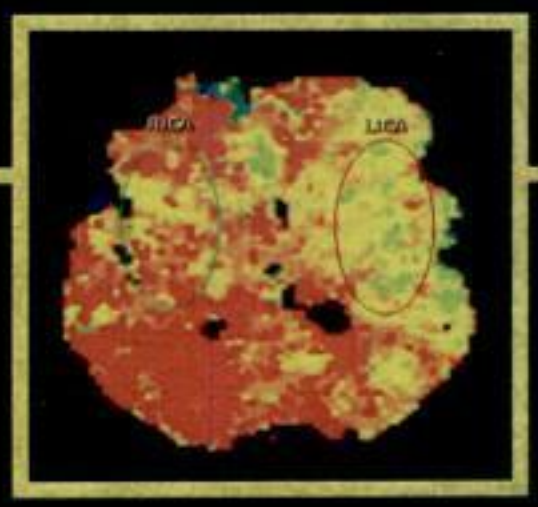
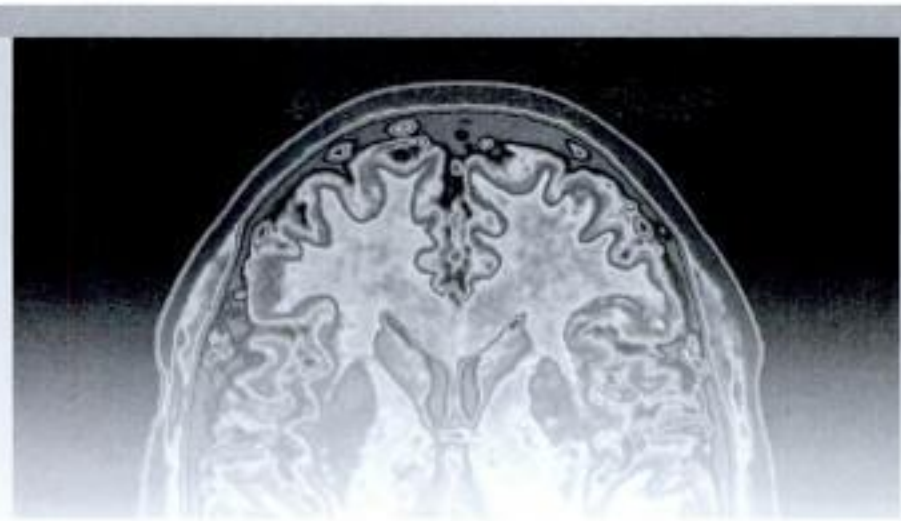
STROKE

A PRACTICAL APPROACH

James D. Geyer
Camilo R. Gomez





STROKE

A Practical Approach

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Finally, in our view the preciseness with which we communicate reflects the clarity of our thoughts and the depth of our knowledge. As such, communication between the health care professional and the patient also leaves a lot to be desired, as evidenced by the continued and pervasive use of the term *cerebrovascular accident* (CVA). For more than 20 years we have pointed out why this term is inappropriate (i.e., stroke does not occur by accident, but it occurs in stroke-prone individuals) and inaccurate (i.e., the term does not specify the type of stroke), yet it remains anchored in the mainstream of everyday clinical communication. With this in mind, we take the position that the most important step health care professionals can take toward improving stroke management is to optimize their communication skills, striving toward more precise, concise, and focused discussions with peers as well as patients.

DIAGNOSTIC MYTHS

The "Self-Evident" Cause of Ischemic Stroke

Despite all the educational campaigns, conferences, symposia, and discussions, not a day goes by without a patient presenting to an emergency department with symptoms of ischemic stroke and an electrocardiogram (ECG) showing de novo atrial fibrillation, which is immediately blamed for the event. Largely, such a scenario obviates any critical analysis of concurrent risk factors or a thorough evaluation of the patient. The fallacy of this approach is easy to identify: Having any one risk factor for stroke does not exclude the presence of concurrent ones. The dire consequence is that patients are undiagnosed and only partially treated. How many times have patients been sent home from emergency rooms after having had a normal carotid ultrasound, only to come back a week later with an acute basilar occlusion due to an intracranial stenosis that was never identified because of inadequate testing? An old saying goes, "We find what we look for . . . and we recognize what we know!" In our view, every stroke patient represents a diagnostic mystery that must be investigated in its entirety, allowing for the possibility of concurrent and coexistent risk factors, which we have come to call *double jeopardy*. Both philosophically and practically we view stroke risk factors as functions of one of three categoric dimensions: vascular, cardiac, and hematologic. From this point of view, every stroke patient deserves a critical evaluation, including stratification of the type and number of risk factors present, to be the subject of an all-inclusive secondary prevention strategy that ensures optimal reduction of subsequent stroke risk. Otherwise, any focused preventive strategy is unlikely to sufficiently protect the patient.

Lacunes, Lacunar Infarcts, and Small Vessel Disease

Lacunes, lacunar infarcts, and small vessel disease are among the most misunderstood subjects in vascular neurology, which leads to significant miscommunication. The premise for this myth is the oversimplified belief that every small subcortical infarction should be labeled as *lacunar*, manifesting itself as a *lacunar syndrome*, and is the direct result of *small vessel disease*. In our view, such train of thought demonstrates a lack of understanding of the differences between phenomenology, pathophysiology, and pathology of such conditions. We must state our view on this subject by transporting the reader back to the 19th century, when Durand-Fardel used the term *lacune* for the first time in the medical literature. It is unclear whether the author differentiated these pathological findings as the result of infarction or simply as perivascular dilatations (considering that he also introduced the term *etat criblé* in the same manuscript). Then, 20 years later, Proust published a thesis in which he addressed the subject, for the first time pointing out that three different processes can result in the postmortem finding of lacunes: infarction, hemorrhage, or perivascular disorganization. The years that followed brought with them a series of reports largely emphasizing the clinicopathologic correlation between lacunes and certain specific lacunar syndromes, culminating with a 1965 paper in which Fisher equated lacunes to small deep infarctions. Interestingly, this manuscript concluded by drawing a direct association between hypertension and these deep infarcts.

Each of these communications, with immense historical value, must be placed in the context of the primitive status of the imaging techniques of that era. Inferences were being made by drawing conclusions from the autopsy table and depending on preexisting clinical observations that were often poorly recorded. Nevertheless, reviewing these papers in toto should quickly uncover what has come to be proved by modern, imaging-based studies: (a) not every lacune represents an underlying infarction, (b) lacunar infarction does not have to course with a classic lacunar syndrome, and (c) deep small infarctions have more than one potential pathogenesis. Along these lines, it is our view that the term *lacune* should be reserved for more generic references relative to small brain cavities that can be caused by several processes, only one of which is ischemia due to perforating arterial occlusion. The literature cited earlier also notes that many of the patients who display these lesions at autopsy have not had any previous history of stroke symptoms. Furthermore, the literature on lacunar syndromes shows over and over again the lack of localizing value of such a presentation, as each of these syndromes has been associated with a multitude of lesion locations.

Finally, the most uncritical aspect of this subject is the de facto association of lacunar infarction with small vessel disease. The truth is that such a disease does not exist! In other words, anyone who uses the term should be challenged to describe the etiology, pathogenesis, treatment, and prognosis of that illness. Any answer to such a challenge is bound to represent an inaccurate or incomplete description of another entity the precise name of which has been ignored. Our view is that the term *lacunar infarction* should be reserved for those small deep infarcts secondary to direct occlusion of penetrating small arterioles chronically affected by lipohyalinosis and fibrinoid necrosis (i.e., hypertensive arteriolopathy), satisfying the direct association between the two conditions emphasized by Fisher and others. In turn, we recommend that the term *small vessel disease* should not be used as such, since it carries an inherent lack of specificity. After all, there are many conditions that primarily affect the so-called small vessels, including meningovascular syphilis, granulomatous vasculitis, and lupus. Finally, we recommend that *lacunar infarction* not be used to describe small deep infarcts when the pathogenic mechanism is known to be other than hypertensive arteriolopathy. This is important because the existing literature clearly supports the notion that small deep infarcts are caused by embolism and by hemodynamic compromise.

Cryptogenic Stroke and Relative Ignorance

No term in the stroke nomenclature seems to have gained more popularity in the last decade than *cryptogenic stroke*. It has been the source of reports, publications, discussions, seminars, and clinical trials, and has attracted the attention of other specialists (namely

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The inferior division of the middle cerebral artery supplies the parietal and temporal lobes, and lesions on the left side result in severe inhibition of language comprehension. The optic radiation is usually involved, resulting in partial or complete homonymous hemianopia on the contralateral side. Lesions affecting the right hemisphere often result in neglect of the left side of the body. Initially, the patient may completely ignore the affected side and even assert that the arm on his left side belongs not to him but to somebody else. Such severe neglect seen initially often gradually improves but may be followed by a variety of persisting impairments, such as constructional apraxia, dressing apraxia, and perceptual deficits.

The lenticulostriate arteries are branches arising from the main stem of the middle cerebral artery that penetrate into the subcortical region and perfuse the basal ganglia and posterior internal capsule. Several characteristic and rather common isolated syndromes have been described when discrete focal lesions occur. These are frequently referred to as *lacunar strokes*. The most common is a lesion in the internal capsule causing a pure motor hemiplegia. An anterior lesion in the internal capsule may cause dysarthria with hand clumsiness, and a lesion of the thalamus or adjacent internal capsule causes a contralateral sensory loss with or without weakness. The neurological deficits in these lesions often show early and progressive recovery with good ultimate outcome.

Patients with hypertension and diabetes are at risk for recurrent lacunar strokes. Pseudobulbar palsy is a syndrome that develops when multiple small lesions affect the anterior limb of both internal capsules, including the corticobulbar pathways. This syndrome consists of excessive emotional lability and spastic bulbar (pseudobulbar) paralysis, which is characterized by dysarthria, dysphonia, dysphagia, and facial weakness (see Table 2.2). There are often sudden outbursts of inappropriate and uncontrolled crying and laughter, at times blending into each other, without corresponding emotional stimulus. Drooling is often prominent. The term *pseudobulbar* is applied to this syndrome to distinguish it as an upper motor neuron lesion in contrast to a lower motor neuron lesion in the medulla. More widespread and posterior subcortical lacunar infarctions will often produce a dementia, often called multi-infarct dementia.

Anterior Cerebral Artery Syndromes

Branches of the anterior cerebral arteries supply the median and paramedian regions of the frontal cortex and the strip of the lateral surface of the hemisphere along its upper border. There are deep penetrating branches that supply the head of the caudate nucleus and the anterior limb of the internal capsule. Occlusions of the anterior cerebral artery are not common, but when they occur, there is contralateral hemiparesis with relative sparing of the hand and face and greater weakness of the leg. There is associated sensory loss of the leg and foot. Lesions affecting the left side may produce a transcortical motor aphasia characterized by diminution of spontaneous speech but preserved ability to repeat words. A grasp reflex is often present along with a sucking reflex and paratonic rigidity (*gegenhalten*). Urinary incontinence is common. Large lesions of the frontal cortex often produce behavioral changes, such as lack of spontaneity, distractibility, and tendency to perseverate. Patients may have diminished reasoning ability (see Table 2.3).

TABLE 2.2 Bulbar versus Pseudobulbar Signs

	Bulbar	Pseudobulbar
Tongue		
Size	Atrophy	Normal
Movement	Decreased	Decreased
Fasciculation	Present	Absent
Speech	Flaccid	Spastic
Face	Weak	Weak
Emotional lability	Absent	Present
Jaw jerk	Absent	Present
Gag	Absent	Hyperactive
Extraocular movements	Decreased	Decreased

TABLE 2.3 Anterior Cerebral Artery Syndrome

Contralateral hemiparesis and sensory loss (greater in the legs and feet)
Disconnection syndromes
Behavior disturbances (abulia, akinetic mutism)

VERTEBROBASILAR SYNDROMES

The two vertebral arteries join at the junction of the medulla and pons to form the basilar artery. Together, the vertebral and basilar arteries supply the brainstem through the paramedian and short circumferential branches and supply the cerebellum by long circumferential branches. The basilar artery terminates by bifurcating at the upper midbrain level to form the two posterior cerebral arteries. The posterior communicating arteries connect the middle to the posterior cerebral arteries, completing the circle of Willis.

Some general clinical features of lesions in the vertebrobasilar system should be noted. In contrast to lesions in the hemispheres, which are unilateral, lesions involving the pons and medulla often cross the midline and cause bilateral features. When motor impairments are present, they are often bilateral, with asymmetric corticospinal signs, and they are frequently accompanied by cerebellar signs. Cranial nerve lesions are very frequent and occur ipsilateral to the main lesion, producing contralateral corticospinal signs. There may be dissociated sensory loss (involvement of the spinothalamic pathway with preservation of the dorsal column pathway or vice versa), dysarthria, dysphagia, disequilibrium and vertigo, and Horner syndrome. Of particular note is the absence of cortical deficits, such as aphasia and cognitive impairments. Visual field loss and visuospatial deficits may occur if the posterior cerebral artery is involved, but not with brainstem lesions. Identification of a specific cranial nerve lesion allows precise anatomic localization of the lesion.

Lacunar infarcts are common in the vertebrobasilar distribution, arising from occlusion of small penetrating branches of the basilar artery or posterior cerebral artery. In contrast to cerebral lacunes, most brainstem lacunes produce clinical features. There are a variety of characteristic brainstem syndromes associated with lesions at various levels in the brainstem. These brainstem syndromes are not infrequently encountered in patients referred for rehabilitation. The reader is referred to neurological texts for a comprehensive discussion of these lesions.

The lateral medullary syndrome (Wallenberg syndrome) is produced by an infarction in the lateral wedge of the medulla. It may occur as an occlusion of the vertebral artery or the posterior

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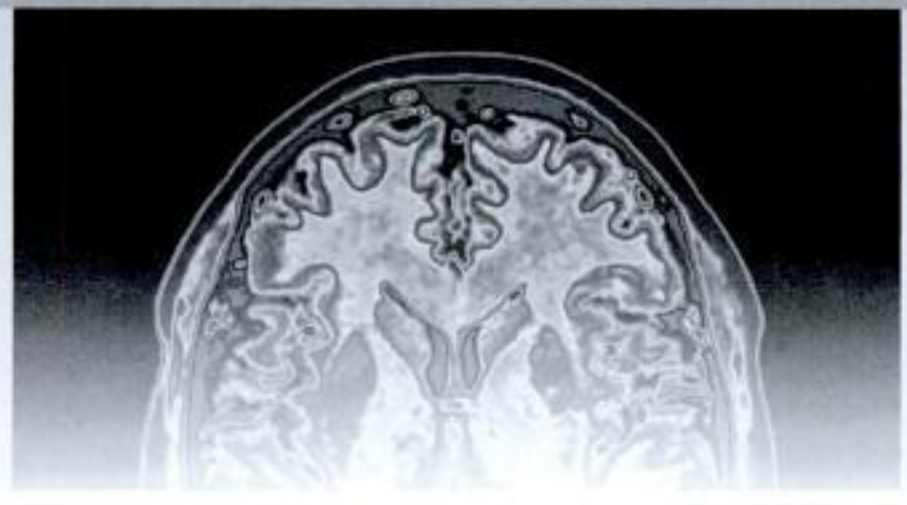

Prevention

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Lifestyle Modifications

JNC 7 recommends lifestyle modifications as an integral part of treatment of hypertension. Although highly underestimated, this has proven benefits and is the first-line treatment in patients who are pre-hypertensive and those who have first-line hypertension. The American Heart Association (AHA) has stated the following: "in non hypertensive individuals, including those with pre hypertension, dietary changes that lower BP have the potential to prevent hypertension and more broadly to reduce BP and thereby lower risk of BP related clinical complications." The AHA recommends starting lifestyle modifications as an essential part of treatment in all patients with hypertension.

The Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in fruits, vegetables, and low-fat dairy products, has shown to decrease BP in patients with hypertension. These changes are evident as quickly as 2 weeks after starting the diet plan. The PREMIER trial compared the effects of DASH diet and lifestyle changes (weight loss, low sodium diet, increased physical activity, and moderate alcohol consumption) with DASH diet alone. It found following the DASH diet plus lifestyle changes can decrease the prevalence of BP by more than 20%. Some lifestyle modifications and their effects are mentioned in Table 4.3.

Pharmacotherapy

Once a patient is diagnosed as having hypertension, lifestyle modifications are started prior to drug therapy. When lifestyle modifications fail, drug therapy is considered. The 1967 Veterans Affairs (VA) cooperative study was a landmark study that showed the benefits of lowering BP with medications. The group that received active intervention showed a decrease in mortality and complications of hypertension. This was the start of a new era and the beginning of BP screening.

Significant advances have been made in available drugs and treatment strategies. Once initiated, two thirds of the patients will require two or more drugs for optimal control of BP. Data suggests that for every 20/10 mm Hg increase after 115/75 mm Hg, the risk of CVD doubles. If SBP is >20 mm Hg or DBP is >10 mm Hg of goal, therapy is initiated with two drugs, one being a diuretic.

There are various classes of medications for treatment of hypertension. The clinician must be familiar with the various drug options available and have the ability to tailor treatment to specific patients. The list that follows enumerates these drug categories along with some examples of the drugs in each category:

- Diuretics: thiazides (e.g., chlorothiazide), loop diuretics (e.g., furosemide) potassium-sparing diuretics (e.g., amiloride, triamterene)
- β-blockers: atenolol, metoprolol, propranolol
- β-blockers with intrinsic sympathomimetic activity: acebutolol, pindolol
- Angiotensin-converting enzyme inhibitors (ACEI): lisinopril, ramipril, captopril, enalapril
- Aldosterone receptor antagonists: spironolactone
- Angiotensin II receptor blockers (ARB): candesartan, eprosartan, losartan, valsartan
- Calcium channel blockers (CCB)
  - Nondihydropyridines: diltiazem, verapamil
  - Dihydropyridines: amlodipine, nifedipine
- α1-blockers: doxazosin, prazosin
- Centrally α2-agonists and other centrally acting drugs: clonidine, methyl dopa, reserpine
- Direct vasodilators: hydralazine, minoxidil

Therapy for treatment of hypertension has changed significantly over the last few decades. Multiple options are now available that decrease complications and mortality to a varying extent. But which drug therapy should be the first? Some recommendations are given in Table 4.4.

Since the publication of the 1967 VA study, the recommended first-line therapy for treatment of hypertension in patients still remains thiazide diuretics. Multiple trials have consistently shown beneficial effects of treatment with thiazides as compared with any

TABLE 4.3 Lifestyle Modifications to Treat Hypertension

Modification	Recommendation	Approximate SBP Reduction (range)
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m^2)	5–20 mm Hg/10 kg
Adopt DASH eating plan	Diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	2–8 mm Hg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol/d (2.4 g sodium or 6 g sodium chloride)	4–9 mm Hg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/d, most days of the week)	4–9 mm Hg
Moderate alcohol consumption	Limit consumption to no more than two drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than one drink per day in women and lighter weight persons	2–4 mm Hg

SBP, systolic blood pressure; DASH, Dietary Approach to Stop Hypertension.

Adapted from Chobanian AV, Bakris GL, Black HR, et al., *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA* 2003; 289(19):2560-72 with permission.

