtPA trials were combined, however, efficacy was confirmed in the <3-h time window, and efficacy likely extended to 4.5 h and possibly to 6 h. Based on these combined results, the European Cooperative Acute Stroke Study (ECASS) III explored the safety and efficacy of rtPA in the 3- to 4.5-h time window. Unlike the NINDS study, patients aged >80 years and diabetic patients with a previous stroke were excluded. In this 821-patient randomized study, efficacy was again confirmed, although the treatment effect was less robust than in the 0- to 3-h time window. In the rtPA group, 52.4% of patients achieved a good outcome at 90 days, compared to 45.2% of the placebo group (odds ratio [OR] 1.34, p = .04). The symptomatic intracranial hemorrhage rate was 2.4% in the rtPA group and 0.2% in the placebo group (p = .008). Based on these data, rtPA is approved in the 3- to 4.5-h win dow in Europe and Canada but is only approved for 0–3 h in the United States. A dose of 0.6 mg/kg is typically used in Japan and other Asian countries based on observation of >600 patients given this lower dose and observing similar outcomes to historical con trols and a lower rate of intracranial hemorrhage. This dose also mitigates concerns that patients of Asian descent have a higher propensity to bleed from most antithrombotic and thrombolytic medications. The infrastructure to efficiently administer IV rtPA to eligible patients is a

central component of primary stroke centers (see below). It represents the first treatment proven to improve clinical outcomes in ischemic stroke and is cost-effective and cost-saving. The time of stroke onset is defined as the time the patient's symptoms were witnessed to begin or the time the patient

TABLE 438-1 Administration of Intravenous Recombinant Tissue Plasminogen Activator (rtPA) or Tenecteplase for Acute Ischemic Stroke (AIS)a INDICATION CONTRAINDICATION Clinical diagnosis of stroke Onset of symptoms to time of drug administration ≤4.5 hb Sustained BP >185/110 mmHg despite treatment Bleeding diathesis Recent head injury or intracerebral hemorrhage Major surgery in preceding 14 days Gastrointestinal bleeding in preceding 21 days Recent myocardial infarction CT scan showing no hemorrhage, and no edema > 1/3 of the MCA territory Age ≥18 years Administration of stroke thrombolysis IV access with two peripheral IV lines (avoid arterial or central line placement) CHAPTER 438 Review eligibility for stroke thrombolysis Administer 0.9 mg/kg IV (maximum 90 mg) rtPA IV as 10% of total dose by bolus, followed by remainder of total dose over 1 hc Or Administer 0.25 mg/kg IV (maximum 25 mg) tenecteplase IV push over 5 sd Frequent cuff BP monitoring Ischemic Stroke No other antithrombotic treatment for 24 h For decline in neurologic status or uncontrolled BP, stop infusion, give cryoprecipitate, and reimage brain emergently Avoid urethral catheterization for ≥2 h aSee Activase (tissue plasminogen activator) package insert for complete list of contraindications and dosing. bDepending on the country, IV rtPA may be approved for up to 4.5 h with additional restrictions. cAn rtPA dose of 0.6 mg/kg is commonly used in Asia (Japan and China) based on randomized data indicating less hemorrhage and similar efficacy using this lower dose. dUse of tenecteplase for acute ischemic stroke is off-label. Abbreviations: BP, blood pressure; CT, computed tomography; MCA, middle cerebral artery. was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed. Advanced neuroimaging techniques (see Chap. 437) may help to select patients beyond the 4.5-h window who will benefit from thrombolysis. Two trials using MRI selection beyond 4.5 h have shown clinical benefit from IV rtPA. Patients with minor stroke (nondisabling deficit and National Institutes of Health Stroke Scale [NIHSS] 0–5) appear to respond to acute aspirin or short-term dual antiplatelet therapy using the com bination of aspirin and clopidogrel as well as IV rtPA. Table 438-1 summarizes eligibility criteria and instructions for administration of IV rtPA. The plasminogen activator tenecteplase (0.25 mg/kg IV bolus over 5 s with a maximum dose of 25 mg) has been directly com pared to rtPA and is being adopted by many centers because it is given without need for a 1-h infusion. This improves the effi ciency of transferring patients to comprehensive stroke centers for thrombectomy because the IV infusion required for IV rtPA is not required for tenecteplase, thus obviating need for critical care trans port. Several trials using tenecteplase prior to endovascular therapy have found it to be safe. ENDOVASCULAR REVASCULARIZATION Ischemic stroke from large-vessel intracranial occlusion results in high rates of mortality and morbidity. Occlusions in such large vessels (middle cerebral artery [MCA], intracranial internal carotid artery, and the basilar artery) generally involve a large clot burden and often fail to open with IV thrombolysis alone. Endovascular mechanical thrombectomy has been studied as an alternative or adjunctive treatment of acute stroke in patients who are ineligible for, or have contraindications to, thrombolytics or in those who failed to achieve vascular recanalization with IV thrombolytics (Fig. 438-3). In 2015, the results of six randomized trials were published, all demonstrating that endovascular therapy improved clinical outcomes for internal carotid and MCA occlu sions proven by CT angiography (CTA), under 6 h from stroke

A B C PART 13 Neurologic Disorders E G F D FIGURE 438-3 (A) Noncontrast head computed tomography (CT) scan of a 78-year-old man with atrial fibrillation and hypertension who was not taking oral anticoagulants and awoke with right hemiparesis and expressive aphasia. The head CT shows no intracerebral hemorrhage. He was not treated with plasminogen activators because his last seen normal time was 8 h prior. Head CT also shows hyperdensity in the left middle cerebral artery (MCA, arrow); this finding is highly specific for MCA occlusion but is poorly sensitive, as only 20% of patients with MCA occlusion show hyperdensity. (B) To confirm a large-vessel occlusion, CT angiography (CTA) performed in the same session reveals an occlusion of a secondary branch of the left MCA (arrow). (C) CT perfusion performed immediately following the CTA shows no core infarct (no pink signal in the left image) but a large region (green shading in the right image) of ischemic tissue that will die if revascularization is not achieved. (D) Catheter angiography shows the occluded branch of the left MCA (arrow) and (E) restored flow after successful clot removal (F). (G) A subsequent diffusion-weighted imaging scan shows a very small residual brain infarction. CBF, cerebral blood flow. onset, with or without pretreatment with IV tissue plasminogen activator (tPA). One study concluded that patients were home nearly 2 months earlier if they received endovascular therapy. A combined meta-analysis of all patients in these trials confirmed a large benefit with endovascular therapy (OR, 2.49; 95% confidence interval [CI], 1.76–3.53; p <.001). The percentage of patients who achieved modi fied Rankin scores of 0–2 (normal or symptomatic but independent) was 46% in the endovascular group and 26.5% in the medical arm. A more recent meta-analysis reveals a mortality benefit with throm bectomy as well. As with IV rtPA treatment, clinical outcome is dependent on time to effective therapy. The odds of a good outcome exceed 3 if groin puncture occurs within 2 h of symptom onset but is only 2 if 8 h elapse. Over 80% of patients who had vessel open ing within 1 h of arrival to the emergency department had a good outcome, whereas only one-third had a good outcome if 6 h elapsed. The outcomes from endovascular therapy are likely improved with IV rtPA treatment prior to thrombectomy if the patient is eligible for rtPA and it is safe to administer. Recent data support replacing IV rtPA with IV tenecteplase because its simple bolus administration makes transporting the patient to an endovascular center less cumbersome. Extending the time window beyond 6 h appears to be effective if the patient has specific imaging findings demonstrating good vas cular collaterals (CT perfusion or magnetic resonance [MR] perfu sion techniques, see Chap. 437) and can be treated within 24 h. The Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN) trial reported good outcomes more frequently with endovascular ther apy than with medical care alone (47 vs 13%, p <.0001). The Endo vascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE-3) trial confirmed these results (45 vs 17%, p <.001) if