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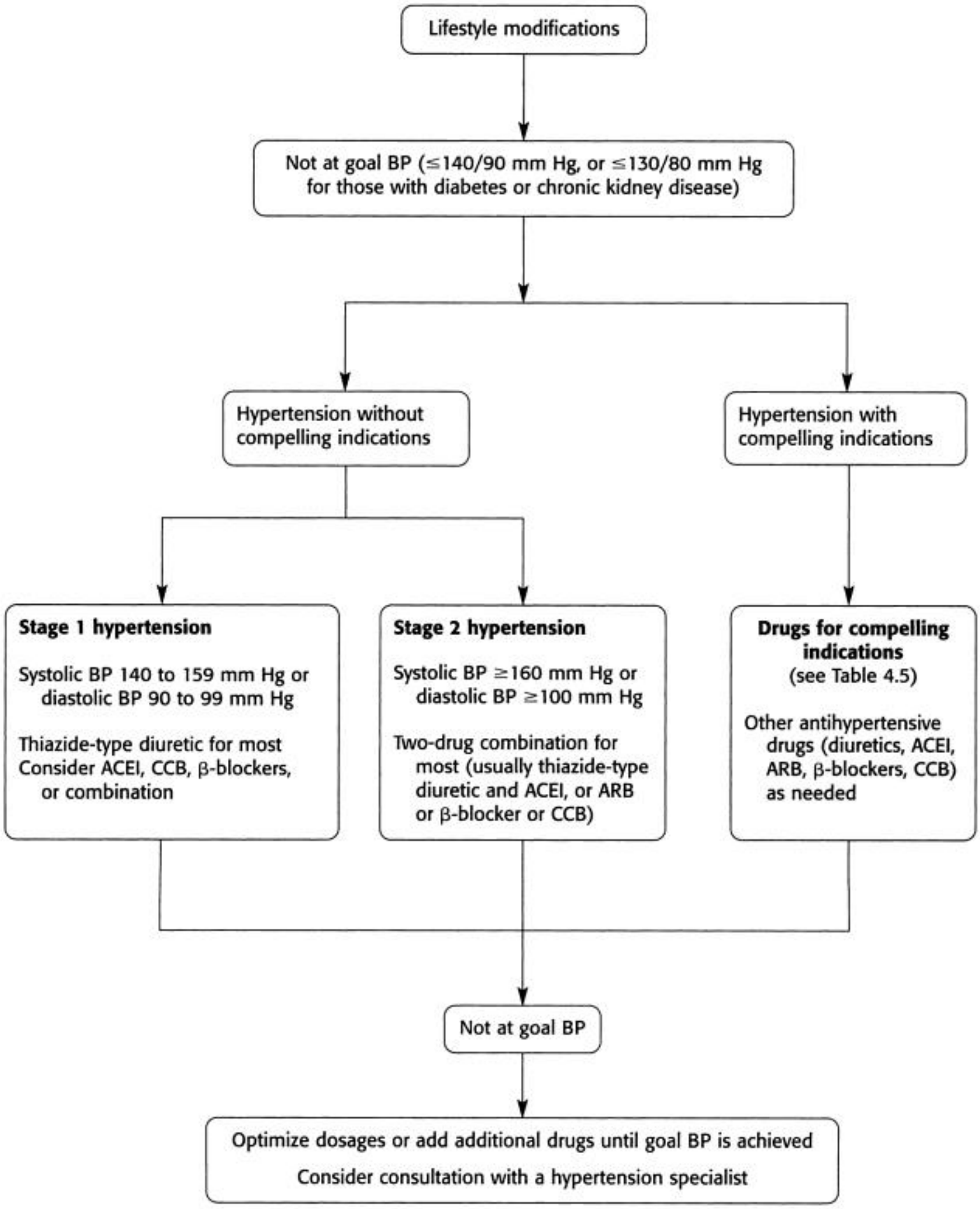
CRITICAL PATHWAY
Treatment of Chronic Hypertension Algorithm



BP, blood pressure; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blockers. (Adapted from Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003;289 (19):2560–2572.)

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of macrovascular complications was detected. In a follow-up study, hypertensive patients were randomized to a group with rigidly controlled blood pressure (<150/<85 mm Hg) or to a group that was allowed to maintain a slightly higher pressure (<180/<105 mm Hg). The patients with the lower blood pressure had a significant reduction in diabetes-related complications, both micro- and macrovascular, which included a 44% reduction in the risk of stroke. The seventh Joint National Committee report (JNC-7) recommends a goal blood pressure for patients with diabetes maintained at <130/80 mm Hg.

For hypertensive patients, the choice of antihypertensive medication may have an impact that extends beyond the effects of maintaining normotensive blood pressures. The Heart Outcomes Prevention Evaluation (HOPE) study examined a subgroup of patients dubbed the MICRO-HOPE substudy group (**MI**croalbuminiuria, **C**ardivovascular and **R**enal **O**utcomes) and sought to evaluate the effectiveness of the angiotensin-converting enzyme (ACE) inhibitor ramipril and vitamin E for the prevention of diabetic nephropathy and cardiovascular disease in patients with diabetes. The study recruited 3,577 diabetic patients who were randomly assigned to receive ramipril or placebo and vitamin E or placebo. Although vitamin E showed no clinical efficacy, the results of ramipril treatment were so striking that the study was terminated 6 months early for safety reasons. Ramipril reduced the risk of myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, and total mortality by 24%. The cardiovascular effects persisted even after statistical adjustment for the effects of the decrease in blood pressure.

The "statin" class of lipid-lowering medication has also proved beneficial in the prevention and treatment of vascular complications. The Heart Protection Study looked at the benefits of a 40-mg-per-day dose of simvastatin in 20,536 men and women at high risk of vascular disease. Eligible patients included those with coronary artery disease, other occlusive arterial diseases, and/or diabetes. Roughly 30% of the study participants had diabetes. Patients were randomly assigned to receive simvastatin or placebo. During the 5-year follow-up, patients taking the statin showed a statistically significant reduction in overall morbidity and mortality from coronary disease. There were highly significant reductions in first event rate for myocardial infarction, stroke, and coronary or noncoronary (i.e., carotid artery) revascularization procedures. The rate of reduction was similar for all subtypes of patients including those without coronary disease who had cerebrovascular disease, peripheral artery disease, or diabetes. It was estimated that the addition of simvastatin appeared to reduce the risk of stroke and myocardial infarction and revascularization procedures including bypass and angioplasty of coronary and/or carotid vasculature by 25%, although the calculated benefit was estimated to be closer to one third when noncompliance was taken into account. One of the most notable findings of the study was the lack of evidence for a threshold low-density lipoprotein (LDL) level where the benefits of treatment could first be seen. The trial demonstrated that the benefits of medication were equivalent in patients with nominally elevated LDL and in patients with much greater degrees of hypercholesterolemia. The reduced risk of vascular disease was seen not only in patients with markedly elevated LDL levels but also in patients with baseline LDL cholesterol levels below 116 mg per dL, which decreased to below 77 mg per dL with treatment. Meta-analysis has shown that the benefits reported for simvastatin are similar to those seen with other statin drugs, and the benefits in reducing the rate of stroke and cardiovascular events were independent of measured cholesterol levels.

The Steno-2 study was an open, parallel trial that sought to examine the effects of simultaneously addressing the multiple risk factors for metabolic syndrome X. A total of 160 patients with type 2 diabetes and microalbuminuria were enrolled and followed up for an average of 7.8 years. Eighty were randomized into an intensive, targeted treatment regime that included behavior modification such as smoking cessation, dietary intervention, and pharmacologic therapy targeting hyperglycemia, hypertension, hyperlipidemia, and microalbuminuria. The other 80 participants were assigned to conventional therapy based on the recommendations of the Danish Medical Association. Table 5.2 indicates the threshold of treatment for each of the elements that the study addressed. Since the Danish Medical Association changed their recommendations for the treatment of diabetes in 2000, the treatment criteria were altered for the last year of the study. Elevated levels of glycosylated hemoglobin were treated first with oral hypoglycemics, and if this was unsuccessful, with insulin injections. Patients in the intensive treatment arm of the study were

TABLE 5.2 Steno-2 Study—Treatment Criteria for Conventional and Intensive Therapy Groups

	Conventional Therapy		Intensive Therapy	
	1993–1999	2000–2001	1993–1990	2000–2001
Systolic blood pressure (mm Hg)	<160	<135	<140	<130
Diastolic blood pressure (mm Hg)	<95	<85	<85	<80
Glycosylated hemoglobin (%)	<7.5	<6.5	<6.5	<6.5
Fasting serum total cholesterol (mg/dL)	<250	<190	<190	<175
Fasting serum triglycerides (mg/dL)	<195	<180	<150	<150
Treatment with ACE inhibitor regardless of blood pressure	No	Yes	Yes	Yes
Prophylactic aspirin therapy in patients with known ischemia; or	Yes	Yes	Yes	Yes
peripheral vascular disease;	No	No	Yes	Yes
without coronary artery disease, or peripheral vascular disease	No	No	No	Yes

ACE, angiotensin-converting enzyme.

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TABLE 6.1 Diseases or Conditions Influenced by Cigarette Smoking

Cardiovascular	Cancer	Respiratory	Other
Coronary heart disease	Lung	COPD (emphysema)	Infertility
Stroke	Larynx	Bronchitis	Impotence
Subarachnoid hemorrhage	Esophagus	Pneumonia	Osteoporosis
Aortic aneurysm	Pancreas	Asthma	Premature wrinkling
Hypertension	Uterine	Otitis media	Peptic ulcer
Peripheral vascular disease	Cervix		Alzheimer disease
	Ovary		Graves disease
	Colon		Insomnia
	Bladder		Depression
	Kidney		
	Breast		
	Brain		
	Blood (leukemia)		

COPD, chronic obstructive pulmonary disease.

The risk of myocardial infarction is proportional to the number of cigarettes smoked. The trend toward the use of filtered cigarettes does not appear to have reduced the risk of coronary heart disease. Theoretically, filters on cigarettes reduce the amount of tar (the condensate of tobacco smoke that comprises over 3,000 compounds, including more than 40 carcinogens), but they may increase the amount of carbon monoxide, thus contributing to the increased mortality from coronary heart disease. Persons who smoke cigarettes containing low amounts of nicotine have the same degree of risk of myocardial infarction as those who smoke cigarettes containing larger amounts. Smokers of these low-dose cigarettes still have three times the risk of myocardial infarction as nonsmokers. The good news is that the risk of sudden death decreases immediately on stopping, and within a few years of stopping, the risk of myocardial infarction decreases to a level similar to that in people who have never smoked, even in heavy smokers who have a positive family history of coronary heart disease.

Three-fourths of myocardial infarctions in women younger than 50 years have been attributed to smoking. The risk of myocardial infarction increases progressively to as much as 20-fold in persons smoking 35 or more cigarettes per day. There is no safe level of smoking. Women who smoke and use oral contraceptives have a risk of heart attack that is ten times greater than that of women who do neither.

Silent ischemia probably accounts for most of all cardiac ischemic events. Patients with coronary heart disease who smoke have three times as many episodes of silent ischemia as nonsmokers, and the duration of each is 12 times longer. Frequent episodes of myocardial ischemia, even though asymptomatic, damage the heart. Because smoking also increases platelet adhesiveness and lowers high-density lipoprotein cholesterol, the association with a higher incidence of myocardial infarction is no surprise.

Benefits from stopping smoking can be demonstrated at all ages. No decrease in benefits is seen as one gets older, so it is still worthwhile for someone older than 65 to break the addiction. This benefit can be demonstrated in the cerebral as well as the coronary circulation. Older individuals who stop smoking have significantly higher cerebral perfusion levels than those who continue to smoke. Even those who have smoked for 30 to 40 years have improved cerebral circulation within a relatively short time after stopping smoking.

Stroke

Cigarette smoking is one of the most important modifiable risk factors for stroke. The incidence of stroke in smokers is 50% higher than in nonsmokers (40% higher in men and 60% higher in women). The risk of stroke increases in proportion to the amount of smoking; it is twice as great in those who smoke more than 40 cigarettes per day than in those smoking fewer than 10 cigarettes per day.

When compared with women who have never smoked, the risk of stroke increases 2.2-fold in women smoking 1 to 14 cigarettes per day and 3.7-fold in women smoking 25 or more cigarettes daily. Bonita et al. found a threefold increase in the risk of stroke in smokers in comparison to nonsmokers. Cigarette smokers who are also hypertensive have a 20-fold increased risk of stroke.

Sclerosis of the carotid arteries is directly proportional to the amount of smoke exposure. Smoking increases the risk of ischemic heart disease and cerebrovascular disease regardless of the level of serum cholesterol. Jee et al. found that a low cholesterol level did not protect against smoking-related arteriosclerotic cardiovascular disease in patients in South Korea, where the prevalence of smoking is among the highest in the world at 72% of men.

The risk of stroke declines rapidly after cessation of smoking, and after 5 years, is at the level of nonsmokers, which emphasizes that it is never too late to quit no matter how long one has been smoking.

Subarachnoid Hemorrhage

Habitual smoking also increases the risk of subarachnoid hemorrhage, with an increased relative risk of 3.9 times for men and 3.7 times for women. The risk increases to 22 times that of nonsmokers in women who both smoke and use oral contraceptives.

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the individual build up resolve or to permit a gradual reduction in daily cigarette consumption. Giving patients a few written reminders is very helpful (such as lists of the advantages and disadvantages of smoking, the rewards for not smoking and the penalties for lighting up, the situations and environmental influences that encourage one to smoke, and the myths of smoking and smoking cessation). A prescription with a no-smoking symbol signed by the physician and included with the other prescriptions is a thoughtful gesture. The physician should not advise switching to a low-tar cigarette, or changing to a pipe or cigar.

PRACTICAL RECOMMENDATIONS

A tailored approach to smoking cessation must be developed for each patient who smokes. The approach to a teenage woman should be quite different from the approach to an older man. Counseling is the cornerstone of treatment but medication can play an ancillary role as described in this chapter. The patient should be counseled about the role of the medications—helping to begin the transition to a smoke-free life, although drugs are not a magical treatment with immediate and complete results.

An excellent motivational Web site for all patients who use tobacco products is www.whyquit.com. Patients can also obtain self-help materials from the National Quitline, sponsored by the U.S. Department of Health and Human Services, by dialing 1-800-QUITNOW (1-800-332-8615 for hearing impaired) or online at www.smokefree.gov.

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Bile Acid Sequestrants

These agents bind bile acids in the intestine, thus reducing the enterohepatic recirculation of bile acids. Ultimately, reduction of enterohepatic bile acid recirculation leads to reduction in the liver content of cholesterol, enhancement of expression of the LDL-C receptors, and consequently reduction of serum LDL-C. Commercially available bile acid derivatives include cholestyramine, colestipol, and colesevelam. They can reduce LDL-C by 15% to 30% and increase the HDL-C by 3% to 5%. Triglyceride levels are not affected or may potentially be increased by these agents. The daily dosage range for cholestyramine, colestipol, and colesevelam are 4 to 24 g, 5 to 30 g, and 2.6 to 4.4 g, respectively. When used in combination with statins, bile acid sequestrants can decrease LDL-C by up to 70%; low or moderate doses of the sequestrant are sufficient in this case as high doses do not add much. It is best to give the statin at night and the sequestrant in divided doses with each meal; they should not be given concomitantly. However, if colesevelam is used with a statin, separation of the time of administration is not necessary. Nicotinic acid can be added to the sequestrant–statin combination if the LDL-C goal cannot be successfully achieved. Bile acid sequestrants may cause gastrointestinal side effects. All of these agents, except colesevelam, can decrease the absorption of other medications; therefore other drugs should be administered 4 hours after or 1 hour before the dose of the sequestrant. Absolute contraindications to use of bile acid sequestrants include familial dysbetalipoproteinemia and triglyceride level >400 mg per dL.

Ezetimibe

Ezetimibe is approved by the FDA for the treatment of primary hypercholesterolemia, mixed hyperlipidemia, familial homozygous hypercholesterolemia, and familial homozygous sitosterolemia. Ezetimibe selectively inhibits absorption of cholesterol from the intestine by blocking the Niemann-Pick C1 Like 1 (NPC1L1) sterol transporter. At a dose of 10 mg once daily, ezetimibe can lower LDL-C by 17% to 18%. It can be used as monotherapy but its primary usefulness may be in combination with statins in patients who are not able to achieve their target LDL-C level with statin monotherapy. The combination of ezetimibe with a statin achieves reduction of LDL-C level by "dual inhibition,"—that is, inhibition of cholesterol absorption from the intestine by ezetimibe and inhibition of cholesterol synthesis by the statin; ezetimibe can potentially enhance the cholesterol-lowering effect of statins. When combined with a statin, ezetimibe can reduce the LDL-C by 34% to 53%. An additional advantage of combination therapy is that it may achieve the patient's target LDL-C while allowing reduction in dose of statin in patients who have side effects from high-dose statin therapy. Other benefits that can occur with this combination therapy include a small decrease in triglycerides, a small increase in HDL-C, and a decrease in C reactive protein. Contraindications to combination therapy with statins include active liver disease or persistently elevated liver enzymes.

EFFICACY OF CHOLESTEROL-LOWERING DRUGS FOR PREVENTION OF ISCHEMIC STROKE

Large-scale randomized trials that have explored the potential utility of cholesterol-lowering drugs for stroke prevention have primarily focused on statins. In all but one of these trials, stroke was a secondary outcome event since these trials were primarily designed to evaluate the effects of these drugs on cardiac events and mortality. The majority of participants in these trials had no history of stroke; thus the risk reduction of stroke in these studies reflects risk reduction of primary stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study is the only multicenter, randomized, placebo-controlled study that has examined the utility of a statin in a population of patients with recent stroke. This study provides information regarding risk reduction of secondary stroke and vascular events produced by a statin. Randomized, double-blind, placebo-controlled studies have demonstrated that bile acid sequestrants decrease the risk of CHD, and other studies showed that nicotinic acid and fibric acid derivatives decrease the risk of MI. These studies were not primarily designed to determine if these agents reduce the risk of stroke. However, in one study, there was a 24% reduction (95% CI, 11% to 36%; p <0.001) of a composite secondary outcome (combined death due to CHD, nonfatal MI, and stroke).

Statins

The Cholesterol Treatment Trialists conduct periodic meta-analyses of all relevant large-scale randomized trials of lipid-modifying treatments. Their first meta-analyses of trials of statins was published in 2005. Randomized trials were eligible for inclusion if (i) the main effect of at least one of the trial interventions was to modify lipid levels; (ii) the trial was unconfounded with respect to this intervention (i.e., no other differences in risk factor modification between the relevant treatment groups was intended); and (iii) the trial aimed to recruit at least 1,000 participants with treatment duration of at least 2 years. The primary meta-analysis was on the effects on clinical outcome in each trial weighted by the absolute LDL-C difference in that trial at the end of the first year of follow-up. The main prespecified outcomes were all-cause mortality, CHD mortality, and non-CHD mortality. Stroke was a prespecified secondary outcome of the analysis. Fourteen trials, which included 90,056 participants, were included in the meta-analysis. All participants had coronary artery disease. At the time of study entry, 42,131 (47%) had pre-existing CHD, 21,575 (24%) were women, 18,686 (21%) had diabetes mellitus, 49,689 (55%) had a history of chronic hypertension, and 13,255 (15%) had other pre-existing vascular disease including history of stroke or transient ischemic attack (TIA). The mean pretreatment LDL-C was 3.79 mmol per L (146.5 mg per dL). In these trials the weighted average difference in LDL-C at 1 year was 1.09 mmol per L (42.1 mg per dL). There were 2,282 strokes among 65,138 participants in nine trials that sought information on stroke type. Hemorrhagic stroke was confirmed in 204 (9%), 1,565 (69%) were ischemic, and 513 (22%) were of unknown type. The incidence of first stroke of any type was proportionally reduced by 17% in favor of statins [1,340 (3.0%) statin vs 1,617 (3.7%) control relative risk (RR) 0.83; 95% CI, 0.78 to 0.88; p <0.0001] per 1 mmol per L LDL-C reduction. This overall reduction in stroke reflected a significant 19% proportional reduction in strokes not attributed to hemorrhage (i.e., presumed IS); RR 0.81; 99% CI, 0.74 to 0.89; p <0.0001 per 1 mmol per L, LDL-C reduction. There was no apparent difference in hemorrhagic stroke. There was a 12% reduction in all-cause mortality for every 1 mmol per L reduction in LDL-C (rate ratio 0.88; 95% CI, 0.84 to 0.91; p <0.0001). The meta-analysis demonstrated that

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TABLE 8.2 Etiology of Hemorrhagic Infarcts in Cancer Patients

Etiology	Mechanism	Tumors/Associations
Coagulopathy	Dysfunction or deficiency of clotting factors and/or platelets	Hematologic malignancies (especially APML), bone marrow dysfunction, liver disease, vitamin K deficiency, consumptive coagulopathies, chemotherapy, sepsis, XRT
Tumor associated hemorrhage (intraparenchymal)	Tumor cell necrosis, angiogenesis, blood vessel invasion	Lung cancer, melanoma, glioblastoma, renal cell, thyroid carcinoma, choriocarcinoma, leukemia, hyperleukocytosis
Tumor associated hemorrhage (subdural)	Bridging vein invasion or compression leading to rupture	Meningioma, lung cancer, gastric cancer, prostate adenocarcinoma
Tumor associated hemorrhage (subarachnoid)	Ruptured neoplastic or infectious aneurysms, leptomeningeal compression/rupture of arteries	Choriocarcinoma, cardiac myxoma, bacterial/fungal endocarditis, *Aspergillus*, Mucor/Rhizophus, immunosuppression
Tumor associated hemorrhage (epidural)	Arterial invasion or compression leading to rupture	Hepatocellular carcinoma
Venous sinus thrombosis	Hypercoagulable state or neoplastic compression causing thrombosis and rupture	Leukemia, breast cancer and chemotherapy, solid tumors; L-asparaginase
Hypertension	End arteriole lipohyalinosis and subsequent rupture	No specific cancer predilection though cyclosporine, tacrolimus, and cisplatin are associated with PRES (occasionally hemorrhagic)
MAHA	Platelet-rich microvascular thrombi	Mucinous adenocarcinomas, BMT, chemotherapy
Vasculitis	Infectious and inflammatory invasion of vessel wall	Leukemia; *Aspergillus*, Mucor, Rhizophus, VZV

APML, acute promyelocytic leukemia; XRT, radiation therapy; PRES, posterior reversible leukoencephalopathy; MAHA, microangiopathic hemolytic anemia; BMT, bone marrow transplantation; VZV, varicella zoster virus.

apeutic measure, with subsequent immune compromise producing significant risk of sepsis and DIC.

Tumor-related hemorrhages have been reported with nearly all solid malignancies but are most frequently associated with histologically vascular tumors. Melanoma, choriocarcinoma, renal cell carcinoma, papillary thyroid carcinoma, and lung neoplasms are some common examples. Metastases-associated hemorrhages are postulated to be multifactorial in pathophysiology, with elements of neoangiogenesis, tumor cell necrosis, and parenchymal blood vessel invasion. Of the primary brain tumors, oligodendroglioma and glioblastoma multiforme are most likely to produce parenchymal brain hemorrhage. Subdural hematomas are rare compared to parenchymal hemorrhages in cancer patients but are of obvious import given their potential for rapid neurologic compromise and the need for emergency surgical correction. Meningiomas can occasionally present as subdural hematomas when there is venous sinus invasion. In addition, lung, gastric, and prostate carcinoma have all been reported to cause dural metastases and consequent hematomas.

Combined Ischemic and Hemorrhagic Stroke

Venous sinus thrombosis, which can lead to both ischemic and hemorrhagic stroke, occurs frequently in leukemic patients, particularly those who have received L-asparaginase treatment. This chemotherapeutic agent alters the coagulation cascade by reducing the levels of antithrombin III, protein C, fibrinogen, and plasminogen. However, venous sinus thrombosis can also occur from neoplastic compression of venous structures, particularly in tumors of solid origin.

Patients with cancer are often immunocompromised from chemotherapy, steroid use, or their neoplasm and thus are at risk for opportunistic infections and atypical presentations of common organisms. Infection and sepsis can cause strokes in these patients via a multitude of mechanisms. Cancer patients often have long-term indwelling catheters that predispose them to septicemia followed by bacterial or candidal endocarditis and subsequent septic emboli. They can also suffer from mycotic aneurysms leading to subarachnoid hemorrhage or infectious vasculitis causing potential catastrophic intracranial hemorrhage via the angiophilic species *Aspergillus* and Mucor/Rhizophus.

CLINICAL APPLICATIONS AND METHODOLOGY

The diagnosis and appropriate management of stroke in cancer patients is often complicated by severe systemic illness, numerous toxic medications, and multiple comorbidities. Thus when approaching a stroke in a cancer patient, we recommend following certain guidelines in a stepwise approach to maximize diagnostic accuracy and efficiency. The first guideline is to evaluate the type, duration, and extent of cancer given that many forms of cancer have predilection for specific stroke mechanisms. In addition, the duration between initial cancer diagnosis and presentation may imply a specific pathophysiology. For instance, NBTE is usually a late complication of malignancy, occurring when cancer is widespread and infarction has occurred in other organs. However, there are clearly many exceptions to this as NBTE has been reported as the presenting manifestation of an occult malignancy. This is particularly true in mucin-producing tumors that can result in cata-

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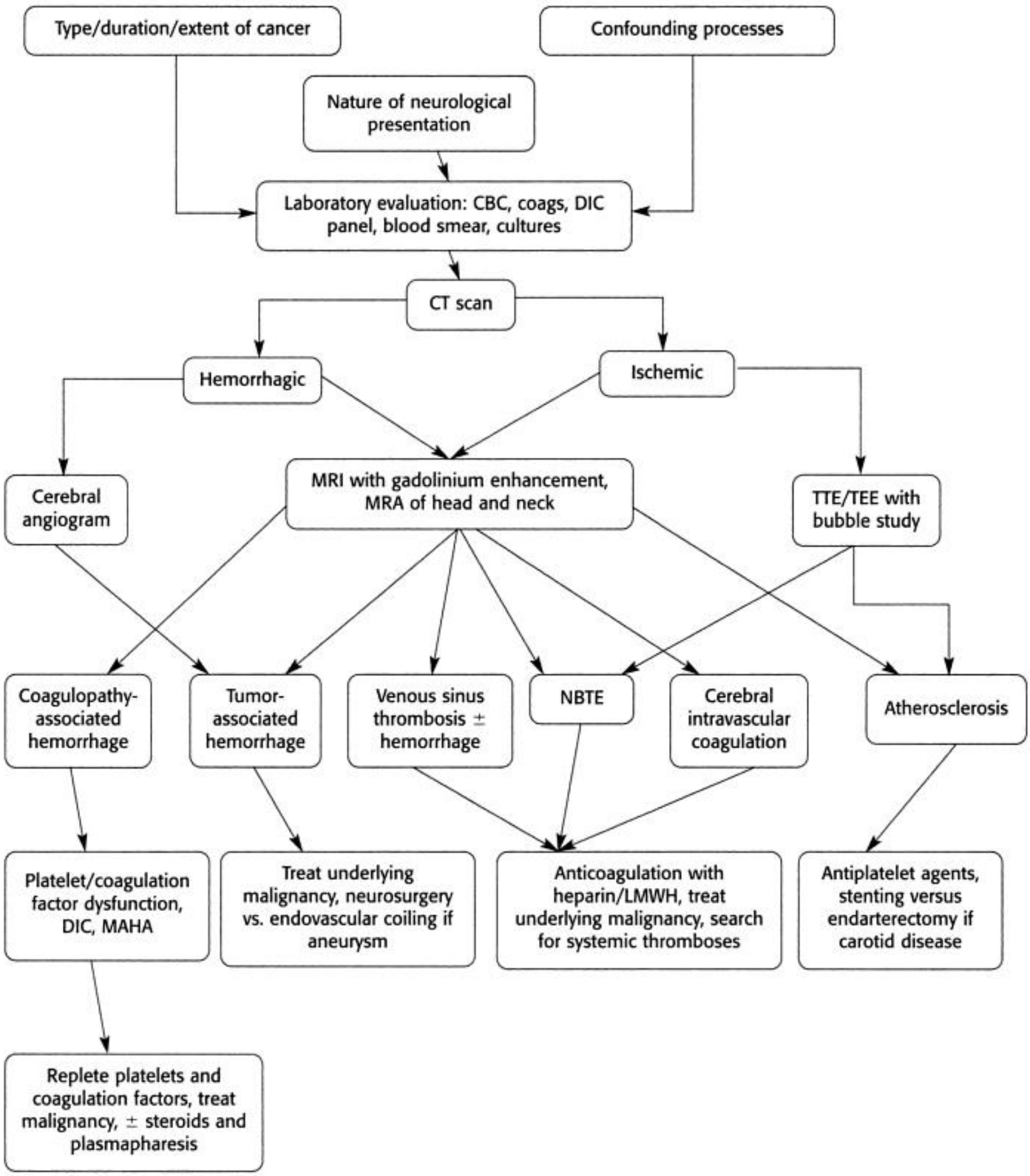
CRITICAL PATHWAY
Approach to a Cancer Patient with Stroke



CBC, calcium channel blocker; DIC, disseminated intravascular coagulation; MAHA, microangiopathic hemolytic anemia; CT, computerized tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; NBTE, nonbacterial thrombotic endocarditis; LMWH, low molecular weight heparin.

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TABLE 9.1 Stroke Risk in Nonvalvular Atrial Fibrillation According to the CHADS2 Index

CHADS2 Risk Criteria	Score
Prior stroke or TIA	2
Age >75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

CHADS2, Cardiac failure, Hypertension, Age, Diabetes, Stroke (doubled).

Patients (n = 1,733)	Adjusted Stroke Rate (%/yr, 95% CI)	CHADS2 Score
120	1.9 (1.2–3.0)	0
463	2.8 (2.0–3.8)	1
523	4.0 (3.1–5.1)	2
337	5.9 (4.6–7.3)	3
220	8.5 (6.3–11.1)	4
65	12.5 (8.2–17.5)	5
5	18.2 (10.5–27.4)	6

CHADS2, Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled); TIA, transient ischemic attack.
From Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864–2870 and van Walraven WC, Hart RG, Wells GA, et al. A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. *Arch Intern Med* 2003;163:936–943, with permission.

(AFI – c-index = 0.61, SPAF – c-index = 0.62, CHADS2 – c-index = 0.62), while the risk score for stroke and death was slightly better (c-index = 0.70). Application of these risk scores may be useful to guide the choice of antithrombotic therapy in AF patients.

Systemic (especially cerebral) embolism is an important complication of valvular heart disease. For rheumatic mitral valvular disease, the incidence of emboli varies from 1.5% to 4.7% per year and is increased in case of older patients, lower cardiac indices, presence of left atrial clot, and significant aortic regurgitation; atrial fibrillation increases the risk by approximately sevenfold. Maintenance of normal sinus rhythm with an enlarged left atrium and mitral valvuloplasty do not appear to reduce the risk of thromboembolism. Observational studies have shown reduction in annual stroke risk (10% to 0.8% to 3%) and death from embolism with oral anticoagulation therapy. Mitral annular calcification (MAC) is associated with a 2.1-fold increase in stroke risk and can be associated with AF (12-fold increase), aortic atheroma, and carotid atheroma. In the absence of associated mitral valve disease or AF, systemic embolism in patients with aortic valve disease is uncommon.

Thromboembolic complications of the various types of prosthetic valves are common and have recently been reviewed. The rate of embolism in patients with mechanical prosthetic valves is estimated to be 2% to 4% per year, even with proper anticoagulant therapy. Factors associated with thrombus formation include left atrial enlargement, atrial stasis, coexistent AF, valve type and position, and the presence of ventricular pacemakers. In patients who experience additional thromboembolic events despite adequate anticoagulation, TEE should be performed to look for atrial, ventricular, or valve thrombi, infective vegetations, and spontaneous echodensities. In selected cases, the dose of vitamin K antagonists (VKA) can be increased or an antiplatelet agent can be added, albeit with an increased risk of bleeding.

With combined antiplatelet and oral anticoagulant therapy, the risk of major hemorrhage varies from 1.3% to 24.7% . The observation in some studies that the risk of thromboembolism is reduced with the addition of aspirin is tempered by the observation of poor international normalized ratio (INR) control. Anticoagulation may be continued in the setting of infective prosthetic valve endocarditis, although the opinion is divided on the effectiveness of anticoagulation in reducing thromboembolic events in this setting.

ACUTE MANAGEMENT OF ATRIAL FIBRILLATION

Acute stroke patients may have AF with rapid ventricular response (RVR) on presenting at the hospital or they develop it during the acute hospitalization. The three major issues in this setting are determination of the type of AF (paroxysmal, persistent, recurrent or permanent), rate control, and cardioversion. Drugs that prolong the refractory period of the AV node are generally effective for rate control, resulting in rate reduction and improved cardiovascular hemodynamics. Criteria for rate control vary with age, but usually involve achieving ventricular rates of 60 to 80 per minute at rest and between 90 and 115 per minute during moderate exercise. Intravenous therapy is indicated if rapid rate control is necessary or if oral therapy is not feasible, while oral therapy may be used in hemodynamically stable patients. If pharmacological rate control therapy offers inadequate symptom relief or if the patient develops symptomatic hypotension, angina, or heart failure, then pacing, AV node ablation in conjunction with permanent pacing, or cardioversion are indicated. If cardioversion is considered, it should not be delayed to deliver therapeutic anticoagulation. In this setting, intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight (LMW) heparin should be initiated before

cardioversion or intravenous antiarrhythmic therapy. Treatment must be tailored to each individual, depending on the nature, severity, and frequency of symptoms; patient preferences; comorbid conditions; and the ongoing response to treatment.

If the patient has newly discovered paroxysmal AF, the only therapy needed is anticoagulation, unless there are significant symptoms. For the patient who has recurrent paroxysmal AF, anticoagulation and rate control are needed; if there are significant symptoms, then antiarrhythmic drugs or AV nodal ablation for antiarrhythmic drug–resistant cases may be necessary. If the patient has newly discovered persistent AF or has symptomatic AF lasting many weeks, initial therapy may be anticoagulation and rate control, while the long-term goal is to restore sinus rhythm with antiarrhythmic drugs or cardioversion. For the patient who has recurrent persistent AF, anticoagulation and rate control are needed; if there are significant symptoms, then antiarrhythmic drugs or electrical cardioversion may be necessary. In cardioversion-resistant cases, AV nodal ablation should be considered. Depending on symptoms, rate control may be a reasonable initial therapy in older patients with persistent AF who have hypertension or heart disease. For younger individuals, especially those with paroxysmal or lone AF, rhythm control may be a better initial approach. Table 9.2 shows

TABLE 9.2 Pharmacological Agents for Heart Rate Control in Atrial Fibrillation

Drug	Recommendation	Loading Dose	Onset	Maintenance Dose
Acute Setting				
No accessory pathway				
Esmolol	1C	500 μg/kg IV, 1 min	5 min	60–200 μg/kg/min IV
Metoprolol	1C	2.5–5.0 mg IV, 2 min X 3	5 min	–
Propanolol	1C	0.15 mg/kg IV	5 min	–
Diltiazem	1B	0.25 mg/kg IV, 2 min	2–7 min	5–15 mg/h IV
Verapamil	1B	0.075–0.15 mg/kg IV, 2 min	3–5 min	–
Accessory pathway				
Amiodarone	2aC	150 mg, 10 min	Days	0.5–1.0 mg/min IV
Heart failure, no accessory pathway				
Digoxin	1B	0.25 mg IV q2h to 1.5 mg	60+ min	0.125–0.375 mg/d
Amiodarone	2aC	150 mg, 10 min	Days	0.5–1.0 mg/min IV
Nonacute Setting, Chronic Maintenance				
Heart rate control				
Metoprolol	1C	–	4–6 h	25–100 mg BID
Propanolol	1C	–	60–90 min	80–240 mg daily
Diltiazem	1B	–	2–4 h	120–360 mg daily
Verapamil	1B	–	1–2 h	120–360 mg daily
Heart failure, no accessory pathway				
Digoxin	1C	0.5 mg PO	2 ds	0.125–0.375 mg daily
Amiodarone	2bC	800 mg daily 1 wk, 1–3 wk	200 mg daily	
		600 mg daily 1 wk	400 mg daily 4–6 wk	

IV, intravenous; PO, orally; BID, twice daily.

From Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2006;48:854–906, with permission.

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hypothesis. The largest trial, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, showed that there was no difference in all strokes, individual stroke subtypes, and mortality between the rate- and rhythm-management groups but that warfarin use reduced stroke risk regardless of assigned treatment strategy. When one considers all five trials, the rates of thromboembolism were 1.6% to 6.0% in the rhythm-control group and 0% to 4.3% in the rate-control group. The rates of mortality were 1.6% to 17.5% in the rhythm-control group and 1.0% to 15.3% in the rate-control group. There are two likely explanations for these results. First, many patients were likely to not be in sustained normal sinus rhythm. In another study of intensive monitoring of paroxysmal AF patients, there were 12 asymptomatic episodes of asymptomatic AF for every sympto-matic episode. Second, anticoagulation was more commonly discontinued in the rhythm-control group in the two largest studies. While it appears that rate control and rhythm control have similar outcomes, optimal management may require both, as well as anticoagulation.

BLEEDING RISK ASSOCIATED WITH ANTICOAGULANT THERAPY

Hemorrhage is the most important complication of anticoagulant therapy. For purposes of comparison, Table 9.6 summarizes data on systemic and intracranial hemorrhage complicating anticoagulant therapy in diverse disease states.

In an early pooled analysis, the annual rate of major hemorrhage was 1.0% in control patients and 1.3% in warfarin-treated patients. The most recent meta-analysis showed that the risk of major extracranial hemorrhage was higher in warfarin-containing regimens—adjusted-dose warfarin versus aspirin: RRR = −70% (95% CI, −234% to 14%); adjusted-dose warfarin versus control or placebo: RRR = −66% (95% CI, −235% to 18%); and aspirin versus placebo or no treatment: RRR = 2% (95% CI, −98% to 52%). In the SPORTIF III and SPORTIF V trials, the annual rates of major bleeding were: warfarin = 1.5%; warfarin + aspirin = 4.95% ($p = 0.004$); ximelagatran = 2.35%; ximelagatran + aspirin = 56.09% ($p = 0.046$). Although the number of observations in NASPEAF was small, the risk of severe bleeding was 0.92% to 2.09% in the combined treatment group and 1.80% to 2.13% in the anticoagulant therapy group. In general, factors associated with systemic bleeding include increasing age, hypertension, history of cerebrovascular disease, ischemic stroke, serious heart disease, renal insufficiency, history of gastrointestinal bleeding, history of malignancy, concomitant medications (such as aspirin), intensity of anticoagulation, and increased variation in INR values independent of the mean INR. Models for prediction of hemorrhage risk have been generated, but they should be used in conjunction with the

TABLE 9.6 Hemorrhagic Complications of Anticoagulant Therapy According to Disease State

Disease State	INR Range	Frequency of Hemorrhage (%)		
		Major	Fatal	Intracranial
Atrial fibrillation	1.5–4.5	0–6.6	0–1.1	0.2–0.5
Coronary artery disease				
UFH	–	1.0–6.8	0–0.2	–
LMWH	–	0–6.5	0–0.2	–
VKA	1.3–5.0	0–19.3	0–2.9	up to 0.4
Prosthetic heart valves	2.0–9.0	1.0–19.2	0-0.7	0–1.5
Venous thromboembolism	2.0–4.4	0–16.7	0–0.9	–
Acute ischemic stroke				
Control	–	0.3	0.1	0.3
Aspirin	–	0–1.8	0.2–1.9	0.5
UFH-SC	–	0–1.4	0.4–0.5	0.7–9.6
LMWH-SC	–	0–5.9		0–6.1
Stroke prevention				
Noncardioembolic	1.4–4.5	3.4–8.1	0.6–2.6	4.1
Intracranial stenosis	2.0–3.0	8.3	0.7	0.7

Note: Intracranial hemorrhage in atrial fibrillation or stroke prevention trials primarily refers to parenchymal or subdural hematoma, and hemorrhagic transformation in acute ischemic stroke trials.

INR, international normalized ratio; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist; SC, subcutaneous.

From Adams HP, Davis PH. Antithrombotic therapy for acute ischemic stroke. In: Mohr JP, Choi DW, Grotta JC, Weir B, Wolf PA, eds. *Stroke: Pathophysiology, Diagnosis and Management*. 4th ed. Philadelphia, PA: Churchill Livingstone; 2004:953–969; Benavente O, Sherman D. Secondary prevention of cardioembolic stroke. In: Mohr JP, Choi DW, Grotta JC, Weir B, Wolf PA, eds. *Stroke: Pathophysiology, Diagnosis, and Management*. 4th ed. Philadelphia, PA: Churchill Livingstone; 2004:1171–1186; and Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–867; and Sloan MA. Use of anticoagulant agents for stroke prevention. *Continuum* 2005;11:97–127, with permission.

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TABLE 9.8 2004 ACCP Recommendations: Antiplatelet/Anticoagulant Therapy for Stroke Prevention in Atrial Fibrillation

Indication	Agent	aPTT/INR Range	Grade
Nonvalvular AF			
Age <65 y, no stroke risk factors	Aspirin 325 mg	–	1B
Age 65–75 y, no stroke risk factors	Aspirin 325 mg or VKA	2.5 (2.0–3.0)	1A
Any age, ≥1 stroke risk factor	VKA	2.5 (2.0–3.0)	1A
After cardiac surgery, >48 h duration	VKA	2.5 (2.0–3.0)	2C
Cardioversion			
Elective CV planned, AF duration >48 h or unknown	VKA3 wk pre, 4 wk post	2.5 (2.0–3.0)	1C+
CV urgent/emergent, AF duration <48 h	UFH	50-70 s	
	VKA 4 wk post	2.5 (2.0–3.0)	2C
TEE shows clot, CV cancelled	VKA	2.5 (2.0–3.0)	1B
Contraindication to anticoagulant therapy	Aspirin	–	1A
Valvular AF	VKA	2.5 (2.0–3.0)	1C+
Rheumatic mitral valve disease	VKA	2.5 (2.0–3.0)	1C+
Prosthetic heart valves (mechanical, tissue)	VKA	2.5 (2.0–3.0)	2C
Atrial Flutter, with or without CV			

aPTT, activated partial thromboplastin time; INR, international normalized ratio; AF, atrial fibrillation; VKA, vitamin K antagonist; UFH, unfractionated heparin; TEE, transesophageal echocardiography.