CBF <30%: 0 ml Tmax >6.0s: 57 ml Mismatch volume: 57 ml Mismatch ratio: infinite treated up to 16 h from stroke onset. Nonrandomized data of throm bectomy for basilar occlusion have found this treatment to be safe up to 24 h from symptom onset and associated with lower 3-month Rankin scores. An example of how advanced imaging techniques (CT, CTA, CT perfusion, catheter-based angiography), endovascu lar thrombectomy with clot removal, and follow-up MRI can lead to a better than predicted stroke outcome is shown in Fig 438-3. Now that endovascular stroke therapy is proven to be effective, the creation of comprehensive stroke centers designed to rapidly identify and treat patients with large-vessel cerebral ischemia has been a major focus internationally. Creating regional systems of care whereby stroke patients are first evaluated at acute stroke ready hospitals or primary stroke centers (which can administer IV rtPA or tenecteplase) then transferred to thrombectomy-capable or comprehensive stroke centers if

needed, or directly triaged to thrombectomy-capable or comprehensive centers based on field assessment, appears to be an effective strategy to improve outcomes. ANTITHROMBOTIC TREATMENT Platelet Inhibition Aspirin is the only antiplatelet agent that has been proven to be effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke (see below). Two large trials, the International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST), found that the use of aspirin within 48 h of stroke onset reduced both stroke recurrence risk and mortality minimally. Among 19,435 patients in IST, those allocated to aspirin, 300 mg/d, had slightly fewer deaths within 14 days (9.0 vs 9.4%), significantly fewer recurrent ischemic strokes (2.8 vs 3.9%), no excess of hemorrhagic strokes (0.9 vs 0.8%), and a trend toward a reduction in death or dependence at 6 months (61.2 vs 63.5%). In CAST, 21,106 patients

with ischemic stroke received 160 mg/d of aspirin or a placebo for up to 4 weeks. In the aspirin group, there were very small reductions in early mortality (3.3 vs 3.9%), recurrent ischemic strokes (1.6 vs 2.1%), and dependency at discharge or death (30.5 vs 31.6%). These trials demonstrate that the use of aspirin in the treatment of acute ischemic stroke is safe and produces a small net benefit. For every 1000 acute strokes treated with aspirin, ~9 deaths or nonfatal stroke recurrences will be prevented in the first few weeks, and ~13 fewer patients will be dead or dependent at 6 months. The short-term combination of aspirin with clopidogrel or with ticagrelor following minor stroke or TIA is effective at preventing early second stroke (see below). Anticoagulation Numerous clinical trials have failed to demon strate any benefit of routine anticoagulation in the primary treat ment of atherothrombotic cerebral ischemia and have also shown an increase in the risk of brain and systemic hemorrhage. Therefore, the routine use of heparin or other anticoagulants for patients with atherothrombotic stroke is not warranted. Heparin and oral anticoagulation are likely no more effective than aspirin for stroke associated with arterial dissection. However, there may be benefit of anticoagulation for halting progression of dural sinus thrombosis. NEUROPROTECTION Neuroprotection is the concept of providing a treatment that pro longs the brain’s tolerance to ischemia. Drugs that block the excit atory amino acid pathways have been shown to protect neurons and glia in animals, but despite multiple clinical trials, they have not yet been proven to be beneficial in humans. Hypothermia is a powerful neuroprotective treatment in patients with cardiac arrest (Chap. 318) and is neuroprotective in animal models of stroke, but it has not been adequately studied in patients with ischemic stroke and is associated with an increase in pneumonia rates that could adversely impact stroke outcomes. Hypothermia combined with hemicrani ectomy is no more effective than hemicraniectomy with euthermia. STROKE CENTERS AND REHABILITATION Patient care in stroke units followed by rehabilitation services improves neurologic outcomes and reduces mortality. Use of clinical Intracranial atherosclerosis Penetrating artery disease Carotid plaque with arteriogenic emboli Flowreducing carotid stenosis Atrial fibrillation Cardiogenic emboli Valve disease Left ventricular thrombi A B C FIGURE 438-4 Pathophysiology of ischemic stroke. A. Diagram illustrating the three major mechanisms that underlie ischemic stroke: (1) occlusion of an intracranial vessel by an embolus (e.g., cardiogenic sources such as atrial fibrillation or artery-to-artery emboli from carotid atherosclerotic plaque), often affecting the large intracranial vessels; (2) in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries that arise from the major intracranial arteries; and (3) hypoperfusion caused by flow-limiting stenosis of a major extracranial (e.g., internal carotid) or intracranial vessel, often producing “watershed” ischemia. B. and C. Diagram and reformatted computed tomography angiogram of the common, internal, and external

carotid arteries. High-grade stenosis of the internal carotid artery, which may be associated with either cerebral emboli or flow-limiting ischemia, was identified in this patient.

pathways and staff dedicated to the stroke patient can improve care. This includes use of standardized stroke order sets. Stroke teams that provide emergency 24-h evaluation of acute stroke patients for acute medical management and consideration of thrombolysis or endovascular treatments, potentially provided using telemedicine/ telestroke services, are essential components of primary and com prehensive stroke centers, respectively.

Proper rehabilitation of the stroke patient includes early physical, occupational, and speech therapy. It is directed toward educating the patient and family about the patient's neurologic deficit, pre venting the complications of immobility (e.g., pneumonia, DVT and pulmonary embolism, pressure sores of the skin, and muscle contractures), and providing encouragement and instruction in overcoming the deficit. Use of pneumatic compression stockings is of proven benefit in reducing risk of DVT and is a safe alternative to heparin. The goal of rehabilitation is to return the patient home and to maximize recovery by providing a safe, progressive regimen suited to the individual patient. Additionally, the use of constrained movement therapy (immobilizing the unaffected side) has been shown to improve hemiparesis following stroke, even years after the stroke, suggesting that physical therapy can recruit unused neural pathways. Controversy exists regarding whether selective serotonin uptake inhibitors improve motor recovery, but they may be helpful in preventing poststroke depression. Newer robotic therapies and neuromodulation approaches using transcranial magnetic stimu lation or transcranial direct current stimulation are under active investigation (Chap. 500). The human nervous system is more adaptable than previously thought, and developing physical and pharmacologic strategies to enhance long-term neural recovery are the subject of ongoing research. CHAPTER 438 Ischemic Stroke ■ ■ETIOLOGY OF ISCHEMIC STROKE (Fig. 438-4 and Table 438-2) Although the initial management of acute ischemic stroke often does not depend on the etiology, establishing a cause is essential to reduce the risk of recurrence. Focus should be on atrial fibrillation and carotid atherosclerosis, because these etiologies Internal carotid External carotid Common carotid

TABLE 438-2 Causes of Ischemic Stroke COMMON CAUSES UNCOMMON CAUSES Thrombosis Lacunar stroke (small vessel) Large-vessel thrombosis Dehydration Embolic occlusion Artery-to-artery Carotid bifurcation Aortic arch Arterial dissection Cardioembolic Atrial fibrillation Mural thrombus Myocardial infarction Dilated cardiomyopathy Valvular lesions Mitral stenosis Mechanical valve Bacterial endocarditis Paradoxical embolus Atrial septal defect Patent foramen ovale Atrial septal aneurysm Spontaneous echo contrast Stimulant drugs: cocaine, Hypercoagulable disorders Protein C deficiencya Protein S deficiencya Antithrombin III deficiencya Antiphospholipid syndrome Factor V Leiden mutationa Prothrombin G20210A mutationa Systemic malignancy Sickle cell anemia β Thalassemia Polycythemia vera Systemic lupus erythematosus Homocysteinemia Thrombotic thrombocytopenic purpura Disseminated intravascular coagulation Dysproteinemiasa PART 13 Neurologic Disorders Nephrotic syndromea Inflammatory bowel diseasea Oral contraceptives COVID-19 infection Venous sinus thrombosisb Fibromuscular dysplasia Vasculitis Systemic vasculitis (PAN, granulomatosis amphetamine with polyangiitis, Takayasu's, giant cell arteritis) Primary CNS vasculitis Meningitis (syphilis, tuberculosis, fungal, bacterial, zoster) Noninflammatory vasculopathy Reversible vasoconstriction syndrome Fabry's disease Angiocentric lymphoma Cardiogenic Mitral valve calcification Atrial myxoma Intracardiac tumor Marantic