From Guyatt G, Schunemann HJ, Cook D, et al. Applying the grades of recommendation for antithrombotic and thrombolytic therapy. *Chest* 2004;126:179S–187S; Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic. *Chest* 2004;126:457S–482S; Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation. *Chest* 2004;126:429S–456S. and Sloan MA. Use of anticoagulant agents for stroke prevention. *Continuum* 2005;11:97–127, with permission.

antiarrhythmic therapy has not been administered, it should be given following anticoagulation and before cardioversion. If TEE shows no clot, then anticoagulation followed by cardioversion may be performed at unknown but likely higher stroke risk. If TEE shows clot, anticoagulation followed by cardioversion may be performed at high risk. In a life-threatening situation, the benefits of this approach may outweigh the risks.

The results of clinical trials translate well into clinical practice, with similar rates of stroke and major bleeding and an increased risk of minor bleeding. Despite these findings, warfarin therapy for stroke prevention in nonvalvular AF in fee-for-service Medicare beneficiaries is either underutilized or inappropriately utilized, with little incremental change from 1998 to 2001. It is possible that clinicians may fear selection of warfarin therapy because of the risk of falls. Interestingly, a recent Markov decision analytic model determined that for patients with average risk of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient, aspirin therapy was associated with 11.17 quality-adjusted life-years per patient, and no antithrombotic therapy was associated with 10.15 quality-adjusted life-years per patient. Sensitivity analyses demonstrated that regardless of age or baseline stroke risk, the risk of falling was not an important factor in determining the choice of antithrombotic therapy. However, in practice, the nature and severity of the stroke-related neurological deficit and any preexisting neurological findings (such as loss of proprioception due to peripheral neuropathy or a gait disorder) are important factors in choosing antithrombotic therapy. The greater the degree of gait instability of any cause, the less likely a patient will be placed on oral anticoagulation.

Fortunately, patients may only infrequently experience intracerebral, subdural, or subarachnoid hemorrhage while on anticoagulant therapy. Data from CT and MRI scans have assumed more importance in the resumption of antithrombotic therapies in this setting. The presence of microhemorrhages on the gradient echo sequence of MRI studies may indicate the presence of an underlying cerebral microangiopathy or cerebral amyloid angiopathy. In one study, the risk of anticoagulant-related intracranial hemorrhage was 9.3% in patients with microhemorrhages and 1.3% in patients without microhemorrhages. A recent decision analysis recommended against restarting anticoagulation in patients with lobar hemorrhage (possibly secondary to cerebral amyloid angiopathy) and AF. Such findings would increase the likelihood that an otherwise appropriate patient may not receive warfarin therapy. However, if the CHADS2 score indicates high stroke risk, then under certain circumstances one might favor more tightly controlled warfarin therapy, such as INR 2.0 to 2.5, unless a contraindication exists. In general, anticoagulation may be resumed 3 to 4 weeks after intracerebral or subdural hemorrhage. Patients with aneurysmal subarachnoid hemorrhage must have the aneurysm secured before anticoagulation can be resumed. However, recent data suggest that the risk of oral anticoagulant-related intracerebral hemorrhage appears to be increasing; stringent control of the INR assumes even greater importance.

On occasion, patients may require interruption of long-term oral anticoagulation for diagnostic or therapeutic procedures. In patients with mechanical prosthetic heart valves, it is generally appropriate to substitute UFH or LMW heparin to prevent thrombosis. In patients with AF who do not have mechanical prosthetic valves, anticoagulation may be interrupted for up to 1 week for diagnostic or surgical procedures that carry a high risk of bleeding without substituting heparin. In high-risk patients

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TABLE 10.3 Studies and Registries Showing Competitive Complication Rates for Carotid Artery Stenting

Study (y)	Patients (Type)	Primary Endpoints (30 d)	CAS Risk (vs. CEA)
SAPPHIRE (2004)	334 (Sx and Asx)	Death, stroke, and MI	4.8% (9.8%)
SPACE (2006)	1,200 (Sx)	Stroke and death	6.84% (6.34%)
CAPTURE (2007)	3,500	Death, stroke, and MI	6.3%

CAS, carotid artery stenting; CEA, carotid endarterectomy; SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; Sx, symptomatic; Asx, asymptomatic; MI, myocardial infarction; SPACE, Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs Endarterectomy; CAPTURE, Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events.

CEA complications reported in the literature depends in part on the specialty of the authors of the study being published. As such, studies in which a neurologist was one of the investigators have reported a higher rate of complications. This may result from the inherent ability of neurologists to recognize neurological complications, and this suggests that the involvement of a neurologist in the decision-making process about CEA is of significant value.

At present, the *endovascular* treatment of carotid pathology largely includes carotid artery stenting (CAS) because balloon angioplasty alone has been widely abandoned. Its application is based on the results of various randomized prospective studies, as well as several registries (see Table 10.3). Among these, we must discuss the ones we consider most important from the perspective of their effect on the acceptance of CAS by the medical community, insurance carriers, and government regulatory agencies are discussed. In 2004, Medicare announced its intention to cover payments for CAS performed under specific circumstances, largely derived from the inclusion criteria in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) report. This was a randomized study of CAS versus CEA in *surgical high-risk* patients. The surgical high risk patient was determined by either medical comorbidities or lesion characteristics (see Table 10.4), and a CEA expert surgeon was required to declare a patient as being at surgical high risk. The results, as displayed in Table 10.3, showed rates of stroke, death, and myocardial infarction as 4.8% versus 9.8% in favor of CAS versus CEA at 30 days. Moreover, the superiority of CAS over CEA in this patient population has remained even 1 year after the procedure (see Fig. 10.1).

TABLE 10.4 Criteria Used in SAPPHIRE and Other Studies to Define High Surgical Risk for CEA

- Clinically significant cardiac disease (i.e., Ejection Fraction <30% or NYHA ≥III)
- Severe pulmonary disease (FEV_1<30%)
- Contralateral carotid occlusion
- Contralateral laryngeal nerve palsy
- Previous radical neck surgery
- Previous radiation to the neck
- Recurrent stenosis after CEA
- Age >80 y
- Surgically inaccessible lesion
- Tracheostomy stoma

SAPPHIRE, Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; CEA, carotid endarterectomy; NYHA, New York Heart Association; Forced Exploratory Volume; FEV_1, forced expiratory volume in 1 second.

Along the same lines, other studies have confirmed that the complication rate of CAS is sufficiently competitive to warrant its application in high-risk patients (Table 10.3). Nevertheless, we would be remiss if we did not examine other studies are not examined whose results have not been as favorable to CAS as those listed earlier have. Such studies, shown in Table 10.5, generally underscore the importance of operator's experience and expertise as a requirement for CAS to be of any benefit to patients. In fact, the common denominator of the studies cited is the relative inexperience of the interventionists, evidenced not only in procedural technique but also in the patients' care (e.g., inadequate antiplatelet therapy perioperatively). In fact, to illustrate the importance of this issue, we steer the reader to look at our own experience of over a decade of performing this procedure (see Fig. 10.2). The graph illustrates the effect of experience, as well as that of the introduction of technological advances (i.e., distal protection devices). Furthermore, we must emphasize the fact that all credible studies of CAS have systematically required for neurologists to be involved in the assessment, selection, and postoperative monitoring of the patients, enhancing the accuracy of the identification of neurological complications.

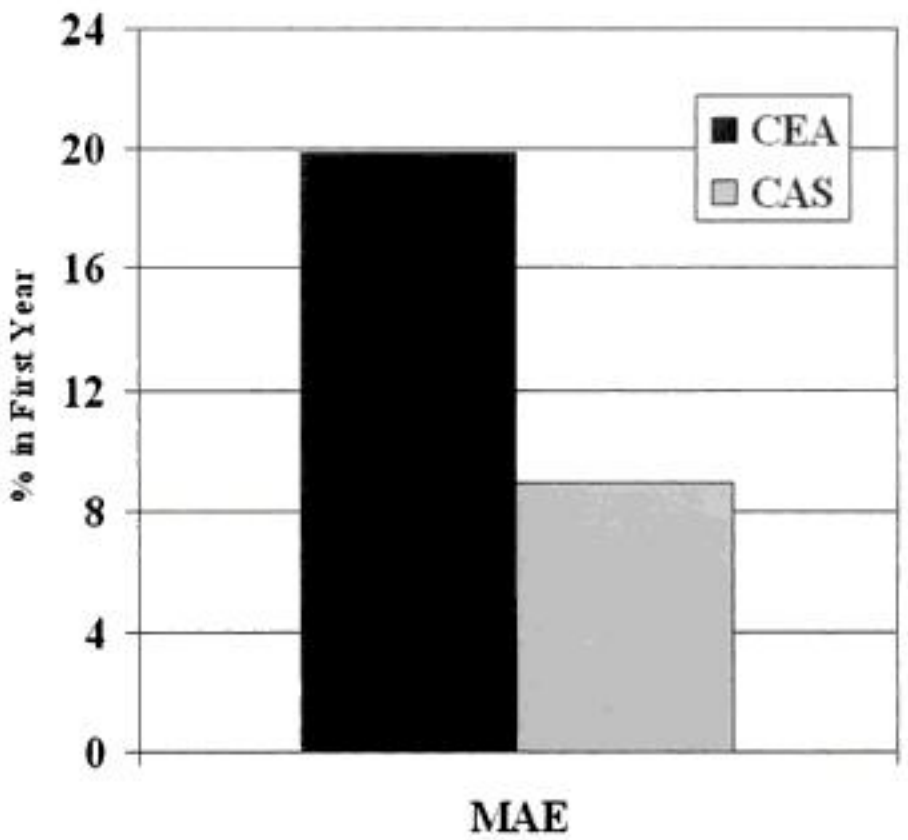

FIGURE 10.1. Comparison of the number of major adverse events (MAEs) occurring in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) patients within the first 365 days of follow-up, showing the superiority of stenting. CAS, carotid artery stenting; CEA, carotid endarterectomy.

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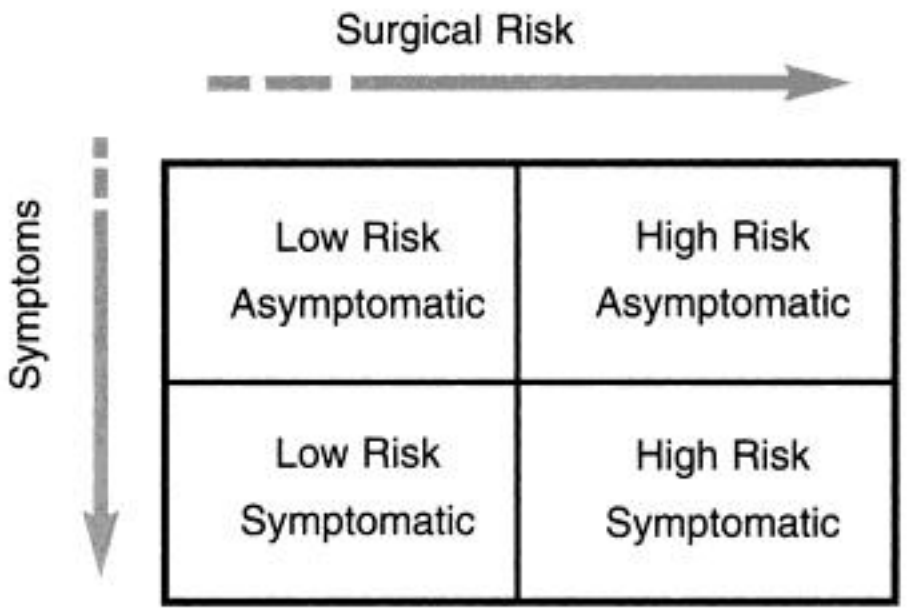

FIGURE 10.3. Contingency table displaying the four major patient subgroups based on whether they have had symptoms of brain ischemia, and their surgical risk.

already been found to be capable of producing brain ischemia (transient or not). From this perspective, and drawing from the existing literature, the sense of urgency and need to revascularize hemodynamically significant lesions (i.e., causing >50% stenosis by NASCET criteria) overwhelms the benefit of any strategy that does not include correction of the hemodynamic compromise. Clearly, in low-surgical-risk patients, CEA has been shown to be extremely effective when performed by expert surgical teams that maintain a high volume practice. The benefit of CAS in these patients, although intuitively expected, awaits the results of ongoing prospective randomized trials. On the basis of current information, high-surgical-risk patients may be better off treated by CAS, provided the operator is an experienced interventionist with ample understanding of the cerebral circulation, both anatomically and physiologically. Finally, surgically inaccessible or nonatherosclerotic lesions should be considered for endovascular therapy only, provided the operator meets the criteria noted earlier in this section. Under these circumstances, we cannot overemphasize the importance of having neurological expertise during the decision-making process, particularly as the literature available to conduct a risk-to-benefit assessment is scant.

Asymptomatic patients, on the other hand, represent a very different problem. Their risk for stroke is relatively small, and the benefits of revascularization may be marginal. In these patients, only lesions that cause severe hemodynamic compromises (i.e., >80% stenosis by NASCET criteria) should be considered for revascularization. Even in these cases, the presence of a high surgical risk should be a major warning about the pitfalls involved in blindly applying data from the literature without considering the individual characteristics of the patient. Considering the existing evidence that both CEA and CAS carry a higher procedural risk in patients such as those described in Table 10.4 than that in low-risk patients, clinicians must find compelling reasons to suggest revascularization by any method. In such circumstances, it is even more important that the operator's expertise is equivalent to "best in class" to minimize the chances of catastrophic complications.

Procedural Safety

The safety of both CEA and CAS has been a subject of concern spanning the last two decades. To arrive at a positive risk-to-benefit assessment, the risk imposed by the procedure must be smaller (for that patient) than the risk of stroke from the carotid artery pathology if only medical treatment is applied. Safety data now exist for both CEA and CAS, although the former is an older and more mature procedure. In fact, the relative immaturity of CAS must be taken into consideration when reviewing the literature to put each of the studies published in the context of the evolution of a technique that has only recently been considered fully developed.

A major advance in the evolution of CAS and its safety record was the introduction of distal embolic protection devices (see Fig. 10.4). The early experience of CAS invariably showed that a few patients (approximately 6% to 7%) had small nondisabling stroke during the intervention (Fig. 10.2). These largely resulted in subtle neurological deficits from which the patients usually recovered within a few days. Nevertheless, such an unpredictable occurrence led to the development of devices that, when deployed distally in the internal carotid artery, would essentially capture the embolic debris and limit the chances of complicating stroke during the procedure (Fig. 10.4). The introduction of distal embolic protection devices resulted in an immediate decrease in the rates of procedural strokes complicating CAS (Figs. 10.2 and 10.5).

Operator's Expertise

Operator's expertise is perhaps the single most important variable that affects the outcome of both CEA and CAS. From the surgical perspective, it is important to point out that large randomized CEA trials (e.g., NASCET, ACAS, and ECST) owe their success to the technical expertise of their surgeons. All operators in these studies were handpicked, screened for a number of months before the study, and closely monitored. In daily practice, on the other hand, this may or may not be the case. The same cannot be said about all the CAS studies. In fact, a close scrutiny of those studies with unusually high procedural complication rates reveals a lack of systematic credentialing of the operators (e.g., Wallstent study) or the inclusion of inexperienced operators [e.g., Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy (SPACE)].

Three major features characterize expert operators: (a) patient selection skills, (b) phenotypic and genotypic interventional attributes, and (c) high volume of cases (i.e., experience). The best operators spend considerable amount of time making sure that the patient in question is as close an ideal candidate for the procedure as possible. They do not take chances by operating on patients who may not benefit from the procedure or whose circumstances are such that they pose an unusually high procedural risk. To be able to select patients properly, operators must have fundamental knowledge of neuroanatomy, neurophysiology, clinical neurology, neuroimaging, neuropathology, and neuropharmacology.

The phenotypic characteristics of an operator derive from his or her procedural education; that is, having performed a large number of procedures under the supervision of a qualified mentor, affording him the ability to learn all aspects of the

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figures quoted are probably affected by adverse selection, since many of the reported patients already had failed medical therapy. Despite the recent advances in technology and experience, there are potential technical problems with the performance of balloon angioplasty, including the risk of dissection, elastic recoil, and acute closure, all of which fueled the interest in intracranial stenting.

The conceptual advantages of stenting over balloon angioplasty include (a) lesser risk of acute closure from intimal dissection and thrombus formation and (b) improved long-term patency rates from larger postprocedural lumen diameters and avoidance of recoil. The main limiting factor for the utilization of stents to treat intracranial lesions has been the availability of stents that could be tracked and deployed within the intracranial cavity. In spite of such a limitation, the published major intracranial stenting series (excluding small case reports) report better results than balloon angioplasty. The small sample size of all of these series precludes a generalization of the results. However, series reporting the natural history or effect of medical therapy in intracranial stenoses are only slightly larger and are subject to similar criticism.

It is important to consider in our discussion the results of the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) study, since they are relevant to the recommendations we are bound to make later in the chapter. The SSYLVIA study was designed to investigate the effectiveness of a stenting system designed for neurologic use (i.e., NEUROLINK). Enrollment of 61 patients (43 with intracranial lesions and 18 with extracranial vertebral lesions) resulted in one of the largest series reported. The rates of complicating strokes were 6.6% at 30 days and 7.3% between 30 days and 1 year. The rates of restenosis at 6 months were 32.4% for intracranial lesions and 42.9% for extracranial vertebral arteries. These results were generally considered lukewarm at best, and no additional investigation of the NEUROLINK system has been conducted since then.

Several important comments must be made about the SSYLVIA results, particularly because there is such a disparity between the results of the study and our experience of >10 years in elective intracranial stenting. The first comments have to do with the NEUROLINK system itself. The original design of the NEUROLINK stent was that of a balloon-expandable 316L stainless steel stent that, by design, had significantly less metal than the existing coronary stents. In retrospect, this was probably a mistake, particularly for treating extracranial VA lesions, which *cannot be compared* with intracranial stenoses. In addition, the shaft of the balloon catheter was excessively long, a problem that became evident in the only patient we treated under this protocol, as we found it impossible to perform an over-the-wire exchange using standard 300 cm microwires. This forced us to have to recross the lesion, a step commonly avoided in endovascular treatment.

The second set of comments is technical, relating to the variability of the procedures performed. Operators were allowed to use either local or general anesthesia, the latter presenting a separate variable in the therapeutic equation. Over the years, the authors have almost invariably performed elective intracranial stenting under local anesthesia, a technique that allows for monitoring the patients during the procedure. Review of the data also shows that, in general, the degree of diameter enlargement achieved in the study was suboptimal. This is a problem, for there is a large body of literature that correlates the postprocedural diameter with the risk of restenosis in other vascular beds, particularly the coronary arteries. Finally, predilation was left up to the discretion of the operator. Therefore, predilation should be performed in all cases, particularly as it allows the operator to test the vessel before deploying a stent and improves the ability to measure the ultimate target vascular segment before choosing the size of the stent to be used.

Finally, the rate of postdischarge strokes is concerning. In the authors' experience, once the patient leaves the catheterization laboratory, it is very unusual to see a complicating stroke. This is even rarer after 30 days following the procedure. This raises the question of whether the treatment of the patient following the procedure should have been handled differently. For example, the patients in the SSYLVIA study were kept on clopidogrel alone for about 4 weeks, but these patients should be maintained on double antiplatelet therapy indefinitely.

Experience with the Wingspan Stent

More recently, additional research has allowed the introduction of a self-expandable stent designed specifically for intracranial deployment (i.e., Wingspan, Boston Scientific, Boston, MA). The attractiveness of this stent, from the beginning, has been its deliverability to distal intracranial locations (i.e., the stent is delivered via a microcatheter). Also, since it does not require a balloon for deployment, the radial force exerted is not as large as that of balloon-expandable stents. The initial experience in the United States has shown a high rate of procedural success (98.8%), with a 6.1% rate of 30-day stroke and death rate. The latter statistics makes this procedure much more competitive than previously recognized.

CLINICAL APPLICATIONS AND METHODOLOGY

General Considerations

The application of endovascular techniques to the treatment of intracranial atherosclerotic pathology involves two different issues: feasibility and reasonableness. The former relates to whether a procedure *can be performed* as the treatment of a specific lesion, while the latter relates to whether such a procedure *should be performed*, even if feasible. The discussion in the previous section should illustrate to the reader that, at present, the quality of technology and operator's expertise makes endovascular treatment of these lesions feasible. However, the ability to revascularize a lesion should not automatically translate into a procedure that may or may not be needed.

Candidacy for Endovascular Intervention

The heterogeneity of intracranial stenoses is also reflected in their potential for endovascular therapy. Thus, treatment of lesions in the petrous and cavernous portions of the ICA, at present, represents little technical challenge (see Fig. 12.1). However, the ability to track the stents beyond the carotid artery siphon into the clinoid portion of the carotid, or even the MCA, has become reliable only following the introduction of self-expandable stents. Stenting of the intracranial portions of the vertebrobasilar system, namely the V3 and V4 portions of the VA, has also been shown to be feasible and relatively safe and has proved to be an easier system in which to work than the carotid territory (see Fig. 12.2).

Then there is the BA. One of the potential risks of deploying stents intracranially is that of jailing perforating branches from the

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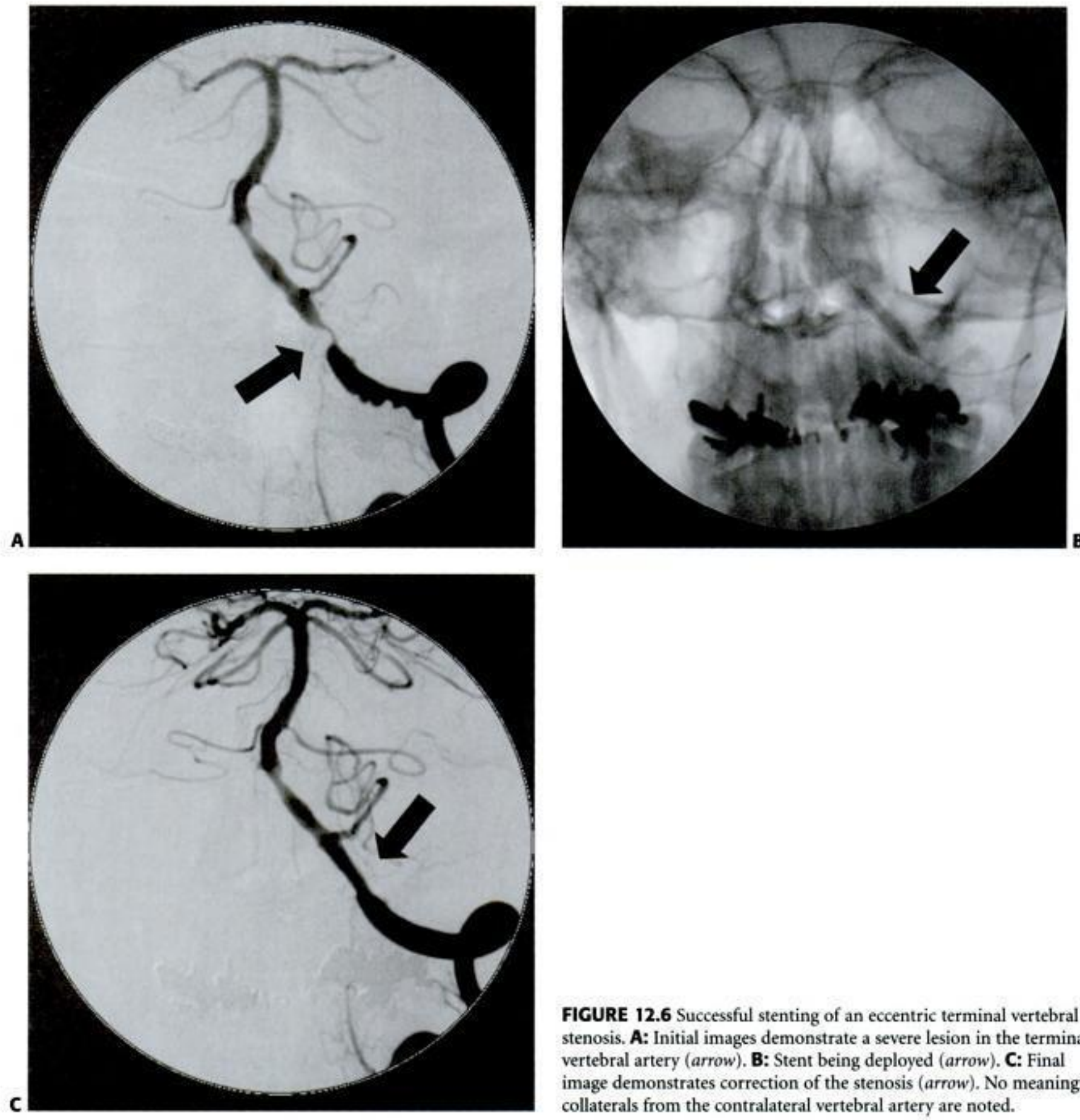

FIGURE 12.6 Successful stenting of an eccentric terminal vertebral stenosis. **A:** Initial images demonstrate a severe lesion in the terminal vertebral artery (*arrow*). **B:** Stent being deployed (*arrow*). **C:** Final image demonstrates correction of the stenosis (*arrow*). No meaningful collaterals from the contralateral vertebral artery are noted.

patients with intracranial arterial lesions and no evidence of significant hemodynamic compromise must be placed in an imaging surveillance program to ensure early detection of progression of the underlying process. An important practical point about the aforementioned recommendation has to do with the definition of significant hemodynamic compromise. This subject is covered extensively in Chapter 22 later in the book but suffice to say, it is imperative that the limitations of every imaging technique are understood, as well as the inherent inadequacy of using diameter stenosis as a surrogate for flow compromise (the actual variable to consider) (see Fig. 12.8).

The management of symptomatic intracranial atherosclerotic lesions that cause significant hemodynamic compromise should always include a consideration for stenting. This should follow the guidelines outlined earlier. A final word about medical therapy for all patients undergoing stenting: It is imperative for these individuals to be treated with aspirin and clopidogrel prior to the procedure to remove the risk of acute stent thrombosis. Once the procedure is completed, both antiplatelet agents must be continued for at least 4 weeks, but preferably indefinitely. Also, with regard to the follow-up of these patients, the myth that following intracranial stent deployment they cannot undergo magnetic resonance imaging (MRI) is simply not true. The authors have performed MRI studies within hours of deployment in up to 3.0 Tesla instruments, without any complications. The only limitation is the metallic susceptibility artifact caused by the stent (Fig. 12.5).

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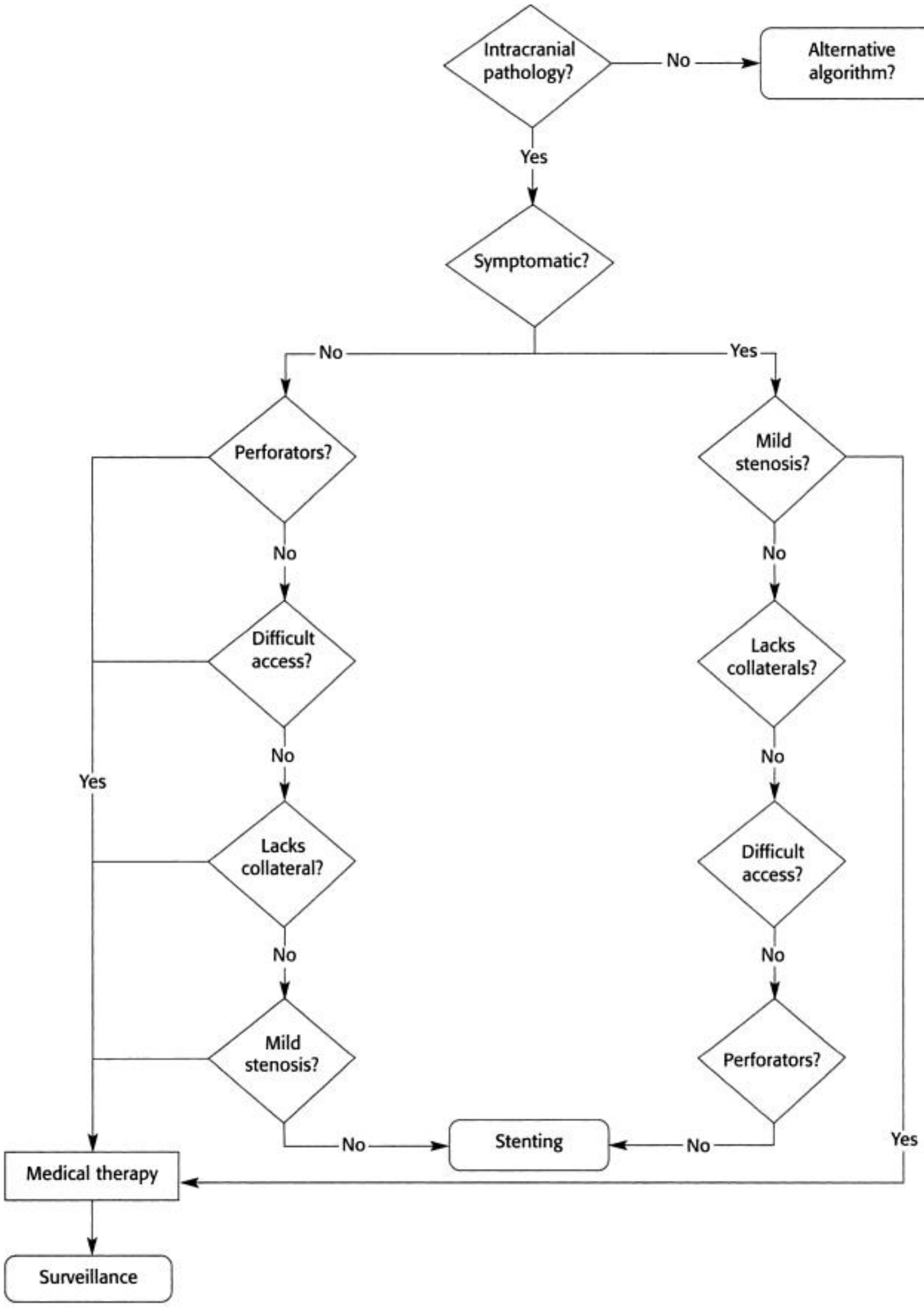
CRITICAL PATHWAY
Intracranial Stenosis Management



CHAPTER

13 Sleep and Vascular Disorders

JAMES D. GEYER, PAUL R. CARNEY, STEPHENIE C. DILLARD, AND JULIE C. TSIKHLAKIS

OBJECTIVES

- What is obstructive sleep apnea?
- What is the relationship between sleep and hypertension?
- What is the relationship between sleep and stroke?
- What is the relationship between sleep and congestive heart failure?
- What is the effect of treatment of sleep related breathing disorders with positive airway pressure on vascular disease?

Vascular diseases, including myocardial infarction, stroke, cerebrovascular disease, congestive heart failure (CHF), and cardiac arrhythmias, are the most common cause of morbidity and mortality in industrialized countries. Sleep-related breathing disorders are also widespread and increasing in prevalence, in part because of the increasing incidence of obesity. Approximately 20 million Americans suffer from obstructive sleep apnea. Given the frequency of sleep disorders and vascular disorders, it is not surprising that the two conditions often coexist. The interaction between the obstructive sleep apnea/hypopnea syndrome and vascular diseases is much more complex than originally thought, and their comorbidity is more than mere coexistence. Sleep-related breathing disorders, insomnia, and even normal autonomic changes associated with rapid eye movement (REM) sleep can adversely affect vascular diseases. This chapter reviews the normal autonomic processes that occur during sleep and discusses the role that sleep disorders may play in heart disease, hypertension, and stroke.

INTRODUCTION TO SLEEP MEDICINE

Normal Autonomic Physiology of Sleep

The autonomic nervous system regulates the involuntary, automatic functions of the visceral organs. It is composed of the parasympathetic and sympathetic divisions, the two opposing systems, the balance of which determines autonomic function. The sympathetic system has a stimulant effect and is responsible for the so-called fight or flight response. Its primary neurochemical mediator is noradrenaline, an adrenalinelike substance that results in increased heart rate, increased respiratory rate, vasoconstriction of visceral organs with concomitant vasodilatation of skeletal muscles, increased blood pressure, pupillary dilation, and inhibition of digestion, urination, and defecation. In contrast, the parasympathetic system counterbalances these effects. Its primary neurotransmitter is acetylcholine, and its effects include slowing of the heart rate and respirations, vasodilatation of visceral organs with decreased blood pressure, pupillary constriction, increased peristalsis, and emptying of the bladder and the rectum.

Since vasoconstriction and hypertension are major contributors to myocardial infarction and stroke, it is useful to examine the body's normal sympathetic and parasympathetic responses during sleep. In general, at sleep onset there is a decrease in sympathetic tone and an increase in parasympathetic tone, which causes a lowering of the heart rate, blood pressure, respiratory rate, and tidal volume. These changes continue during non-REM (NREM) sleep. With the transition to tonic REM sleep, the portion of REM sleep that occurs without REMs, the parasympathetic activity continues to increase and the sympathetic activity is further suppressed. During phasic REM sleep, the portion of REM sleep that has accompanying REMs, there are bursts of sympathetic activity.

During normal inspiration, the heart rate has a brief acceleration to accommodate venous return and increased cardiac output. During expiration, there is a progressive decrease in heart rate. This normal variability in cardiac rhythm is a marker for cardiac health, and its absence is associated with increasing age and/or cardiac disease. During REM sleep, it is normal for the heart rate to become increasingly variable with episodes of moderate tachycardia and bradycardia. Respiratory patterns are also irregular and may result in mild oxygen desaturations even in healthy subjects. The neurons controlling the principal diaphragmatic respiratory muscles typically are not significantly inhibited during REM sleep, but accessory airway muscles in the ribcage and neck may have partial muscle atonia, causing the diaphragm to bear most of the load of respiration. This may lead to partial diaphragmatic fatigue, hypoventilation, and decreased oxygenation, which can last for several minutes. These episodes are referred to as *REM sleep hypoventilation episodes* and are not necessarily pathologic.

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TABLE 13.3 Polysomnographic Findings in Obstructive Sleep Apnea Syndrome

AHI >5
AHI REM >AHI NREM
Apnea duration longer in REM
AHI supine >AHI lateral
Snoring
Reduced deep sleep (stages 3, 4)
Reduced REM sleep
Oxygen desaturations
Tachycardia with arousal
Bradycardia with apnea onset

AHI, apnea-hypopnea index; REM, rapid eye movement; NREM, non–rapid eye movement.

TREATMENT

Identifying the subpopulation of patients requiring treatment for a sleep-related breathing disorder can be challenging. The threshold for initiating therapy in patients with stroke or other vascular disorders should be lower than that in the general population. In this group, even relatively mild sleep apnea may warrant treatment, even if there is little or no associated daytime sleepiness. Special attention should be given to the severity of the obstructive sleep apnea during REM sleep and in each sleep position. The detrimental aspects of obstructive sleep apnea are frequently worse during REM sleep. In most patients, the severity of the sleep-related breathing disorder is worst in the supine position. Following strokes with hemiparesis, one lateral position may be associated with severe apnea while the other may be associated with relatively normal sleep.

Nasal CPAP is the treatment of choice for most patients with obstructive sleep apnea (see Table 13.4). Positive airway pressure (PAP) treatment maintains upper airway patency via a pneumatic splint, with the air pressure preventing airway collapse. CPAP maintains a constant pressure throughout the respiratory cycle. Bilevel PAP provides a higher pressure on inhalation than on exhalation, which may be more comfortable, especially in patients with weakness from stroke or neuromuscular disease.

Empiric selection of a pressure setting for these devices is fraught with danger (see Table 13.5 for a review of problems associated with PAP theory). An inadequate setting will leave the patient undertreated and an excessive pressure may result in patient noncompliance (see Table 13.6 for methods of improving compliance) or central apnea. The patient should be evaluated with formal polysomnography and then with a CPAP titration. In select patients this can be accomplished during a combined or split-night study.

TABLE 13.4 Benefits of Positive Airway Pressure Treatment

Decreased sleepiness and fatigue
Improved sleep quality
Improved quality of life
Decreased sympathetic tone
Decreased systemic blood pressure
Decreased pulmonary blood pressure
Decreased platelet activation
Decreased C-reactive protein
Decreased fibrinogen level
Decreased overall vascular risk
Improved cognitive function
Reduced insulin resistance

TABLE 13.5 Continuous Positive Airway Pressure Problems and Their Treatments

Claustrophobia	Pressure intolerance
Desensitization	Ramp setting
Nasal prong interface	C-flex
Anxiolytics	Bilevel pressure
Mask leaks	Wedge pillow
Careful mask fit	Skin breakdown
Education	Adjust straps
Nasal congestion	Change mask styles
Heated humidity	Tape barrier for skin protection
Nasal steroid spray	Mouth dryness
Nasal saline spray	Humidifier
Decongestants	Chinstrap
Full face mask	Full face mask
Oral mask	Lower pressure setting
	Treat nasal congestion

There is a limited role for surgical treatment of obstructive sleep apnea in the stroke patient. Tracheostomy bypasses the upper airway and therefore the region of obstruction. This procedure should be reserved for patients with severe obstructive sleep apnea who are unable to tolerate or use CPAP or similar devices. The more commonly used surgical procedures such as uvulopalatopharyngoplasty (UPPP), mandibular advancement, and maxillomandibular advancement may be associated with significant morbidity and prolonged recovery times, and should be used judiciously in the stroke population.

Obesity is commonly associated with obstructive sleep apnea. Weight loss can significantly decrease the severity of obstructive sleep apnea in terms of AHI and oxygen desaturation. Maintaining weight loss can often be difficult for the patient. Weight loss in the nonobese patient is of little clinical utility.

Positional therapy is an option for patients with abnormal breathing isolated to a single position. Avoiding that position will then allow normal nocturnal respiration. This positional response should be documented by formal polysomnography. A wedge pillow can also be added to CPAP therapy to decrease the pressure requirement.

Supplemental oxygen alone is typically ineffective in treating the respiratory events and may actually prolong the duration of

TABLE 13.6 Methods to Improve Positive Airway Pressure Compliance

Patient education
Family education
Telephone follow-up
Objective compliance monitoring
Regular clinic visits
Early treatment of problems with CPAP

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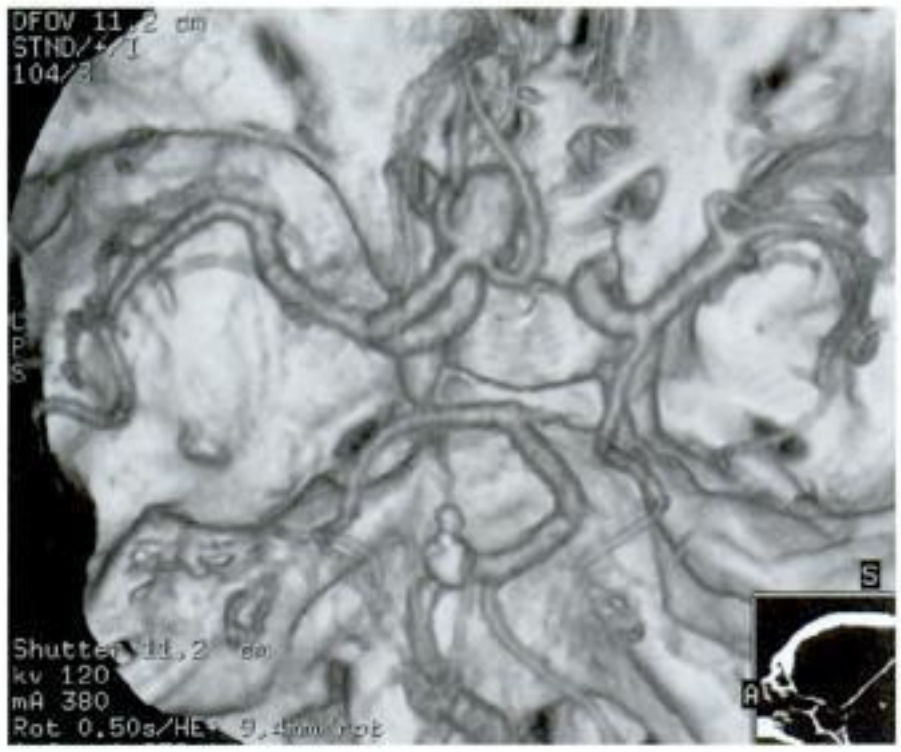

FIGURE 15.3. Three-dimensional reconstruction of a CT-angiogram (superior view). This broad-necked, anterior communicating artery aneurysm was found during the workup for headaches. It is fed by a dominant left A1 segment and there is a hypoplastic right A1 segment.

carried a 52% to 86% mortality rate. A major challenge in evaluating patients with UIA is to determine the risk of rupture and its consequences on the patient's lifetime and to balance this with the risks associated with various treatment options. Understanding the natural history of UIA is therefore critical in this decision-making process.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) is a landmark study that has had an enormous impact on contemporary thoughts about the natural history of UIA and the risks associated with prophylactic intervention. In the first report, the study included both a retrospective and prospective component based on 2,621 enrolled patients from 53 participating centers from across the world. In the retrospective component, the natural history of UIA was evaluated and 1,449 patients (with 1,937 aneurysms) were enrolled and divided into two groups. Group 1 was composed of 727 patients with no history of prior SAH and Group 2 consisted of 722 patients with a history of SAH from a different aneurysm that had been repaired successfully. The data obtained from this component are summarized in Table 15.1. A main point emanating from the data is that small aneurysms in the anterior circulation in patients with no prior history of SAH appear to have an extremely low rate of annual rupture.