endocarditis Libman-Sacks endocarditis Subarachnoid hemorrhage vasospasm Moyamoya disease Eclampsia aChiefly cause venous sinus thrombosis. bMay be associated with any hypercoagulable disorder. Abbreviations: CNS, central nervous system; PAN, polyarteritis nodosa. have proven secondary prevention strategies. The clinical presentation and examination findings often establish the cause of stroke or narrow the possibilities to a few. Judicious use of laboratory testing and imag ing studies completes the initial evaluation. Nevertheless, nearly 30% of strokes remain unexplained despite extensive evaluation. Clinical examination should focus on the peripheral and cervical vascular system (measuring blood pressure), the heart (dysrhythmia, murmurs), extremities (peripheral emboli), and retina (effects of hypertension and cholesterol emboli [Hollenhorst plaques]). A com plete neurologic examination is performed to localize the anatomic site of stroke (Chap. 437). An imaging study of the brain is nearly always indicated and is required for patients being considered for thrombolysis; it may be combined with CT- or MRI-based angiogra phy to visualize the vasculature of the neck and intracranial vessels (see “Imaging Studies,” Chap. 437). A chest x-ray, electrocardiogram (ECG), urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), serum electrolytes, blood urea nitrogen (BUN), creatinine,

blood glucose, serum lipid profile, prothrombin time (PT), and partial thromboplastin time (PTT) are often useful and should be considered in all patients. An ECG, and subsequent cardiac telemetry, may dem onstrate arrhythmias or reveal evidence of recent myocardial infarction (MI). Of all these studies, only brain imaging and finger stick blood glucose are necessary prior to IV thrombolysis; the results of other studies should not delay the rapid administration of IV thrombolysis if the patient is eligible. Cardioembolic Stroke Cardioembolism is responsible for ~20% of all ischemic strokes. Stroke caused by heart disease is primarily due to embolism of thrombotic material forming on the atrial or ventricu lar wall or the left heart valves. These thrombi then detach and embo lize into the arterial circulation. The thrombus may fragment or lyse quickly, producing only a TIA. Alternatively, the arterial occlusion may last longer, producing stroke. Embolic strokes tend to occur suddenly with maximum neurologic deficit present at onset. With reperfusion following more prolonged ischemia, petechial hemorrhages can occur within the ischemic territory. These are usually of no clinical signifi cance and should be distinguished from frank intracranial hemorrhage into a region of ischemic stroke where the mass effect from the hemor rhage can cause a significant decline in neurologic function. Emboli from the heart most often lodge in the intracranial internal carotid artery, the MCA, the posterior cerebral artery (PCA), or one of their branches; infrequently, the anterior cerebral artery (ACA) is involved. Emboli large enough to occlude the stem of the MCA (3–4 mm) or internal carotid terminus lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory depend on the extent of the col lateral circulation. The most significant cause of cardioembolic stroke in most of the world is nonrheumatic (often called nonvalvular) atrial fibrillation. MI, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopa thy are other considerations (Table 438-2). Cardiac disorders causing brain embolism are discussed in the chapters on heart diseases, but a few pertinent aspects are highlighted here. Nonrheumatic atrial fibrillation is the most common cause of cere bral embolism overall. The presumed stroke mechanism is thrombus formation in the fibrillating atrium or atrial appendage, with subse quent embolization. Patients with atrial fibrillation have an average annual risk of stroke of ~5%. The risk of stroke can be estimated by calculating the CHA2DS2-VASc score (Table 438-3). Left atrial enlargement is an additional risk factor for formation of atrial thrombi. Rheumatic heart

disease usually causes ischemic stroke when there is prominent mitral stenosis or atrial fibrillation. Recent MI may be a source of emboli, especially when transmural and involving the antero apical ventricular wall, and prophylactic anticoagulation following MI with left ventricular thrombus has been shown to reduce ischemic stroke risk. Mitral valve prolapse is not usually a source of emboli unless the prolapse is severe. Paradoxical embolization occurs when venous thrombi migrate to the arterial circulation, usually via a patent foramen ovale (PFO) or atrial septal defect. Bubble-contrast echocardiography (IV injection of agitated saline coupled with either transthoracic or transesopha geal echocardiography) can demonstrate a right-to-left cardiac shunt, revealing the conduit for paradoxical embolization. Alternatively, a right-to-left shunt is implied if immediately following IV injection of agitated saline, the ultrasound signature of bubbles is observed during transcranial Doppler insonation of the MCA; pulmonary arteriove nous malformations should be considered if this test is positive yet an echocardiogram fails to reveal an intracardiac shunt. Both tech niques are highly sensitive for detection of right-to-left shunts. Besides venous clot, fat and tumor emboli, bacterial endocarditis, IV air, and amniotic fluid emboli at childbirth may occasionally be responsible for paradoxical embolization. The importance of a PFO as a cause of stroke is debated, particularly because they are present in ~15% of the general population. The presence of a venous source of embolus,

TABLE 438-3 Recommendations on Chronic Use of Antithrombotics for Various Cardiac Conditions CONDITION RECOMMENDATION Nonvalvular atrial fibrillation Calculate CHA2DS2-VASc scorea • CHA2DS2-VASc score of 0 Aspirin or no antithrombotic • CHA2DS2-VASc score of 1 Aspirin or OAC • CHA2DS2-VASc score of ≥2 OAC Rheumatic mitral valve disease • With atrial fibrillation, previous OAC embolization, or atrial appendage thrombus, or left atrial diameter >55 mm • Embolization or appendage clot despite OAC plus aspirin OAC • Mitral valve prolapse • Asymptomatic No therapy • With otherwise cryptogenic stroke or TIA Aspirin • Atrial fibrillation OAC Mitral annular calcification • Without atrial fibrillation but systemic Aspirin embolization, or otherwise cryptogenic stroke or TIA • Recurrent embolization despite aspirin OAC • With atrial fibrillation OAC Aortic valve calcification • Asymptomatic No therapy • Otherwise cryptogenic stroke or TIA Aspirin Aortic arch mobile atheroma • Otherwise cryptogenic stroke or TIA Aspirin or OAC Patent foramen ovale • Otherwise cryptogenic ischemic stroke Aspirin or closure with device or TIA • Indication for OAC (deep-venous OAC thrombosis or hypercoagulable state) Mechanical heart value • Aortic position, bileaflet or Medtronic Hall VKA INR 2.5, range 2–3 tilting disk with normal left atrial size and sinus rhythm • Mitral position tilting disk or bileaflet valve VKA INR 3.0, range 2.5–3.5 • Mitral or aortic position, anterior-apical VKA INR 3.0, range 2.5–3.5 myocardial infarct or left atrial enlargement • Mitral or aortic position, with atrial Aspirin plus VKA INR 3.0, range 2.5–3.5 fibrillation, or hypercoagulable state, or low ejection fraction, or atherosclerotic vascular disease • Systemic embolization despite target INR Add aspirin and/or increase INR: prior target was 2.5, increase to 3.0, range 2.5–3.5; prior target was 3.0, increase to 3.5, range 3–4 Bioprosthetic valve • No other indication for VKA therapy Aspirin Infective endocarditis Avoid antithrombotic agents Nonbacterial thrombotic endocarditis • With systemic embolization Full-dose, unfractionated heparin or SC LMWH, or Xa inhibitor aCHA2DS2-VASc score is calculated as follows: 1 point for congestive heart failure,

1 point for hypertension, 2 points for age ≥75 years, 1 point for diabetes mellitus,

2 points for stroke or TIA, 1 point for vascular disease (prior myocardial infarction, peripheral vascular disease, or aortic plaque), 1 point for age 65–74 years, 1 point for female sex category;

sum of points is the total CHA2DS2-VASc score. Note: Dose of aspirin is 50–325 mg/d; target INR for VKA is between 2 and 3 unless otherwise specified. Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant (VKA, thrombin inhibitor, or oral factor Xa inhibitors); TIA, transient ischemic attack; VKA, vitamin K antagonist. Sources: Data from DE Singer et al: Chest 133:546S, 2008; DN Salem et al: Chest 133:593S, 2008; CT January et al: JACC 64:2246, 2014.

most commonly a deep-venous thrombus, may provide confirmation of the importance of a PFO with an accompanying right-to-left shunt in a particular case. Meta-analysis of three recent randomized trials reported a hazard ratio of 0.41 for recurrent stroke (about a 1% per year absolute reduction) using percutaneous occlusion devices in patients with larger PFOs and no other explanation for their stroke. Guidelines now endorse PFO closure with percutaneous devices after consultation with a neurologist and a cardiologist.

Bacterial endocarditis can be a source of valvular vegetations that give rise to septic emboli. The appearance of multifocal symptoms and signs in a patient with stroke makes bacterial endocarditis more likely. Infarcts of microscopic size occur, and large septic infarcts may evolve into brain abscesses or cause hemorrhage into the infarct, which generally precludes use of anticoagulation or thrombolytics. Mycotic aneurysms caused by septic emboli may also present as subarachnoid hemorrhage (SAH) or intracerebral hemorrhage. Artery-to-Artery Embolic Stroke Thrombus formation on ath erosclerotic plaques may embolize to intracranial arteries producing an artery-to-artery embolic stroke. Less commonly, a diseased vessel may acutely thrombose. Unlike the myocardial vessels, artery-to-artery embolism, rather than local thrombosis, appears to be the dominant vascular mechanism causing large-vessel brain ischemia. Any diseased vessel may be an embolic source, including the aortic arch, common carotid, internal carotid, vertebral, and basilar arteries. CHAPTER 438 Ischemic Stroke CAROTID ATHEROSCLEROSIS Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurca tion and proximal internal carotid artery; the carotid siphon (portion within the cavernous sinus) is also vulnerable to atherosclerosis. Male gender, older age, smoking, hypertension, diabetes, and hypercholes terolemia are risk factors for carotid disease, as they are for stroke in general (Table 438-4). Carotid atherosclerosis produces an estimated 10% of ischemic stroke. For further discussion of the pathogenesis of atherosclerosis, see Chap. 244. Carotid disease can be classified by whether the stenosis is symp tomatic or asymptomatic and by the degree of stenosis (percent nar rowing of the narrowest segment compared to a nondiseased segment). Symptomatic carotid disease implies that the patient has experienced a recent (within 6 months) stroke or TIA within the vascular distribution of the artery, and it is associated with a greater risk of subsequent stroke than asymptomatic stenosis, in which the patient is symptom free and the stenosis is detected through screening. Greater degrees of arterial narrowing are generally associated with a higher risk of stroke, except that those with near occlusions are at lower risk of stroke. OTHER CAUSES OF ARTERY-TO-ARTERY EMBOLIC STROKE Intracranial atherosclerosis produces stroke either by an embolic mechanism or by in situ thrombosis of a diseased vessel. It is more common in patients of Asian and African-American descent. Recurrent stroke risk is ~15% per year, similar to untreated symptomatic carotid atherosclerosis. Dissection of the internal carotid or vertebral arteries or even ves sels beyond the circle of Willis is a common source of embolic stroke in young (age <60 years) patients. The dissection is usually painful and precedes the stroke by several hours or days. Extracranial dis sections do not cause hemorrhage, presumably because of the tough adventitia of

these vessels. Intracranial dissections, conversely, may produce SAH because the adventitia of intracranial vessels is thin and pseudoaneurysms may form, requiring urgent treatment to prevent rerupture. Treating asymptomatic pseudoaneurysms following extra cranial dissection is likely not necessary. The cause of dissection is usu ally unknown, and recurrence is rare. Ehlers-Danlos type IV, Marfan's disease and related disorders of connective tissue (Chap. 425), and fibromuscular dysplasia (Chap. 292) are associated with dissections. Trauma (usually a motor vehicle accident or a sports injury) can cause carotid and vertebral artery dissections. Spinal manipulative therapy is associated with vertebral artery dissection and stroke. Most dissections heal spontaneously, and stroke or TIA is uncommon beyond 2 weeks. One trial showed no difference in stroke prevention with antiplatelet regimens compared to anticoagulation, with a low recurrent stroke rate of 2%.

TABLE 438-4 Risk Factors for Stroke RELATIVE RISK REDUCTION WITH TREATMENT RISK FACTOR RELATIVE RISK Hypertension 2–5 38% 100–300 50–100 Atrial fibrillation 1.8–2.9 68% warfarin, 21% aspirin 20–83

Diabetes 1.8–6 No proven effect Smoking 1.8 50% at 1 year, baseline risk at 5 years postcessation Hyperlipidemia 1.8–2.6 16–30%

Asymptomatic carotid stenosis 2.0 53%

N/A Symptomatic carotid stenosis (70–99%) 65% at 2 years N/A

Symptomatic carotid stenosis (50–69%) 29% at 5 years N/A

aNumber needed to treat to prevent one stroke annually. Prevention of other cardiovascular outcomes is not considered here. Abbreviation: N/A, not applicable. PART 13 Neurologic Disorders ■ ■SMALL-VESSEL STROKE The term lacunar infarction refers to infarction following atherothrom botic or lipohyalinotic occlusion of a small artery in the brain. The term small-vessel stroke denotes occlusion of such a small penetrating artery and is now the preferred term. Small-vessel strokes account for ~20% of all strokes. Pathophysiology The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communi cating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 30- to 300-μm branches that penetrate the deep gray and white matter of the cerebrum or brainstem (Fig. 438-5). Each of these small branches can occlude either by ath erothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as lacunes (Latin for "lake" of fluid noted at autopsy). These infarcts range in size from 3 mm to 2 cm in diameter. Hypertension and age are the principal risk factors. Anterior cerebral a. Clinical Manifestations The most common small-vessel stroke syndromes are the following: (1) pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or the pons; the face, arm, and leg are almost always involved; (2) pure sensory stroke from an infarct in the ventral thalamus; (3) ataxic hemiparesis from an infarct in the ventral pons or internal cap sule; (4) and dysarthria and a clumsy hand or arm due to infarction in the ventral pons or in the genu of the internal capsule. Internal carotid a. Transient symptoms (small-vessel TIAs) may herald a small-vessel infarct; they may occur several times a day and last only a few minutes. Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is early worsening of symptoms or a stuttering course and severe permanent

disability may result. Basilar a. Vertebral a. FIGURE 438-5 Diagrams and reformatted computed tomography (CT) angiograms in the coronal section illustrating the deep penetrating arteries involved in small-vessel strokes. In the anterior circulation, small penetrating arteries called lenticulostriates arise from the proximal portion of the anterior and middle cerebral arteries and supply deep subcortical structures (upper panels). In the posterior circulation, similar arteries arise directly from the vertebral and basilar arteries to supply the brainstem (lower panels). Occlusion of a single penetrating artery gives rise to a discrete area of infarct (pathologically termed a “lacune,” or lake). Note that these vessels are too small to be visualized on CT angiography. A large-vessel source (either thrombosis or embolism) may manifest initially as a small-vessel infarction. Therefore, the search for embolic sources (carotid and heart) should not be completely abandoned in the evaluation of these patients. Secondary

NUMBER NEEDED TO TREATa PRIMARY PREVENTION SECONDARY PREVENTION prevention of small-vessel stroke involves risk factor modification, specifically reduction in blood pressure (see “Treatment: Primary and Secondary Prevention of Stroke and TIA,” below). ■ ■LESS COMMON CAUSES OF STROKE (Table 438-2) Hypercoagulable disorders (Chap. 69) primarily increase the risk of cortical vein or cerebral venous sinus thrombosis. Systemic Deep branches of the middle cerebral a. Anterior cerebral a. Internal carotid a. Middle cerebral a. Middle cerebral a. Basilar a. Vertebral a. Deep branches of the basilar a.