In the prospective component of this study, treatment-related morbidity and mortality were evaluated in 1,172 patients in whom UIAs had been newly diagnosed. These patients were divided into two groups as before (those with and without a prior history of SAH). Results from the prospective component are summarized in Table 15.2. The overall morbidity and mortality at 1 year was 15.7% in Group 1 patients and 13.1% in Group 2 patients (including neurocognitive outcomes). The only significant predictor of poor surgical outcome was increasing age, as there was insufficient power to examine other potential predictors such as aneurysm location and size. In addition, insufficient numbers of patients were treated with endovascular techniques to allow meaningful analyses.

TABLE 15.1 ISUIA (1998) Retrospective Component

Group I (No prior history of SAH) (n = 727)	**Group II** (History of SAH) (n = 722)
Rates of Rupture	**Rates of Rupture**
<10 mm: 0.05%/y	<10 mm: 0.5%/y
>10 mm: ~1%/y	>10 mm: ~1%/y
>25 mm: 6% in first year	>25 mm: insufficient data (n = 3)
Predictors of Rupture	**Predictors of Rupture**
Increasing size	Location (basilar tip)
Location (basilar tip, posterior cerebral artery, posterior communicating artery)	Older age

ISUIA, International Study of Unruptured Intracranial Aneurysms; SAH, subarachnoid hemorrhage.

The low rates of rupture for certain aneurysms (small, anterior circulation aneurysms in patients with no prior history of SAH) found in the retrospective component were met with some skepticism. Many ruptured aneurysms treated were <10 mm and the patients included in the retrospective study were those who were seen between 1970 and 1991 and they had not received treatment for their aneurysm. The possibility of surgical selection bias arose (as the study population enrolled represented only 40% of the patients with UIAs evaluated at participating centers during that same period). Some patients obviously were treated during that period, creating the possibility that the nontreated study group was composed of those patients left after surgical selection. Nevertheless, this study represented a seminal contribution and the best study to date.

The second phase of ISUIA was reported 5 years later. Four thousand and sixty patients were enrolled prospectively from those who were evaluated at participating centers between 1991 and 1998. One thousand six hundred and ninety-two patients did not have aneurysmal repair, 1,917 patients had open surgery, and 451 patients underwent endovascular procedures. A summary of the rupture rates for aneurysms that were not treated can be found in Table 15.3. The combined morbidity and mortality associated with

TABLE 15.2 ISUIA (1998) Prospective Component

Group I (No prior history of SAH) (n = 961)	Group II (History of SAH) (n = 211)
Treatment modality	Treatment modality
Surgery: 798 (83%)	Surgery: 198 (94%)
Endovascular: 163 (17%)	Endovascular: 13 (6%)
Overall morbidity and mortality	Overall morbidity and mortality
At 1 mo – 17.5%	At 1 mo: 13.6%
At 1 y: 15.7%	At 1 y: 13.1%
Predictor of poor surgical outcome: age	Predictor of poor surgical outcome: age

ISUIA, International Study of Unruptured Intracranial Aneurysms; SAH, subarachnoid hemorrhage.

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Considerable progress has been made over the last decade in noninvasive imaging techniques, in the understanding of the natural history of UIA, in treatment options for UIA (particularly with endovascular therapy), and in delineation of the actual risks (including cognitive morbidity) associated with treatment. However, additional work is still needed in the area of UIA that will hopefully translate into improved outcomes for patients harboring UIA.

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CM, hemorrhage from these lesions is unlikely to cause catastrophic neurological deficits. Not unusually, patients complain of subacute onset of tedious, persistent, lateralizing headache. A significant number of lesions are discovered incidentally in the course of investigations done for a variety of reasons. In the brainstem and spinal cord, the acute/subacute onset of a neurological deficit with or without headache is the most common presentation. This is usually related to intra- or extracapsular hemorrhage.

The natural history of CMs is related to the mode of presentation and lesion location. The risk of hemorrhage is significantly higher after a first hemorrhagic episode. In a series of 122 patients with CMs followed up for a mean of 34 months, the hemorrhage rate was 0.6% per year in patients with incidental lesions. It was much higher (4.5% per year) in those with a prior history of hemorrhage. The risk of recurrent hemorrhage is higher in patients with blood dissecting and violating the capsule of the CM and extending in the surrounding brain parenchyma. In such patients, there seems to be a temporal clustering of rebleedings in the first 2 years following the first hemorrhagic episode. Symptomatic hemorrhages are not uncommon in the brainstem, basal ganglia, and spinal cord. Given the eloquence of such areas, even very small volumetric increases in size may become symptomatic.

The diagnosis of CMs is based on their typical MRI appearance (see Fig. 16.1). On T2-weighted sequences, CMs display a hypointense rim consisting of a hemosiderin ring and a heterogeneous hyperintense internal core representing the endothelial caverns filled with blood of different ages. Zabramski et al. have divided CMs in four different types based on their MRI characteristics, which relate to different pathological states. On CT, CMs appear as hyperdense lesions because of hemorrhage or calcifications. Cerebral angiography is not necessary for diagnosis. These lesions are not usually visualized on conventional catheter angiography, hence the past definition of occult or cryptic vascular malformations.

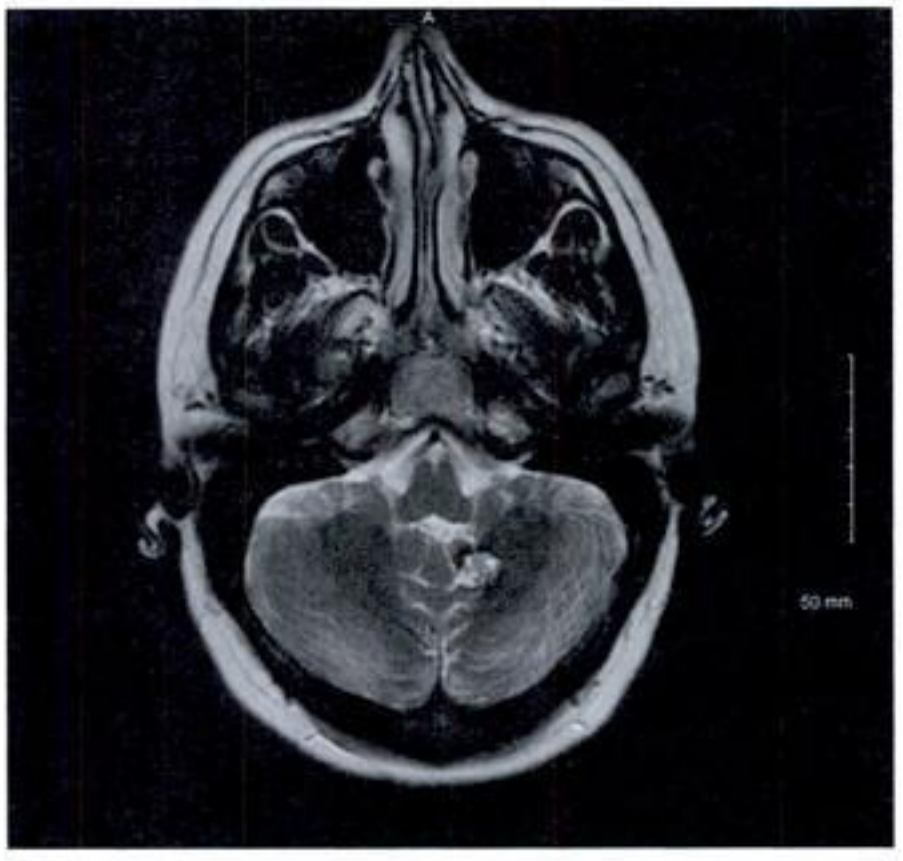

FIGURE 16.1. Characteristic T2-weighted magnetic resonance image (MRI) depicting incidentally discovered vermian cavernous malformation (CM) with hypointense hemosiderin rim and hyperintense core.

Developmental Venous Anomalies

Similar to CMs, a multiplicity of terms has been employed in the literature to define DVAs. These various names have stressed particular aspects of the same clinical entity: their angiographic appearance (*caput medusae, star cluster*), the anatomic/pathological features (*medullary venous malformation*), and their non-neoplastic nature (*venous angioma* and *venous malformation*). *DVA* is a term introduced by Lasjaunias in 1986 in an attempt to indicate their congenital origin and the lack of malformed venous elements. This is the currently recommended term and the one adopted in this chapter.

DVAs represent congenital cerebrovascular anomalies with mature venous vessel walls that lack arterial or capillary elements. They are composed of radially arranged, dilated medullary veins, which converge into an enlarged, transcortical or subependymal, draining vein. These collateral venous channels coalesce to form a physiologically normal venous outflow tract and are separated by intervening normal neuropil. In this context, DVAs may be viewed as extreme anatomic variants of medullary venous drainage. DVAs are most commonly solitary, but may be multiple. They are located at the junction of superficial and deep venous systems, adjacent to the cortical surface or near the ependymal surface of the ventricles. Two thirds are supratentorial and one third infratentorial.

DVAs were once thought to be rare lesions. Current literature though supports that DVAs are the most commonly identified intracranial vascular malformation (63% and 50% of all malformations in autopsy and MRI series, respectively). Their cited prevalence in retrospective imaging and autopsy studies is 0.5% to 0.7% and 2.6%, respectively. There is no gender preference. Initial diagnosis is usually established in the fourth and fifth decades. There is no familial aggregation and a recent report identifies a distinct (from CMs) genetic origin.

Historically, DVAs were diagnosed by their characteristic appearance on cerebral angiography. The pathognomonic angiographic appearance is visualized entirely during the late venous phase and consists of wedge- or umbrella-shaped collections of dilated medullary veins (caput medusae) converging into an enlarged transcortical/subependymal collector vein. DVAs are rarely identified on noncontrast enhanced CT, unless they are associated with a CM. Contrast-enhanced MRI is currently the imaging modality of choice. DVAs exhibit strong enhancement, with stellate, tubular vessels converging into a collector vein, which drains into a dural sinus or ependymal vein (see Fig. 16.2).

In the pre-MRI era, DVAs were considered an underestimated cause of intracerebral hemorrhage (ICH). Up to 43% of DVAs were thought to eventually lead to ICH, especially when infratentorial and encountered in young patients. For this reason, aggressive surgical management was pursued. Unfortunately, surgical excision led to disastrous postoperative complications due to venous infarction and cerebral edema after excision of the DVA. With the introduction of MRI, it has become evident that most, if not all, of the ICHs that were once attributed to DVAs are indeed related to an associated CM. Resection of the CM alone, with sparing of the associated DVA, is sufficient to prevent further hemorrhage. Thus, the previously reported high morbidity of DVAs is now accounted for by the coexistence of the angiographically occult CM that might have been unidentified before the advent of MRI. It is strongly suggested that if a patient with a known DVA presents with ICH, a second lesion should be sought.

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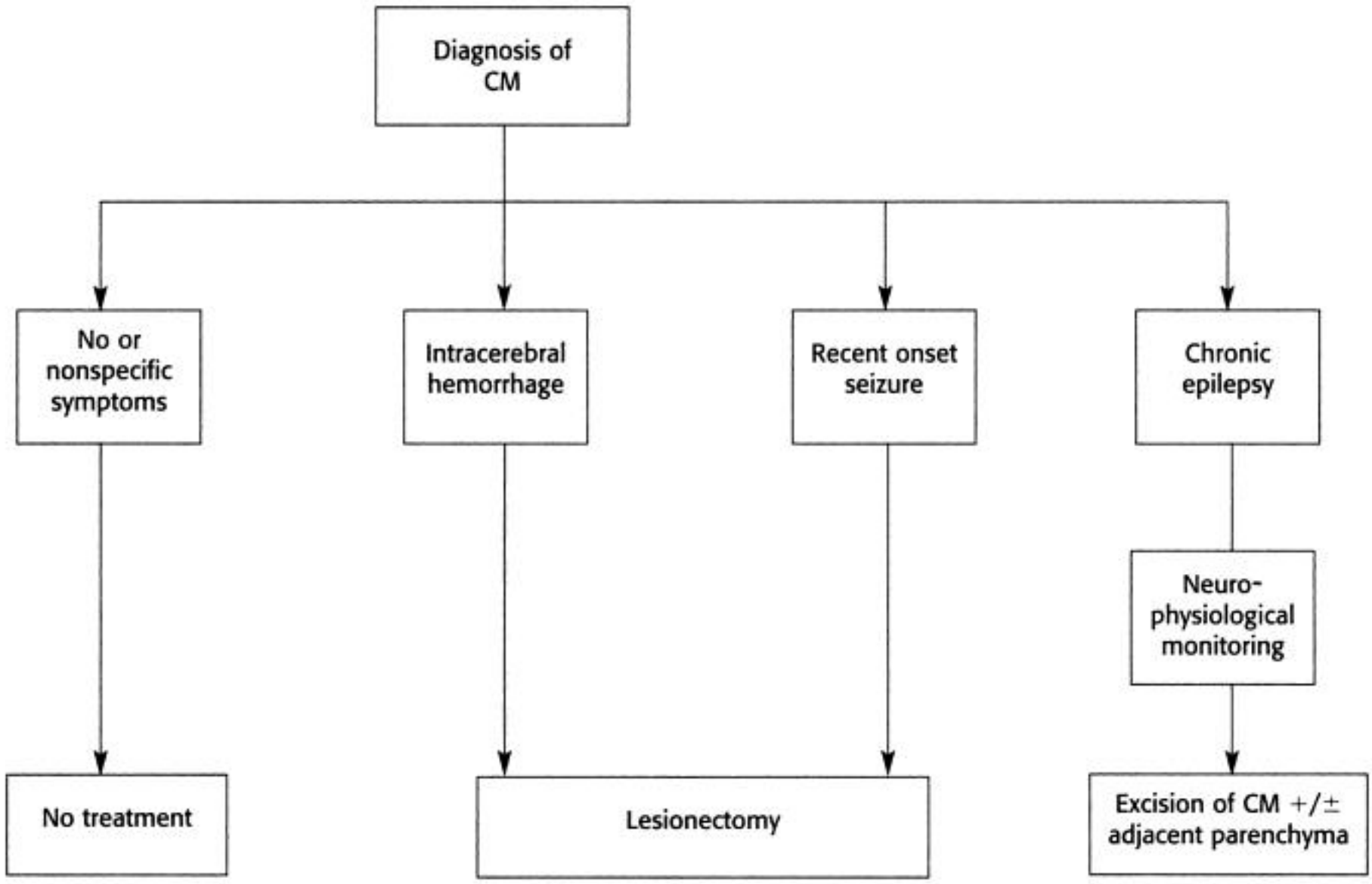
CRITICAL PATHWAY
Diagnosis of Cavernous Malformations



CM, cavernous malformations.

CHAPTER

17 Stroke in Pregnancy

DARA G. JAMIESON

OBJECTIVES

- How can stroke be prevented in women?
- What is the risk of stroke in pregnancy?
- How can cerebrovascular disease be prevented and treated in women?

Stroke is a major cause of death and disability in women, with greatest risk in the later decades of life. According to the 2006 report of the American Heart Association, each year about 46,000 more women than men have a stroke. The differential stroke risk between men and women changes with age. More boys than girls have strokes, and incidence of stroke is greater in men in their 60s and 70s, but stroke is more common in women after age 80 years. Because women live longer than men, more women than men die of stroke each year. Women accounted for 61% of all stroke deaths in 2003.

While women share many of the same stroke risk factors as men, hormonal changes such as pregnancy increase a woman's risk of stroke. Stroke in pregnancy may be specifically related to the pregnancy or it can be due to an unrelated superimposed condition. Causes of stroke are generally the same in men and women but some types of strokes found in both, such as cerebral venous thrombosis (CVT) and subarachnoid hemorrhage (SAH), are more commonly seen in women. Prevention of stroke in pregnancy begins with recognition and treatment of modifiable stroke risk factors prior to pregnancy. The most obvious, but rather impractical, way to prevent stroke associated with pregnancy is to avoid pregnancy. Barrier methods of contraception are essentially risk-free, but hormonal manipulation to prevent pregnancy may pose its own cerebrovascular risk. Prevention of stroke in women in general is outlined in this chapter with the realization that although some features of antiplatelet therapy are unique to women the majority of stroke risk reduction strategies are not gender-specific. The increased risk of stroke associated with pregnancy is reviewed in relation to ways of preventing and treating in women during and after their pregnancies.

STROKE IN WOMEN

In 2006, a National Institute of Neurological Disorders and Stroke (NINDS) sponsored multidisciplinary working group published an overview of our current understanding of the role of estrogen, both endogenous and exogenous, in stroke risk, as well as recommendations for future investigation. Exogenous hormones, oral contraceptives, or hormone replacement therapy increases the risk of venous thrombosis, especially in women with underlying coagulation abnormalities. The factor V Leiden and the prothrombin 20210A gene mutations are especially common and are associated with thrombosis, including CVT. In the setting of a right-to-left cardiac shunt, these thrombophilias, which are generally not associated with intra-arterial thrombosis, can lead to ischemic stroke. The risk appears greatest during the first year of treatment with exogenous hormones.

Diseases more prevalent in women may be associated with stroke risk. Approximately 21 million American women have migraine headaches. The Women's Health Study (WHS) analyzed the correlation between migraine of different types and vascular events. Migraine with aura was found to increase the risk of ischemic stroke, as well as myocardial infarction (MI), coronary revascularization, and angina. Migraine without aura and nonmigraine headaches were not associated with increased vascular risk.

Oral Contraception

While the correlation between oral contraceptives and stroke risk has been debated for decades, the evidence for an association, independent of traditional vascular risk factors, is not clear. The oral contraceptives in current use have lower doses of estrogen than in the earlier studies that showed increased risk. Meta-analyses of studies published up to 2000 (with patient data collection up to 1995) reported variable risk depending on study design, with risk found with case–control, but not cohort, studies. Doses of estrogen >50 μg were associated with greater risk than lower dosages. The absolute risk was noted to be low, with only an additional 4.1 ischemic strokes per 100,000 nonsmoking, normotensive women using low-dose estrogen oral contraceptives.

A population-based cohort study in the Netherlands, the Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study, reported that current oral contraceptive use was associated with a risk of stroke twice that of nonusers (OR 2.1; 95% CI, 1.5 to 3.1), even with risk factor adjustment. Smoking, hypertension, hypercholesterolemia, diabetes, and obesity conferred significantly increased risk in combination with oral contraception.

Thrombophilias, specifically factor V Leiden and the G20210A mutation for the prothrombin gene, increase the risk of CVT with oral contraceptives. Ischemic stroke risk, in association with oral contraceptives, has also been shown to be increased with factor V Leiden and methylenetetrahydrofolate reductase (MTHFR) 677TT polymorphism.

Pregnancy

The risk of stroke, both ischemic and hemorrhagic, in pregnancy is unclear with estimates in the range of 4 to 11 cerebral infarctions and 5 to 9 hemorrhagic strokes per 100,000 births. Greater risk of cerebral infarction and hemorrhagic stroke is found in the postpartum period as compared to the prepartum trimesters. Stroke risk associated with pregnancy is discussed in more detail below.

Menopause

The increase stroke risk in postmenopausal woman appears to be due to a combination of age and hormonal changes with decreasing estrogen levels. Primary prevention studies have not shown benefit with hormone replacement therapy (HRT). Some primary and secondary prevention trials have suggested that HRT may increase the risk of cerebrovascular events. The Women's Health Initiative (WHI) found a 44% increased incidence in ischemic, but not hemorrhagic, stroke with estrogen plus progestin treatment of healthy women who were on average a decade into menopause. In women in WHI who were treated with estrogen alone, because of prior hysterectomy, ischemic stroke risk was increased by 39%. In women with increased vascular risk due to coronary heart disease, HRT offered no protection against ischemic stroke, as found in the Heart and Estrogen/Progestin Replacement study. A nested case–control study of >158,000 women, aged 50 to 69 years, in the United Kingdom General Practice Research Database, found that a combined odds ratio for transient ischemic attack (TIA), ischemic stroke, and hemorrhagic stroke associated with the use of HRT was 1.34 (95% CI, 1.11 to 1.61) with individual statistical significance for TIA only. The increased TIA risk was dependent on an increased dose of estrogen and oral delivery. The data suggested increased risk during the first year of treatment. Estrogen supplementation has not been shown of benefit in secondary stroke prevention. The Women's Estrogen for Stroke Trial (WEST) was a randomized placebo-controlled trial of women with prior TIA or ischemic stroke to study if 17β-estradiol reduced the rate of recurrent stroke. The results showed that estrogen alone had no overall benefit in preventing recurrent stroke of fatality, but there was an increase in the overall stroke rate in the first 6 months of treatment. The estrogen-treated women with nonfatal strokes had worse neurological deficits compared to women with strokes in the placebo group.

STROKE PREVENTION IN WOMEN

Almost all recommendations for primary and secondary stroke prevention apply equally to both men and women. Lifestyle issues, long recognized for their role in cardiovascular disease, have recently been evaluated in women as risk factors for hemorrhagic and ischemic stroke. In general, the same lifestyle advocated for decrease in cardiovascular risk benefits cerebrovascular risk. Kurth et al. (2006) used data from the WHS of almost 38,000 healthy female health professionals aged 45 years and older to look at lifestyle and weight as risk factors for stroke. A composite healthy lifestyle was associated with a significantly reduced total and ischemic stroke risk, but not hemorrhagic stroke risk (see Table 17.1). The association was apparent even after controlling for hypertension, diabetes, and elevated cholesterol. Analysis of the individual components of the healthy lifestyle showed substantial reduction of stroke risk in nonsmokers and women with lower body mass indices. The associations with alcohol consumption and physical activity were weaker. The healthier diet paradoxically increased risk of ischemic and hemorrhagic stroke, but the overall risk outcomes were unchanged with removal of diet data. Obesity is a strong risk factor for ischemic stroke, with a less clear relationship with hemorrhagic stroke. The Northern Manhattan Stroke Study found that waist-to-hip ratio measurement of abdominal fat predicted ischemic stroke risk, especially in young people. In the WHS there was a statistically significant trend for increased risk of total and ischemic stroke with increasing body mass index.

TABLE 17.1 Healthy Lifestyle for Women

- Abstinence from smoking
- Body mass index <22 kg per m^2
- Exercise ≥4 times per wk
- Alcohol consumption of 4 to 10.5 drinks/wk
- Diet high in cereal fiber, folate, omega-3 fatty acids; high polyunsaturated to saturated fat ratio; low in *trans* fat; low in glycemic load

As defined in the Women's Health Study.

Women have different degrees of risk reduction with medical and surgical therapy for stroke prevention. Women may respond differently to aspirin therapy than men, at least in primary prevention. Women appear to benefit from aspirin for prevention of a first stroke, an effect not as striking in men. The WHS, the first primary prevention trial of aspirin therapy specific to women, found that low dose aspirin (100 mg every other day) protected women against a first stroke, but generally offered no protection against MI and vascular death. Women aged 65 years and older accounted for only 10% of the WHS population but experienced 31% of the major cardiovascular events in the trial. An older subgroup did show a significant benefit from aspirin in the prevention of primary cardiovascular events, including ischemic stroke, and MI. A sex-specific meta-analysis of aspirin therapy for the primary prevention of cardiovascular events evaluated studies of aspirin in over 95,000 individuals, including 51,342 women. The analysis noted that the women had relatively few MIs but increased strokes, as compared to men. Aspirin therapy was associated with a 24% reduced rate of ischemic stroke (OR 0.76; 95% CI, 0.63 to 0.93; $p = 0.02$), with no apparent effect on hemorrhagic stroke in women.

PREGNANCY AND STROKE

Ischemic Stroke and Intracerebral Hemorrhage in Pregnancy

Kittner et al. (1996) reviewed data from the Baltimore–Washington Cooperative Young Stroke Study, a hospital-based registry initiated to study the incidence and causes of stroke in young adults. All female patients aged 15 through 44 years who were discharged from 46 hospitals in the central Maryland and the Washington, D.C.,

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secondary hemorrhage. Primary hemorrhagic stroke and other types of intracranial hemorrhages (ICHs) that tend to affect near-term and term infants tend to be associated with specific risk factors. Periventricular hemorrhagic infarction (PVHI), a lesion that mainly affects preterm infants, is a serious complication of germinal matrix–intraventricular hemorrhage. Although these lesions tend to have significant overlap in terms of being hemorrhagic or ischemic, the results may very widely from immediate or eventual death to other long-term consequences, including the effects of these types of events on the neonate may result in immediate or eventual death with other long-term complications including cerebral palsy, epilepsy, blindness, behavioral disturbances, and cognitive dysfunction. Despite the type of lesion, symptoms may be subtle and are often nonspecific. The acute and chronic manifestations of perinatal stroke are reviewed in Table 18.1.

Hemorrhage

Primary hemorrhagic stroke and other types of ICH include subdural, primary subarachnoid, intracerebellar, and intraventricular hemorrhage (IVH), and other miscellaneous types such as focal hemorrhages into the thalamus, basal ganglia, brainstem, or spinal cord. Figure 18.1 shows a hemorrhage in the thalamic region on computed tomography (CT). In general, primary subarachnoid hemorrhages are more frequently seen in the premature infant but tend to be clinically benign, in contrast to intracerebellar hemorrhages that, although also more frequently observed in premature infants, tend to be serious. Subdural and other miscellaneous types of hemorrhages tend to affect full-term infants, and their outcome is variable. Although IVHs tend to predominately occur in premature infants (discussed later), they have been reported to occur in term infants as well. Most of these types of hemorrhages tends

TABLE 18.1 The Acute and Chronic Manifestations of Perinatal Stroke

Signs of Acute Stroke
Seizures
Apnea
Encephalopathy
Poor feeding
Thrombocytopenia
Anemia
Focal neurological symptoms–typically difficult to identify
Murmurs, bruits, tachypnea–absent distal pulses may suggest cardiac anomalies
Skin lesions–may suggest infections or embolic disease
Placental thrombosis–may suggest infectious or embolic disease
Signs of Chronic Infarction
Cerebral palsy
Epilepsy
Cognitive dysfunction
Early hand preference may be indicative of hemiparesis
Abnormal head circumference
Delayed milestones
Hemiparesis
Language dysfunction
Cognitive impairments
Behavioral problems

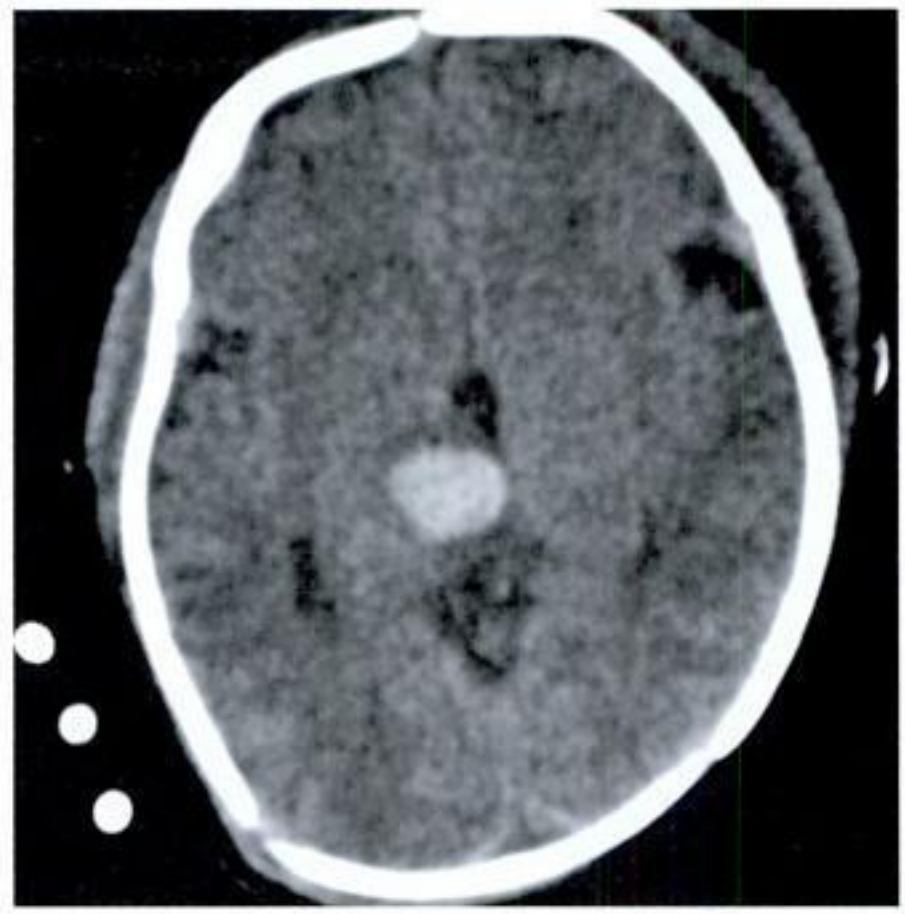


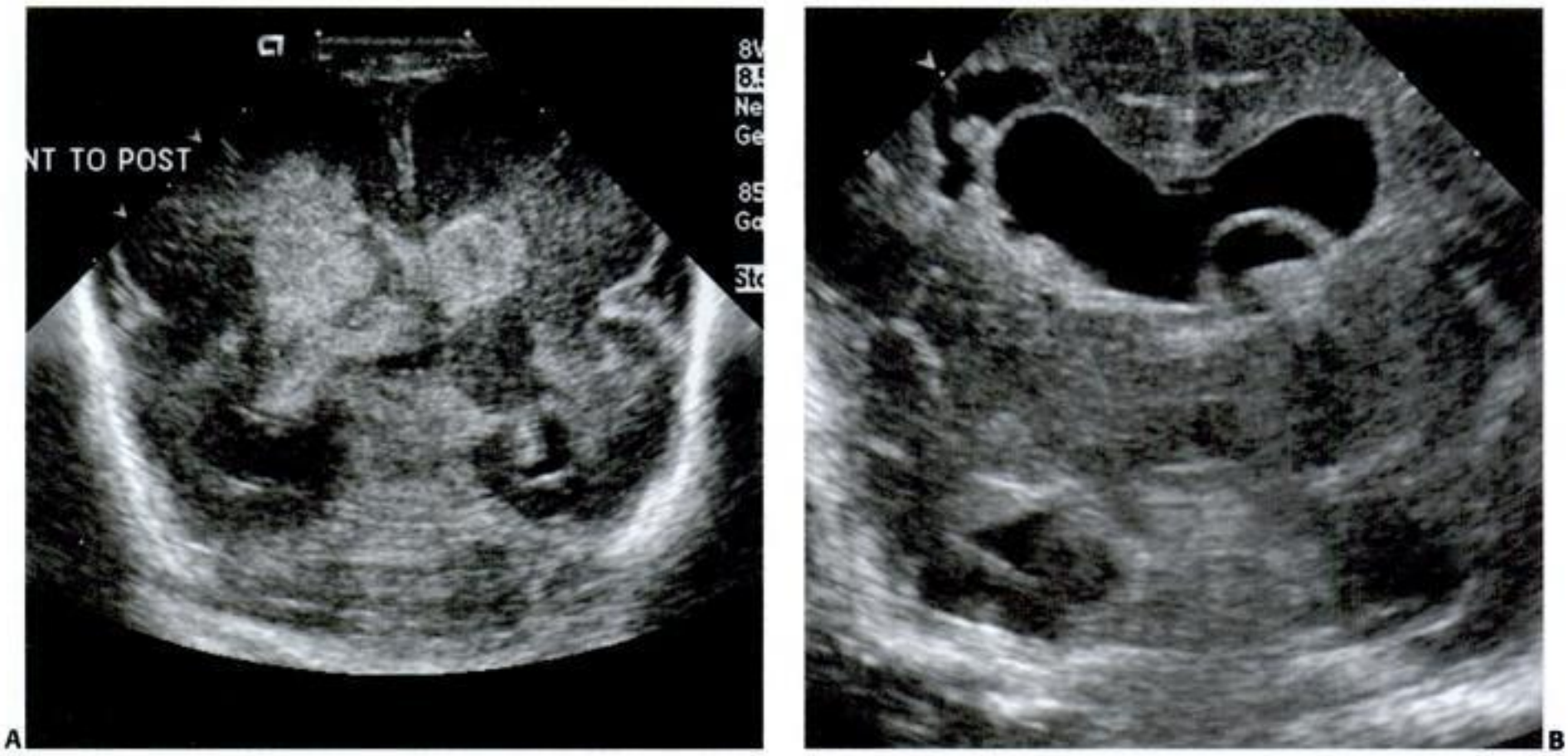
FIGURE 18.1. Computed tomography of the head with a right thalamic hemorrhage. There is also some apparent hypodensity in the right hemisphere.

to be antepartum or occur during the stresses of delivery and are associated with specific risk factors as outlined in Table 18.2.

PVHI usually accompanies a large germinal matrix-IVH. Figure 18.2 illustrates examples of PVHI. The current understanding is that this type of lesion is a venous hemorrhagic infarct in the drainage area of the periventricular terminal vein—a complication mainly associated with prematurity. A recent study found that 1% of infants weighing <2,500 g met the diagnostic criteria for PVHI, with the highest percentage (9.9%) being those weighing

TABLE 18.2 Causes of Perinatal Intracranial Hemorrhage

Coagulation factor deficiencies
Factor V deficiency
Factor X deficiency
Congenital fibrinogen deficiency
Hemophilia (factors VIII and IX)
Hyperhomocystinemia
Hypoprothrombinemia
Alloimmune thrombocytopenia
Vitamin K deficiency
Birth asphyxia
Congenital arterial aneurysm
Arteriovenous malformation
Coarctation of the aorta
Cerebral tumor
Extracorporeal membrane oxygenation
Maternal factors
Idiopathic thrombocytopenic purpura
Warfarin use
Substance abuse
von Willebrand's disease



A B

FIGURES 18.2 A AND B. Ultrasonography with periventricular hemorrhagic infarction.

<750 g. Intrapartum risk factors associated with the development of PVHI include emergent cesarean section, low Apgar scores, and need for respiratory resuscitation, while postnatal factors include pneumothorax, pulmonary hemorrhage, patent ductus arteriosus, acidosis, hypotension requiring pressure support, and significant hypercarbia. Although an exact cause–effect relationship of these risk factors and correct knowledge of when these events occur have been difficult to prove, it is felt that disturbances in systemic and cerebral hemodynamics occurring around the intrapartum and early neonatal period are important in the development of PVHI.

Perinatal Arterial Ischemic Stroke

PAS, occurring more frequently in the near-term and term infant, has a prevalence ranging from 17 to 93 per 100,000 live births. Most lesions occur in the left hemisphere within the distribution of the middle cerebral artery. Rarely, multifocal lesions occur but tend to be embolic in origin. The difficulty with identifying PAS in the neonate is that symptoms tend to be nonspecific and are often difficult to identify. In many cases, the symptoms may not become evident until quite some time after the stroke. The acute and chronic manifestations of PAS are reviewed in Table 18.1. Figure 18.3 reveals a multifocal infarction on diffusion-weighted magnetic resonance imaging (MRI) involving the pons and temporal lobe.

There has been a wide range of risk factors that have been implicated in the etiology of PAS. These are listed in Table 18.3. However, some studies report no finding of an obvious precipitating event in as many as 25% to 77% of cases. The difficulty with identifying a specific risk factor for the development of the lesion is that neonates often have multiple risk factors, making it likely that a combination of environmental risk factors interacting with genetic vulnerabilities is often responsible for the ischemic event.

The exact role of genetic thrombophilias in the pathogenesis of PAS is yet to be defined, but disorders such as factor V Leiden mutation, the prothrombin 20210 promoter mutation, hyperhomocystinemia, elevated lipoprotein (a) levels, antiphospholipid antibodies, and relative protein C deficiency have been described with increased frequency in infants who have PAS when compared with healthy control subjects. Other genetic thrombophilias have also been implicated and are provided in Table 18.3. Further studies are required to better define the potential role of infantile thrombophilia in the pathogenesis and outcome of PAS but experts in the field do recommend a comprehensive thrombophilia

FIGURE 18.3. Axial diffusion-weighted images, $b = 1{,}000$, demonstrate multiple areas of high signal in the left temporo-occipital lobe, left thalamus, and left pons.

TABLE 18.3 Risk Factors Associated with Perinatal Arterial Ischemic Stroke

Male sex
African-American race
Oligohydramnios
Chorioamnionitis
Prolonged rupture of membranes
Birth trauma
Birth asphyxia
Cesarean delivery
Congenital heart disease
Bacterial meningitis
Anemia
Polycythemia (hyperviscosity)
Hereditary endotheliopathy with retinopathy, nephropathy, and stroke
Inherited or acquired prothrombotic disorders
Factor V Leiden mutation
Prothrombin 20210 promoter mutation
Hyperhomocysteinemia
Elevated lipoprotein (a)
Antiphospholipid antibody syndrome
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Methylenetetrahydrofolate reductase deficiency
Maternal factors
Primiparity
History of infertility
Maternal diabetes
Pre-eclampsia

assessment for all infants presenting with PAS, regardless of other risk factors present.

Management of PAS is mainly supportive. Current guidelines from the American College of Chest Physicians suggest that neonates with proven cardioembolic stroke should receive treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). The guidelines do not recommend anticoagulant therapy for neonates with noncardioembolic stroke. However, the guidelines do not mention whether the number of blood vessels affected should be taken into consideration or whether noncardiac-related embolism warrants anticoagulation. In addition, there is a lack of information on how to properly anticoagulate neonates who are found to have a genetic thrombophilia.

Sinovenous Thrombosis

Most cases of sinovenous thrombosis occur in term infants and present with nonspecific clinical features as listed in Table 18.1. The superficial and lateral sinuses are most frequently involved and venous infarction has been reported in up to 30% of cases. Figure 18.4 reveals a normal magnetic resonance venogram (MRV). Risk factors for the development of sinovenous thrombosis are similar to those for PAS and are listed in Table 18.3, although a significant number of cases are reported as idiopathic. Management of neonates with sinovenous thrombosis is controversial and is limited by the fact that there are no current clinical trials evaluating the use of anticoagulation. Current guidelines from the American College of Chest Physicians recommend the use of either LMWH or UFH only for neonates with sinovenous thrombosis but without large ischemic infarctions or evidence of intracerebral hemorrhage due to the theoretical risk of bleeding. Radiological monitoring and initiation of anticoagulation only if extension occurs is recommended for the remainder of cases.

Pediatric and Young Adult

Arterial Ischemic Stroke

Arterial ischemic stroke can be related to a number of vascular, hematologic, cardiac, and metabolic risk factors. Potential causes of ischemic stroke in children are presented in Table 18.4.