lupus erythematosus (Chap. 368) with Libman-Sacks endocarditis can be a cause of embolic stroke. These conditions overlap with the antiphospholipid syndrome (Chap. 369), which probably requires long-term anticoagulation to prevent further stroke. Homocysteinemia may cause arterial thromboses as well; this disorder is caused by vari ous mutations in the homocysteine pathways and responds to different forms of cobalamin depending on the mutation. Disseminated intra vascular coagulopathy can cause both venous and arterial occlusive events; COVID-19 infection may predispose for acute ischemic stroke due to large-vessel occlusion. Venous sinus thrombosis of the lateral or sagittal sinus or of small cortical veins (cortical vein thrombosis) occurs as a complication of oral contraceptive use, pregnancy and the postpartum period, inflammatory bowel disease, intracranial infections (meningitis), and dehydration. It is also seen in patients with laboratory-confirmed thrombophilia including antiphospholipid syndrome, polycythemia, sickle cell anemia, deficiencies of proteins C and S, factor V Leiden mutation (resistance to activated protein C), antithrombin III defi ciency, homocysteinemia, and the prothrombin G20210A mutation. Women who take oral contraceptives and have the prothrombin G20210A mutation may be at particularly high risk for sinus thrombo sis. Patients present with headache and may also have focal neurologic signs (especially paraparesis) and seizures. Often, CT imaging is nor mal unless an intracranial venous hemorrhage has occurred, but the venous sinus occlusion is readily visualized using MR or CT venogra phy or conventional x-ray angiography. With greater degrees of sinus thrombosis, the patient may develop signs of increased ICP and coma. Intravenous heparin, regardless of the presence of intracranial hemor rhage, reduces morbidity and mortality, and the long-term outcome is generally good. Heparin prevents further thrombosis and reduces venous hypertension and ischemia. If an underlying hypercoagulable state is not found, many physicians treat with oral anticoagulants for 3–6 months and then convert to aspirin, depending on the degree of resolution of the venous sinus thrombus. Anticoagulation is often con tinued indefinitely if thrombophilia is diagnosed. Sickle cell anemia (SS disease) is a common cause of stroke in chil dren. A subset of homozygous carriers of this hemoglobin mutation develop stroke in childhood, and this may be

predicted by document ing high-velocity blood flow within the MCAs using transcranial Doppler ultrasonography. In children who are identified to have high velocities, treatment with aggressive exchange transfusion dramati cally reduces risk of stroke, and if exchange transfusion is ceased, their stroke rate increases again along with MCA velocities. Fibromuscular dysplasia (Chap. 292) affects the cervical arteries and occurs mainly in women. The carotid or vertebral arteries show multiple rings of segmental narrowing alternating with dilatation. Vascular occlusion is usually incomplete. The process is often asymp tomatic but occasionally is associated with an audible bruit, TIAs, or stroke. Involvement of the renal arteries is common and may cause hypertension. The cause and natural history of fibromuscular dysplasia are unknown. TIA or stroke generally occurs only when the artery is severely narrowed or dissects. Anticoagulation or antiplatelet therapy may be helpful. Temporal (giant cell) arteritis (Chap. 375) is a relatively common affliction of elderly individuals in which the external carotid system, particularly the temporal arteries, undergoes subacute granulomatous inflammation with giant cells. Occlusion of posterior ciliary arteries derived from the ophthalmic artery results in blindness in one or both eyes and can be prevented with glucocorticoids. It rarely causes stroke because the internal carotid artery is usually not inflamed. Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (Takayasu’s arteritis) may cause carotid or vertebral thrombosis; it is rare in the Western Hemisphere. Necrotizing (or granulomatous) arteritis (Chap. 375), occurring alone or in association with generalized polyarteritis nodosa or granulomatosis with polyangiitis, involves the distal small branches (<2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. The CSF often shows pleocytosis, and the protein level is elevated. Primary

CHAPTER 438 FIGURE 438-6 Cerebral angiogram from a 32-year-old male with central nervous system vasculopathy. Dramatic beading (arrows) typical of vasculopathy is shown. Ischemic Stroke central nervous system vasculitis is rare; small or medium-sized ves sels are usually affected, without apparent systemic vasculitis. The differential diagnosis includes other inflammatory vasculopathies including infection (tuberculous, fungal), sarcoidosis, angiocentric lymphoma, carcinomatous meningitis, and noninflammatory causes such as atherosclerosis, emboli, connective tissue disease, vasospasm, migraine-associated vasculopathy, and drug-associated causes. Some cases develop in the postpartum period and are self-limited. Patients with any form of vasculopathy may present with insidious progression of combined white and gray matter infarctions, prominent headache, and cognitive decline. Brain biopsy or high-resolution con ventional x-ray angiography is usually required to make the diagnosis (Fig. 438-6). A lumbar puncture (elevated white blood cells, elevated IgG index, bands on electrophoresis) can provide support for an inflammatory etiology of a neurovascular problem. When inflamma tion is confirmed, aggressive immunosuppression with glucocorticoids, and often cyclophosphamide, is usually necessary to prevent progres sion; a diligent investigation for infectious causes such as tuberculosis is essential prior to immunosuppression. With prompt recognition and treatment, many patients can make an excellent recovery. Drugs, in particular amphetamines and perhaps cocaine, may cause stroke on the basis of acute hypertension or drug-induced vasculopa thy. This vasculopathy is commonly due to vasospasm or atheroscle rosis, but cases of inflammatory vasculitis have also been reported. No data exist on the value of any treatment, but cessation of stimulants is prudent. Phenylpropanolamine has been linked with intracranial hemorrhage, as has cocaine and methamphetamine, perhaps related to a vasculopathy. Moyamoya disease is a poorly understood occlusive disease involving large intracranial arteries, especially the distal inter nal

carotid artery and the stem of the MCA and ACA. Vascular inflam mation is absent. The lenticulostriate arteries develop a rich collateral circulation around the occlusive lesion, which gives the impression of a “puff of smoke” (moyamoya in Japanese) on conventional x-ray angi ography. Other collaterals include transdural anastomoses between the cortical surface branches of the meningeal and scalp arteries. The dis ease occurs mainly in Asian children or young adults, but the appear ance may be identical in adults who have atherosclerosis, particularly in association with diabetes. Intracranial hemorrhage may result from rupture of the moyamoya collaterals; thus, anticoagulation is risky. Progressive occlusion of large surface arteries can occur, producing large-artery distribution strokes. Surgical bypass of extracranial carotid arteries to the dura or MCAs may prevent stroke and hemorrhage. Posterior reversible encephalopathy syndrome (PRES) can occur with head injury, seizure, migraine, sympathomimetic drug use, and eclampsia and in the postpartum period. The pathophysiology is uncertain but likely involves a hyperperfusion state where blood pressure exceeds the upper limit of cerebral autoregulation resulting

in cerebral edema (Chap. 318). Patients complain of headache and manifest fluctuating neurologic symptoms and signs, especially visual symptoms. Sometimes cerebral infarction ensues, but typically, the clinical and imaging findings reverse completely. MRI findings are characteristic with edema present within the occipital lobes but also can be generalized and do not respect any single vascular territory. A closely related reversible cerebral vasoconstriction syndrome (RCVS) typically presents with sudden, severe headache closely mimicking SAH. Patients may experience ischemic infarction and intracerebral hemorrhage and typically have new-onset, severe hypertension. Con ventional x-ray angiography reveals changes in the vascular caliber throughout the hemispheres resembling vasculitis, but the process is noninflammatory. Oral calcium channel blockers may be effective in producing remission, and recurrence is rare.

Leukoaraiosis, or periventricular white matter disease, is the result of multiple small-vessel infarcts within the subcortical white matter. It is readily seen on CT or MRI scans as areas of white matter injury surrounding the ventricles and within the corona radiata. The patho physiologic basis of the disease is lipohyalinosis of small penetrating arteries within the white matter, likely produced by chronic hyperten sion. Patients with periventricular white matter disease may develop a subcortical dementia syndrome, and it is likely that this common form of dementia may be delayed or prevented with antihypertensive medications (Chap. 444). PART 13 Neurologic Disorders CADASIL (cerebral autosomal dominant arteriopathy with subcor tical infarcts and leukoencephalopathy) is an inherited disorder that presents as small-vessel strokes, progressive dementia, and extensive symmetric white matter changes often including the anterior temporal lobes visualized by MRI. Approximately 40% of patients have migraine with aura, often manifest as transient motor or sensory deficits. Onset is usually in the fourth or fifth decade of life. This autosomal dominant condition is caused by one of several mutations in Notch-3, a member of a highly conserved gene family characterized by epidermal growth factor repeats in its extracellular domain. Other monogenic ischemic stroke syndromes include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). Fabry’s disease also produces both a large-vessel arteriopa thy and small-vessel infarctions. The COL4A1 mutation is associated with multiple small-vessel strokes with hemorrhagic transformation. ■ ■TRANSIENT ISCHEMIC ATTACKS TIAs are episodes of stroke symptoms that last only briefly; the stan dard definition of duration is <24 h, but most TIAs last <1 h. If a rel evant brain infarction is identified on brain imaging, the clinical entity is

now classified as stroke regardless of the duration of symptoms. A normal brain imaging study following a TIA does not rule out TIA; rather, the clinical syndrome is diagnostic. The causes of TIA are simi lar to those of ischemic stroke, but because TIAs may herald stroke, they are an important risk factor that should be considered urgently. TIAs may arise from emboli to the brain or from in situ thrombosis of an intracranial vessel. With a TIA, the occluded blood vessel reopens and neurologic function is restored. The risk of stroke after a TIA is ~10–15% in the first 3 months, with most events occurring in the first 2 days. This risk can be directly esti mated using the well-validated ABCD2 score (Table 438-5). Therefore, urgent evaluation and treatment are justified. Because etiologies for stroke and TIA are identical, evaluation for TIA should parallel that of stroke. TREATMENT Transient Ischemic Attack The improvement characteristic of TIA is a contraindication to thrombolysis. However, because the risk of subsequent stroke in the first few hours and days following TIA is high, some physicians admit the patient to the hospital so a plasminogen activator can be rapidly administered if symptoms return. The combination of aspirin and clopidogrel was found to prevent stroke following TIA better than aspirin alone in a large Chinese randomized trial and

TABLE 438-5 Risk of Stroke Following Transient Ischemic Attack: The ABCD2 Score CLINICAL FACTOR SCORE A: Age ≥60 years

B: SBP >140 mmHg or DBP >90 mmHg

C: Clinical symptoms Unilateral weakness

Speech disturbance without weakness

D: Duration >60 min

10–59 min

D: Diabetes (oral medications or insulin)

TOTAL SCORE SUM EACH CATEGORY ABCD2 Score Total 3-Month Rate of Stroke (%)a

aData ranges are from five cohorts. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure. Source: Data from SC Johnston et al: Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 369:283, 2007. the National Institutes of Health (NIH)–sponsored POINT trial. Failure to respond to the combination of aspirin and clopidogrel is linked to carriage of a common CYP2C19 polymorphism that leads to poor metabolism of clopidogrel into its active form. This muta tion is common, particularly in Asians. Recently, ticagrelor, 180-mg loading dose and then 90 mg twice daily, was tested in combination with aspirin compared to aspirin alone, and this also showed benefit in preventing stroke; this dual antiplatelet regimen may be favored because of the lack of genetic heterogeneity in platelet inhibition. Primary and Secondary Prevention of Stroke and TIA GENERAL PRINCIPLES Many medical and surgical interventions, as well as lifestyle modi fications, are available for preventing stroke. Some of these can be widely applied because of their low cost and minimal risk; others are expensive and carry substantial risk but may be valuable for selected high-risk patients. Identification and control of modifi able risk factors, and especially hypertension, is the best

strategy to reduce the burden of stroke, and the total number of strokes could be reduced substantially by these means (Table 438-4). ATHEROSCLEROSIS RISK FACTORS The relationship of various factors to the risk of atherosclerosis is described in Chaps. 244 and 245. Older age, diabetes mellitus, hypertension, tobacco smoking, abnormal blood cholesterol (par ticularly, low high-density lipoprotein [HDL] and/or elevated lowdensity lipoprotein [LDL]), lipoprotein (a) excess, and other factors are either proven or probable risk factors for ischemic stroke, largely by their link to atherosclerosis. Risk of stroke is much greater in those with prior stroke or TIA. Many cardiac conditions predispose to stroke, including atrial fibrillation and recent MI. Oral contra ceptives and hormone replacement therapy increase stroke risk, and although rare, certain inherited and acquired hypercoagulable states predispose to stroke. Hypertension is the most significant of the risk factors; in general, all hypertension should be treated to a target of <130/80 mmHg. Recent data (the Systolic Blood Pressure Intervention

Trial—SPRINT) suggest that lowering systolic blood pressure <120 mmHg reduces stroke and heart attack by 43% compared to systolic blood pressure <140 mmHg, without an increased risk of syncope or falls, although patients with a history of stroke were specifically excluded from this study. The presence of known cerebrovascular disease is not a contraindication to treatment aimed at achieving normotension. Data are particularly strong in support of thiazide diuretics and angiotensin-converting enzyme inhibitors. Several trials have confirmed that statin drugs reduce the risk of stroke even in patients without elevated LDL or low HDL. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed benefit in secondary stroke reduction for patients with recent stroke or TIA who were prescribed atorvas tatin, 80 mg/d. The primary prevention trial, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), found that patients with an elevated C-reactive protein benefitted by daily use of this statin, despite LDL <130 mg/dL. Primary stroke occurrence was reduced by 51% (hazard ratio, 0.49; p = .004), and there was no increase in the rates of intracranial hemorrhage. Meta-analysis has also supported a pri mary treatment effect for statins given acutely for ischemic stroke. A serum LDL <70 mg/dL lowers recurrent stroke risk better than an LDL of 90–110 mg/dL. Therefore, a statin should be considered in all patients with prior ischemic stroke. Tobacco smoking should be discouraged in all patients (Chap. 465). The use of pioglitazone (an agonist of peroxisome proliferator-activated receptor gamma) in patients with type 2 diabetes and previous stroke does not lower stroke, MI, or vascular death rates but is effective in lowering vas cular events in patients with stroke and prediabetes or insulin resis tance alone. Diabetes prevention is likely the most effective strategy for primary and secondary stroke prevention. ANTIPLATELET AGENTS FOR STROKE PREVENTION Platelet antiaggregation agents can prevent atherothrombotic events, including TIA and stroke, by inhibiting the formation of intra arterial platelet aggregates. These can form on diseased arteries, induce thrombus formation, and occlude or embolize into the distal circulation. Aspirin, clopidogrel, the combination of aspirin plus extended-release dipyridamole, and recently ticagrelor are the anti platelet agents most commonly used for this purpose. Ticagrelor has not been found to be better than aspirin for stroke prevention except in combination with aspirin following TIA. Aspirin is the most widely studied antiplatelet agent. Aspirin acetylates platelet cyclooxygenase, which irreversibly inhibits the formation in platelets of thromboxane A2, a platelet aggregating and vasoconstricting prostaglandin. This effect is permanent and lasts for the usual 8-day life of the platelet. Paradoxically, aspirin also inhibits the formation in endothelial cells of prostacyclin, an antiag gregating and vasodilating prostaglandin. This effect is transient. As soon as aspirin is cleared from the blood, the nucleated endothelial cells

again produce prostacyclin. Aspirin in low doses given once daily inhibits the production of thromboxane A2 in platelets with out substantially inhibiting prostacyclin formation. Higher doses of aspirin have not been proven to be more effective than lower doses. Clopidogrel and ticagrelor block the adenosine diphosphate (ADP) receptor on platelets and thus prevent the cascade result ing in activation of the glycoprotein IIb/IIIa receptor that leads to fibrinogen binding to the platelet and consequent platelet aggrega tion. Clopidogrel can cause rash and, in rare instances, thrombotic thrombocytopenic purpura. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, which led to U.S. Food and Drug Administration (FDA) approval, found that it was only marginally more effective than aspirin in reducing risk of stroke. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial was a large multicenter, randomized, double-blind study that compared clopidogrel in com bination with aspirin to clopidogrel alone in the secondary preven tion of TIA or stroke. The MATCH trial found no difference in TIA or stroke prevention with this combination but did show a small but

significant increase in major bleeding complications (3 vs 1%). In the Clopidogrel for High Atherothrombotic Risk and Ischemic Sta bilization, Management, and Avoidance (CHARISMA) trial, which included a subgroup of patients with prior stroke or TIA along with other groups at high risk of cardiovascular events, there was no ben efit of clopidogrel combined with aspirin compared to aspirin alone. Lastly, the SPS3 trial looked at the long-term combination of clopi dogrel and aspirin versus clopidogrel alone in small-vessel stroke and found no improvement in stroke prevention and a significant increase in both hemorrhage and death. Thus, the long-term use of clopidogrel in combination with aspirin is not recommended for stroke prevention.

The short-term combination of clopidogrel with aspirin may be effective in preventing second stroke, however. A large trial of Chi nese patients enrolled within 24 h of TIA or minor ischemic stroke found that a clopidogrel-aspirin regimen (clopidogrel 300 mg load then 75 mg/d with aspirin 75 mg for the first 21 days) was superior to aspirin (75 mg/d) alone, with 90-day stroke risk decreased from 11.7 to 8.2% ($p < .001$) and no increase in major hemorrhage. This benefit was limited to those not carrying the CYP2C19 polymor phism associated with clopidogrel hypometabolism. An interna tional NIH-sponsored trial demonstrated similar results; therefore, the combination of aspirin and clopidogrel should be administered for TIA or minor ischemic stroke for the first 21 days before switch ing to monotherapy. CHAPTER 438 Ischemic Stroke A recent study of oral ticagrelor plus aspirin versus aspirin alone has shown similar benefits in secondary stroke reduction and car ries the likely advantage that ticagrelor’s antiplatelet effect is not genetically variable, as is the case with clopidogrel. Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of aggre gation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggrega tory effects of prostacyclin and nitric oxide produced by the endo thelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting eleva tion in cyclic AMP inhibits aggregation of platelets. Dipyridamole is erratically absorbed depending on stomach pH, but a newer formu lation combines timed-release dipyridamole, 200 mg, with aspirin, 25 mg, and has better oral bioavailability. This combination drug was studied in three trials. The European Stroke Prevention Study (ESPS) II showed efficacy of both 50 mg/d of aspirin and extendedrelease dipyridamole in preventing stroke and a significantly better risk reduction when the two agents were combined. The open-label ESPRIT (European/Australasian Stroke Prevention in

Reversible Ischaemia Trial) trial confirmed the ESPS-II results. After 3.5 years of follow-up, 13% of patients on aspirin and dipyridamole and 16% on aspirin alone (hazard ratio, 0.80; 95% CI, 0.66–0.98) met the pri mary outcome of death from all vascular causes. In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, the combination of extended-release dipyridamole and aspirin was compared directly with clopidogrel with and without the angioten sin receptor blocker telmisartan; there were no differences in the rates of second stroke (9% each) or degree of disability in patients with median follow-up of 2.4 years. Telmisartan also had no effect on these outcomes. This suggests that these antiplatelet regimens are similar and raises questions about default prescription of agents to block the angiotensin pathway in all stroke patients. The prin cipal side effect of dipyridamole is headache. The combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke. Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular ath erothrombotic events (i.e., ischemic stroke, MI, and death due to all vascular causes) in patients at risk for these events. The overall relative reduction in risk of nonfatal stroke is ~25–30% and of all vascular events is ~25%. The absolute reduction varies consider ably, depending on the patient's risk. Individuals at very low risk

for stroke seem to experience the same relative reduction, but their risks may be so low that the "benefit" is meaningless. Conversely, individuals with a 10–15% risk of vascular events per year experi ence a reduction to ~7.5–11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life threatening. Consequently, not every 40- or 50-year-old should be advised to take aspirin regularly because the risk of atherothrom botic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke or TIA and has no contraindication to antiplatelet therapy (or indication for anticoagulation) should be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%; another few percent will experi ence an MI or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment. PART 13 Neurologic Disorders The choice of antiplatelet agent and dose must balance the risk of stroke, the expected benefit, and the risk and cost of treat ment. However, there are no definitive data, and opinions vary. Many authorities believe low-dose (30–75 mg/d) and high-dose (650–1300 mg/d) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 81–325 mg/d, whereas most Euro peans recommend 50–100 mg. Clopidogrel and extended-release dipyridamole plus aspirin are being increasingly recommended as first-line drugs for secondary prevention. Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher, and this is likely to affect long-term patient adherence. The use of platelet aggregation studies in individual patients taking aspirin is controversial because of limited data. In our practices, when considering antithrombotic therapy for secondary stroke prevention for noncardioembolic strokes and TIAs, we prescribe aspirin 81 mg/d in aspirin-I patients after an initial load of 325 mg. We add either clopidogrel (600-mg load, then 75 mg daily) or ticagrelor (180-mg load, then 90 mg twice daily) for TIA or minor stroke (NIHSS <5) for 21–30 days, followed by monotherapy with aspirin alone at 81 mg daily. We treat stroke due to intracranial

atherosclerosis with aspirin 81 mg plus clopidogrel 75 mg daily for 3 months, after which time treatment is continued with aspirin alone. ANTICOAGULATION THERAPY AND EMBOLIC STROKE PREVENTION Several trials have shown that anticoagulation (international nor malized ratio [INR] range, 2–3) in patients with chronic nonval vular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with a vitamin K antagonist (VKA) reduces the risk by ~67%, which clearly outweighs the 1–3% risk per year of a major bleeding com plication. VKAs are difficult to dose, their effects vary with dietary intake of vitamin K, and they require frequent blood monitoring of the PTT/INR. Several direct oral anticoagulants (DOACs) have recently been shown to be more convenient and efficacious for stroke prevention in NVAF. A randomized trial compared the oral thrombin inhibitor dabigatran to VKAs in a noninferiority trial to prevent stroke or systemic embolization in NVAF. Two doses of dabigatran were used: 110 mg/d and 150 mg/d. Both dose tiers of dabigatran were noninferior to VKAs in preventing second stroke and systemic embolization, and the higher dose tier was supe rior (relative risk, 0.66; 95% CI, 0.53–0.82; p <.001) and the rate of major bleeding was lower in the lower dose tier of dabigatran compared to VKAs. Dabigatran requires no blood monitoring to titrate the dose, and its effect is independent of oral intake of vita min K. Newer oral factor Xa inhibitors have also been found to be

equivalent or safer and more effective than VKAs in NVAF stroke prevention. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, patients were randomized between apixaban, 5 mg twice daily, and dose-adjusted warfarin (INR 2–3). The combined endpoint of ischemic or hemorrhagic stroke or system embolism occurred in 1.27% of patients in the apixaban group and in 1.6% in the warfarin group (p <.001 for noninferiority and p <.01 for superiority). Major bleeding was 1% less, favoring apixaban (p <.001). Similar results were obtained in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). In this trial, patients with NVAF were randomized to rivaroxaban versus warfarin: 1.7% of the factor Xa group and 2.2% of the war farin group reached the endpoint of stroke and systemic embolism (p <.001 for noninferiority); intracranial hemorrhage was also lower with rivaroxaban. Finally, the factor Xa inhibitor edoxaban was also found to be noninferior to warfarin. Thus, oral factor Xa inhibi tors are at least a suitable alternative to VKAs, for both primary and secondary prevention, and likely are superior both in efficacy and perhaps compliance. Recent FDA approval of a reversal agent for the Xa inhibitors apixaban and rivaroxaban (andexanet alfa) provides an antidote in the case of major bleeding. Idarucizumab has been available for reversal of dabigatran. Randomized trials have not demonstrated the superiority of anticoagulants over anti platelet medications for strokes that appear embolic without a clear source, even when limited to the subset with evidence of an atrial cardiopathy. For patients who cannot take anticoagulant medications, clopi dogrel plus aspirin was compared to aspirin alone in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A). Clopidogrel combined with aspirin was more effective than aspirin alone in preventing vascular events, principally stroke, but increased the risk of major bleeding (relative risk, 1.57; p <.001). Left atrial appendage occlusion followed by antiplatelet therapy was found to be noninferior to oral Xa inhibi tors in patients at moderate to high risk of bleeding in a single trial. If confirmed, this may be a safer strategy than management with aspirin alone for these patients at high risk of atrial fibrillation– related stroke. The decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 438-3). The history of a TIA or stroke tips the balance in favor of

anticoagulation regard less of other risk factors. Intermittent atrial fibrillation carries the same risk of stroke as chronic atrial fibrillation, and several ambulatory studies of seemingly “cryptogenic” stroke have found evidence of intermittent atrial fibrillation in nearly 20% of patients monitored for a few weeks. Interrogation of implanted pacemakers also confirms an association between subclinical atrial fibrillation and stroke risk. Therefore, for patients with otherwise cryptogenic embolic stroke (no evidence of any other cause for stroke), ambu latory monitoring for at least 30 days is a reasonable strategy to determine the best prophylactic therapy, and some patients may benefit from placement of longer-term implantable loop recorders. Because of the high annual stroke risk in untreated rheumatic heart disease with atrial fibrillation, primary prophylaxis against stroke has not been studied in a double-blind fashion. These patients generally should receive long-term anticoagulation. Dabi gatran and the oral Xa inhibitors have not been studied in this population. Anticoagulation also reduces the risk of embolism in acute MI. Most clinicians recommend a 3-month course of anticoagulation when there is anterior Q-wave infarction, substantial left ventricu lar dysfunction, congestive heart failure, mural thrombosis, or atrial fibrillation. Oral anticoagulants are recommended long term if atrial fibrillation persists. Stroke secondary to thromboembolism is one of the most serious complications of prosthetic heart valve implantation. The intensity of anticoagulation and/or antiplatelet therapy is dictated by the type

of prosthetic valve and its location. Dabigatran may be less effective than warfarin, and the oral Xa inhibitors have not been studied in this population. If the embolic source cannot be eliminated, anticoagulation should in most cases be continued indefinitely. Many neurologists recommend combining antiplatelet agents with anticoagulants for patients who “fail” anticoagulation (i.e., have another stroke or TIA), but the evidence basis for this is lacking. It is our practice to prescribe apixaban 5 mg twice daily (adjusted to 2.5 mg twice daily if age, weight, and renal function criteria are met) for nonvalvular atrial fibrillation with CHA2DS2-VASc score of ≥2, aspirin 81 mg plus clopidogrel 75 mg daily for patients who cannot take oral anticoagulation, and VKAs for valvular atrial fibrillation or mechanical heart valve. ANTICOAGULATION THERAPY AND NONCARDIOGENIC STROKE Data do not support the use of long-term VKAs for prevent ing atherothrombotic stroke for either intracranial or extracranial cerebrovascular disease. The Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no benefit of warfarin sodium (INR 1.4–2.8) over aspirin, 325 mg, for secondary prevention of stroke but did find a slightly higher bleeding rate in the warfarin group; a Euro pean study confirmed this finding. The Warfarin and Aspirin for Symptomatic Intracranial Disease (WASID) study (see below) demonstrated no benefit of warfarin (INR 2–3) over aspirin in patients with symptomatic intracranial atherosclerosis and found a higher rate of bleeding complications. Two trials testing factor Xa medications for prevention of embolic stroke of undetermined source (ESUS) failed to show benefit compared to treatment with antiplatelet medications and a third trial limited to ESUS patients with atrial cardiopathy had similar results. The oral factor Xa inhibitor apixaban was found to be noninferior to subcutaneous dalteparin for patients with cancer and venous thromboembolism; many oncologists are using Xa inhibitors to prevent second stroke in patients with malignancy. It is our practice to prescribe aspirin for secondary stroke pre vention in noncardiogenic cerebral embolism except for stroke associated with cancer (apixaban 5 mg twice daily) and the antiphos pholipid syndrome (warfarin with target INR 2–3). TREATMENT Carotid Atherosclerosis Carotid atherosclerosis can be removed surgically (endarterec tomy), mitigated with endovascular stenting with or without bal loon angioplasty, or using the transcarotid artery revascularization (TCAR) approach. Anticoagulation has not been directly compared with antiplatelet therapy for carotid disease. SURGICAL THERAPY Symptomatic

carotid stenosis was studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). Both showed a substantial benefit for surgery in patients with stenosis of ≥70%. In NASCET, the average cumulative ipsilateral stroke risk at 2 years was 26% for patients treated medically and 9% for those receiving the same medical treatment plus a carotid endarterectomy. This 17% abso lute reduction in the surgical group is a 65% relative risk reduction favoring surgery (Table 438-4). NASCET also showed a significant, although less robust, benefit for patients with 50–70% stenosis. ECST found harm for patients with stenosis <30% treated surgically. A patient's risk of stroke and possible benefit from surgery are related to the presence of retinal versus hemispheric symptoms, degree of arterial stenosis, extent of associated medical conditions (of note, NASCET and ECST excluded "high-risk" patients with significant cardiac, pulmonary, or renal disease), institutional surgi cal morbidity and mortality, timing of surgery relative to symptoms, and other factors. A recent meta-analysis of the NASCET and ECST

trials demonstrated that endarterectomy is most beneficial when performed within 2 weeks of symptom onset. In addition, benefit is more pronounced in patients >75 years, and men appear to benefit more than women.

In summary, a patient with recent symptomatic hemispheric ischemia, high-grade stenosis in the appropriate internal carotid artery, and an institutional perioperative morbidity and mortal ity rate of ≤6% generally should undergo carotid endarterectomy. If the perioperative stroke rate is >6% for any particular surgeon, however, the benefits of carotid endarterectomy are questionable. The indications for surgical treatment of asymptomatic carotid disease have been clarified by the results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST). ACAS randomized asymptomatic patients with ≥60% stenosis to medical treatment with aspirin or the same medical treatment plus carotid endarterectomy. The surgical group had a risk over 5 years for ipsilateral stroke (and any perioperative stroke or death) of 5.1%, compared to a risk in the medical group of 11%. Although this demonstrates a 53% relative risk reduction, the absolute risk reduction is only 5.9% over 5 years, or 1.2% annually (Table 438-4). Nearly one-half of the strokes in the surgery group were caused by preoperative angiograms. ACST randomized asymptomatic patients with >60% carotid stenosis to endarterectomy or medical therapy. The 5-year risk of stroke in the surgical group (including perioperative stroke or death) was 6.4%, compared to 11.8% in the medically treated group (46% relative risk reduction and 5.4% absolute risk reduction). CHAPTER 438 Ischemic Stroke In both ACAS and ACST, the perioperative complication rate was higher in women, perhaps negating any benefit in the reduction of stroke risk within 5 years. It is possible that with longer follow-up, a clear benefit in women will emerge. At present, carotid endarter ectomy in asymptomatic women remains particularly controversial. In summary, the natural history of asymptomatic stenosis is an ~2% per year stroke rate, whereas symptomatic patients experi ence a 13% per year risk of stroke. Whether to recommend carotid revascularization for an asymptomatic patient is somewhat contro versial and depends on many factors, including patient preference, degree of stenosis, age, gender, and comorbidities. Medical therapy for reduction of atherosclerosis risk factors, including cholesterollowering agents and antiplatelet medications, is generally recom mended for patients with asymptomatic carotid stenosis. As with atrial fibrillation, it is imperative to counsel the patient about TIAs so that therapy can be revised if symptoms develop. ENDOVASCULAR THERAPY Balloon angioplasty coupled with stenting is one option to open stenotic carotid arteries and maintain their patency. These tech

niques can treat carotid stenosis not only at the bifurcation but also near the skull base and in the intracranial segments. The Stent ing and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial randomized high-risk patients (defined as patients with clinically significant coronary or pulmo nary disease, contralateral carotid occlusion, restenosis after end arterectomy, contralateral laryngeal-nerve palsy, prior radical neck surgery or radiation, or age >80) with symptomatic carotid stenosis

> “ 50% or asymptomatic stenosis >80% to either stenting combined with a distal emboli-protection device or endarterectomy. The risk of death, stroke, or MI within 30 days and ipsilateral stroke or death within 1 year was 12.2% in the stenting group and 20.1% in the endarterectomy group (p = .055), suggesting that stenting is at the very least comparable to endarterectomy as a treatment option for this patient group at high risk of surgery. However, the outcomes with both interventions may not have been better than leaving the carotid stenoses untreated, particularly for the asymptomatic patients, and much of the benefit seen in the stenting group was due to a reduction in periprocedure MI. Two randomized trials com paring stents to endarterectomy in lower-risk patients have been published. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) enrolled patients with either asymptomatic

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