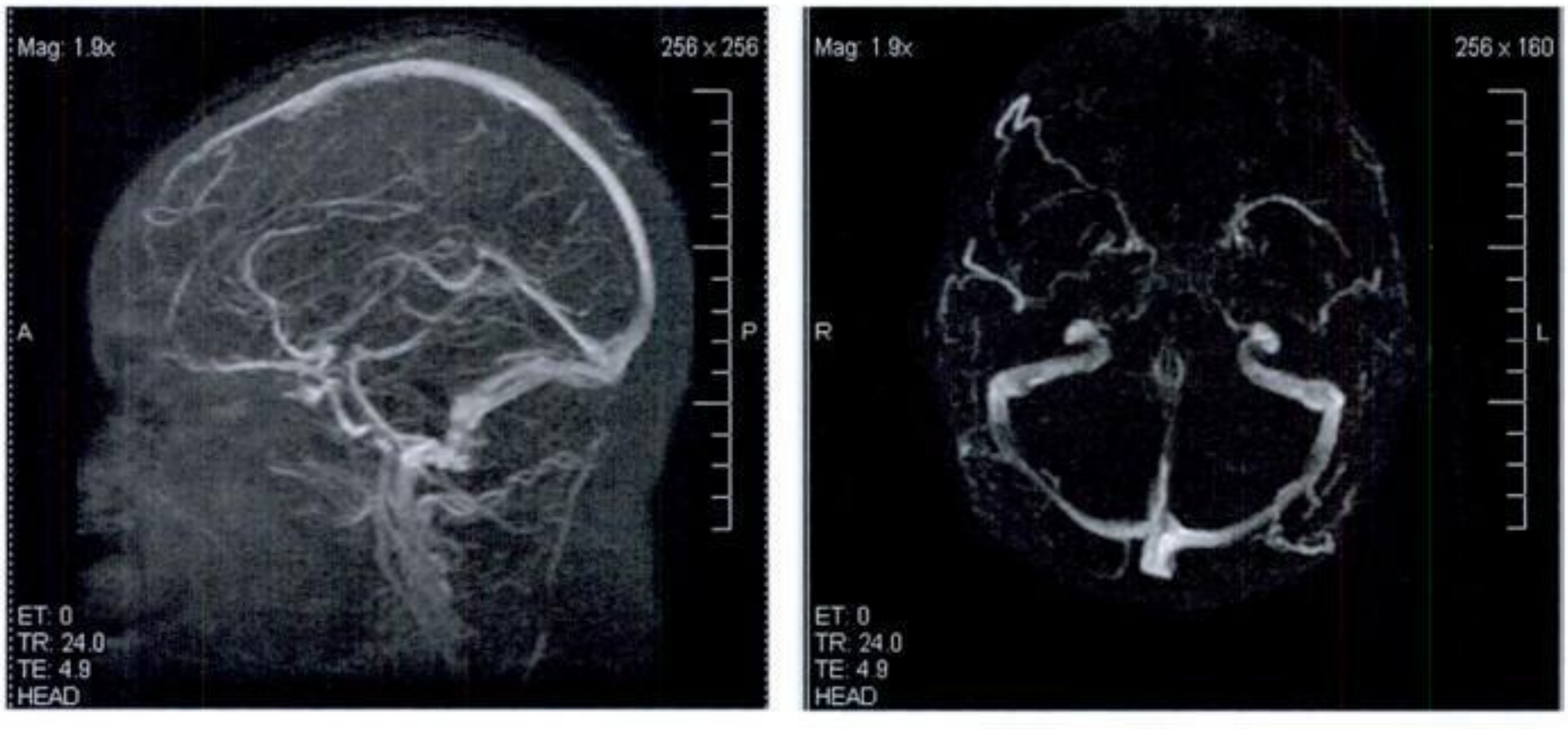


FIGURE 18.4. Magnetic resonance venogram in a healthy individual.

TABLE 18.4 Causes of Ischemic Stroke in Children and Young Adults

1. Vascular dissection (trauma, strangulation, arthritis)
2. Moya-moya disease (large vessel occlusions)
3. Fibromuscular dysplasia
4. Vasculitis
   a. Infectious
   b. Necrotizing
      (1) PAN, Wegener syndrome, Churg-Strauss syndrome, lymphomatosis
   c. Collagen vascular disease
      (1) SLE, RA, Sjögren's disease, scleroderma
   d. Systemic disease
      (1) Behçet's disease, sarcoid, ulcerative colitis
   e. Giant-cell arteritis
      (1) Takayasu syndrome, temporal
   f. Hypersensitivity (drug, chemical)
   g. Neoplastic
   h. Primary CNS vasculitis
5. Migraine (diagnosis of exclusion)
6. Cardiac embolism, patent foramen ovale
7. Hypercoaguable state (primary)
   a. Antithrombin III deficiency
   b. Protein C deficiency
   c. Protein S deficiency
   e. Dysfibrinogenemia
   f. Factor XII deficiency
   g. Antiphospholipid antibodies
   h. Fibrinolytic abnormalities
   i. Activated protein C resistance, factor V Leiden mutation (gene on 1q23)
   j. Hyperhomocysteinemia (gene on 1q36)
   k. CADASIL (gene on 19p13)—Recurrent subcortical infarcts with spared U fibers
   l. MTHFR polymorphism
8. Hypercoaguable state (secondary)
   a. Malignancy
   b. Pregnancy
   c. Oral contraceptives
   d. Disseminated intravascular coagulation
   e. Nephrotic syndrome
   f. Dehydration
9. Platelet abnormalities
   a. Myeloproliferative disease
   b. Diabetes mellitus
   c. Heparin-induced thrombocytopenia
10. Rheology
    a. Homocystinuria (cystathione synthase deficiency)
    b. Polycythemia vera
    c. Sickle cell disease
    d. Thrombotic thrombocytopenia purpura
11. Hyperlipidemia
12. Connective tissue disease (Ehlers-Danlos syndrome, Menkes syndrome, homocystinuria)
13. Organic academia
14. Mitochondrial myopathy (MELAS)
15. Fabry's disease (a-galactosidase A deficiency)
16. Vasospasm (cocaine)

PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; CNS, central nervous system; CNS, central nervous system; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MTHFR, Methylenetetrahydrofolate reductase; MELAS, mitochondrial encephalopathy with lactic acidosis and strokelike.

Arterial dissection most commonly occurs after trauma. These injuries occur more frequently in boys than in girls. Traumatic dissection can result from head or cervical trauma, including whiplash, shaken baby, or intraoral trauma such as falling with a pencil in the mouth. Rarely, dissection occurs atraumatically from a connective tissue disease such as fibromuscular dysplasia (see Table 18.5). Diagnosis is made via characteristic findings on MRI and magnetic resonance angiography (MRA) of the head and neck, extracranial vascular ultrasound, or cerebral angiography. Findings of a double lumen, intimal flap, or bright crescent on T1 fat suppression images confirm the diagnosis. Also, the finding of occlusion or segmental narrowing of an artery within 6 weeks of a known trauma, or of vertebral artery occlusion at the C2 vertebral level even without trauma should raise the possibility of dissection. This is because the C1-2 vertebral level is the most common location for a vertebral artery dissection. Artery-to-artery embolism from the site of endothelial injury is the usual pathogenic mechanism for infarction. In one meta-analysis, 15% of posterior circulation and 5% of anterior circulation dissections were followed by recurrent ischemic events.

TABLE 18.5 Causes of Arterial Dissection

Traumatic
Head trauma
Cervical trauma, including whiplash, shaken baby
Intraoral trauma such as falling with a pencil (or popsicle) in the mouth
Trauma related to tonsillectomy
Nontraumatic
Fibromuscular dysplasia
Marfan Syndrome
Ehlers-Danlos syndrome
Klippel-Feil syndrome

Moya-Moya

Moya-moya is a vascular condition with risk of recurrent stroke. Primary moya-moya disease is an autosomal dominant disease most common in Japanese patients, hence the Japanese name meaning *puff of smoke*. This describes the angiographic blush that occurs because of extensive collateralization in response to occlusion of large intracranial arteries, often with bilateral carotid artery occlusion. Moya-moya syndrome can also occur secondary to sickle cell disease (SCD), Down syndrome, cranial radiation, or neurofibromatosis.

Vasculitis

Vasculitis is another source of stroke risk in the pediatric population. Primary vasculitides include those affecting large and medium vessels, such as Takayasu arteritis, and those affecting small vessels, such as primary central nervous system (CNS) angiitis and Wegener granulomatosis. Unique to children is the importance of secondary, postinfectious vasculitis. In one study of acute ischemic stroke, varicella zoster infection was detected in the preceding 12 months in 31% of children as opposed to 9% of healthy controls. Strokes typically involved the basal ganglia with typical vascular abnormalities of focal stenosis of the distal internal carotid and proximal segments of anterior cerebral (A1), middle cerebral (M1), and posterior cerebral (P1) arteries. Other pathogens including human immunodeficiency virus (HIV) and cytomegalovirus (CMV) may produce similar vasculitis and stroke risk. Radiation to the brain can also be a risk factor for secondary vasculitis.

Sickle Cell Disease

SCD is one of the most prevalent hematologic risk factors for pediatric stroke. An astounding 9% of patients with SCD will have an acute ischemic stroke by the age of 14, and approximately 20% will have MRI evidence of silent ischemic insults. Risk is greatest during the younger years (from 2 to 8), and two thirds of the patients will have a recurrent event if untreated. The sickled erythrocytes can cause thrombosis in large blood vessels or occlusion of small blood vessels leading to hypoperfusion in watershed areas. SCD is the only area of pediatric stroke for which clear evidence-based guidelines exist. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) trial in 1998 was aborted early due to a clear demonstration of 92% relative risk reduction in stroke with exchange transfusion for cerebral blood flow velocities >200 cm per second on transcranial Doppler. This has led to clear recommendations by the American Academy of Neurology for screening SCD patients with transcranial Doppler ultrasound. The frequency of screening has not been established. Sicklers with frequent transfusions are at risk for iron overload, and alternative therapies including hydroxyurea can also be considered in the long-term maintenance of patients with SCD.

Other Hematologic Conditions

Further hematologic variables relevant to ischemic stroke include high concentrations of lipoprotein A, protein C deficiency, and factor V Leiden mutation. These hypercoaguable states are most highly associated with risk of recurrent stroke. Other prothrombotic states include positivity for antiphospholipid antibodies including anticardiolipin antibodies and lupus anticoagulant, protein S deficiency, factor V Leiden mutation, prothrombin gene mutation (G20210A), and antithrombin III deficiency. Extensive discussion of each of these is beyond the scope of this chapter. Hyperviscosity or sludging effect can also be caused by dehydration, thrombocytosis, and polycythemia. Malignancies including leukemia and lymphoma can also create hypercoaguable states with increased risk of stroke. Several chemotherapeutic agents have also been implicated in cerebral infarction, including adriamycin, asparaginase, and methotrexate. Severe anemia, often seen in developing countries, can result in cerebral infarction secondary to the poor oxygen-carrying capacity.

Cardiac Risk Factors

Cardiac risk factors rise in importance in pediatric stroke relative to the adult population. Congenital heart disease is one of the major risk factors for stroke in pediatric patients. The Canadian Pediatric Ischemic Stroke Registry reported that 19% of children with arterial ischemic stroke had heart disease. The risk is particularly high during surgical procedures. Right-to-left shunting can lead to hypoxia and polycythemia, creating a hyperviscous state. Infective endocarditis additionally poses risk for embolic stroke, and patent foramen ovale (PFO) is a risk for thromboembolic strokes due to venous–arterial communication. PFO is three times more prevalent in pediatric stroke patients than in the general population.

Other etiologies to consider are toxic or iatrogenic sources such as cocaine or oral contraceptive pills. Metabolic sources of stroke risk include homocysteinuria, ornithine transcarbamylase deficiency, and mitochondrial encephalopathy with lactic acidosis and strokelike (MELAS) episodes. MELAS is a heritable mitochondrial disease that presents in childhood with proximal muscle weakness, episodic vomiting and lactic acidosis, migraine headaches, and strokelike episodes. The areas of infarction can be inconsistent with any single vascular distribution. Diagnosis is made by muscle biopsy finding ragged red fibers, and the disease is usually progressive. Hearing and visual loss may occur as well. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and hyperhomocyteinemia can lead to endothelial damage and platelet aggregation, which are treated with folate and vitamin B. Neurocutaneous diseases of childhood such as Sturge Weber and neurofibromatosis I can be associated with increased risk of stroke.

Hemorrhagic Stroke

Hemorrhagic stroke in children, in contrast to adults, occurs with a frequency equal to that of ischemic stroke. Trauma and bleeding diathesis are important risk factors for hemorrhagic stroke. Risk factors for hemorrhagic stroke are outlined in Table 18.6.

Aneurym in Subarachnoid Hemorrhage

Intracranial aneurysms are common in the general population. The prevalence of unruptured intracranial aneurysms has been largely determined through autopsy studies and through angiographic series. In adults, the prevalence ranges from 0.2% to 9%, with a

TABLE 18.6 Risk Factors for Hemorrhagic Stroke

Hypertension
Aneurysm
Infection
Autoimmune disorders
Vasculitis
Trauma
Surgery
Vascular malformations (see Fig. 18.5)
Telangiectasias
Sickle cell disease
Leukemia
Thrombocytopenia
Cocaine or amphetamine use
Ephedra
Warfarin
Antiplatelet agents
Alagille syndrome

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seizures and status with midazolam starting at 0.2 mg/kg/hour. However, the management of nonconvulsive status epilepticus is controversial.

Fever Control

Fever after ICH is common, particularly after IVH, and should be treated aggressively. Sustained fever after ICH has been shown to be independently associated with poor outcome, and even small temperature elevations have been shown to exacerbate neuronal injury and death in experimental models of ischemia. As a general standard, acetaminophen and cooling blankets should be given to all patients with sustained fever in excess of 38.3°C (101.0°F), but evidence for the efficacy of these interventions in neurological patients is meager. Newer adhesive surface cooling systems (Arctic Sun, Medivance, Inc.) and endovascular heat exchange catheters (Cool Line System, Alsius, Inc.) have been shown to be much more effective for maintaining normothermia. However, clinical trials are needed to determine whether these measures improve clinical outcome.

Nutrition

As is the case with all critically ill neurological patients, enteral feeding should be started within 48 hours to avoid protein catabolism and malnutrition. A small-bore nasoduodenal feeding tube may reduce the risk of aspiration events.

Ischemic Stroke

In ischemic stroke, maintaining normothermia, a temperature of 36°C to37°C, and normogylcemia is advisable (Hutchison). In general, the treatment guidelines suggested in *Chest* recommend UFH or LMWH for 5 to 7 days regardless of etiology, and the U.K. guidelines suggest aspirin 5 mg per kg immediately. Neither guideline recommends the use of alteplase. Specific situations merit further interventions (deVeber-c).

In patients with SCD, both guidelines suggest exchange transfusion to sickle hemoglobin (HbS) <30%, and intravenous hydration is indicated. Transcranial Doppler ultrasonography is used to screen periodically for increased cerebral flow suggesting need for exchange. Long-term therapy does carry a risk for iron overload, which may require chelation. Possible alternative therapies are hydroxyurea and bone marrow transplantation.

In patients without SCD, noninvasive arterial imaging of extracranial and intracranial arteries should be obtained. Carotid Doppler ultrasonography can quickly evaluate for dissection in suspected cases. Both guidelines recommend anticoagulation for 3 to 6 months after dissection. The *Chest* guidelines specify 5 to 7days of UFH or LMWH followed by LMWH or warfarin for 3 to 6 months, whereas the UK guidelines generally suggest anticoagulation for up to 6 months or until vessel healing.

CT angiography or MRA of the head and neck provide additional information about the patency of vessels and evidence of vasculitis. Vasculitis is usually acutely treated with steroids, with consideration for long-term immunosuppression. The *Chest* guidelines suggest aspirin 2 to 5 mg/kg/day after initial UFH or LMWH for 5 to 7 days in patients with other vasculopathies. The UK guidelines recommend continued aspirin 1 to 3 mg/kg/day after 5 mg per kg on the first day.

ECG should be obtained as soon as possible to evaluate for congenital heart disease and for evidence of a cardioembolic source. Both the guidelines support anticoagulation for cardiogenic embolism, and the *Chest* guidelines specify recommendations for UFH or LMWH for 5 to 7 days followed by LMWH or warfarin for 3 to 6 months.

For suspected cerebral sinus thrombosis— such as in patients with unexplained lethargy, seizure, or headache— MRI/MRV, CV, or cerebral angiography should be obtained. Both the guidelines suggest anticoagulation as therapy. The *Chest* guidelines specify UFH or LMWH for 5 to 7 days, then LMWH or warfarin with target INR 2 to 3 for 3 to 6 months.

PRACTICAL RECOMMENDATIONS

There is a paucity of evidence-based medicine to clearly direct our intervention. The general guidelines for evaluation and management are outlined in this chapter. The diagnosis requires a high level of clinical suspicion, and it is important for the clinician to be mindful of these possibilities.

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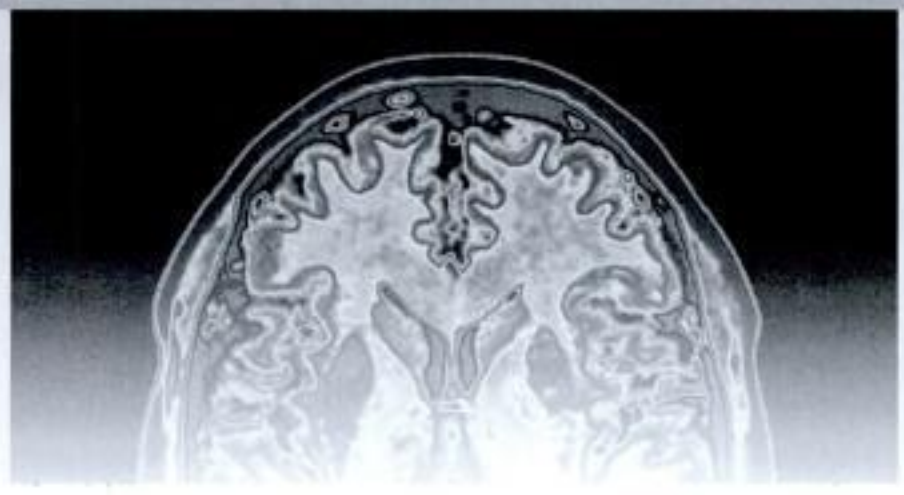
SECTION III



Urgent Stroke Management

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TABLE 19.7 Initial Assessment of Acute Hemorrhagic Stroke Patient in the Rapid Response Room

1. Assess ABCs and evaluate baseline vital signs, establish unresponsiveness.
2. Provide oxygen. Oxygen supplementation via nasal canula or non-rebreather mask should be used on patients with low oxygen saturation (<92%) (grade I) or nonhypoxemia (grade IIB) (2005 AHA guidelines).
3. Establish IV access and obtain blood samples including platelet count and coagulation studies, and blood type and screen. Start intravenous fluid (preferably normal saline).
4. Perform a neurologic screening assessment. Use the NIHSS or similar tool.
5. Obtain a stat CT scan of the brain without contrast.
6. Control systolic blood pressure.
7. Obtain a 12-lead ECG and portable chest x-ray. Do not delay CT scan to obtain these procedure and do not delay CT scan to treat hemodynamically stable patient with arrhythmia (2005 AHA guidelines).
8. Obtain neurosurgical and/or neurology consult to determine whether patient would benefit from surgical procedure. Include patient and/or his or her legal guardian on the decision-making process. Surgical procedure that need to be considered include craniotomy for removal of clot, prevention of herniation, or ventriculostomy.
9. Start seizure prophylaxis and mannitol (if there is mass effect on the CT scan of the brain). Reverse anticoagulation if needed.
10. Identify the etiology of the acute hemorrhage.
11. Admit to neurointensive care unit. Obtain stat repeat CT head with worsening of neurological status.

ABCs, airway/breathing/circulation; NIHSS, National Institute of Health Stroke Scale; electrocardiogram; IV, intravenous; CT, computed tomography.

Choice of Antihypertensive Agents in the Acute Hemorrhagic Stroke Setting Several studies showed safety and efficacy of the use of intravenous nicardipine in the acute setting of ICH.

Prognosis of the ICH

Poor predictors of the outcome include the following:

1. The Glasgow Coma Scale (GCS)
2. Volume of the hematoma: ICH volume can be estimated by selecting the largest area of hematoma on the CT scan of the brain and then multiplying the diameter of the hematoma in three dimensions and dividing by two. Patients with hematoma volume 0 to 29 had a mortality of 19%, 30 to 60 cm^3 had mortality of 46% to 74%, and >60 cm^3 had up to 91% mortality.
3. Intraventricular extension
4. Age (worse in patients older than 80 years)
5. Early hematoma growth
6. International normalized ratio (INR) level: INR level of 2.5 to 4.5 will increase risk of ICH by 10-fold.

Measurement and Management of Intracranial Pressure

Measurement of ICP is appropriate on ICH patients with rapid declining in mental status, stuporous or comatose. Other common management procedures in the acute ICH setting is elevation of the head of bed to 30 degrees and triple H therapy, which include hypervolemia (preferably normal saline), hyperventilation to pCO_2 of 28 to 32 mm Hg and hyperosmolarity by rapid IV mannitol 20% infusion.

Hemostatic Therapy

The eptacog alfa, which is a recombinant activated factor VII (rFVIIa) (Novoseven, NovoNordisk A/S), is currently used for patients with hemophilias. Study of use of this drug for hemostatic therapy in ICH patients with a normal coagulation system initially showed promising results, but the results of the next phase of the study were still not sufficient for FDA approval. A recent study showed the efficacy of this drug for the rapid reversal of INR in ICH patients who are taking coumadin.

Acute Hemorrhagic Stroke Patients Who Require Neurosurgical Intervention

In some cases, an acute stroke patient may need a hemicraniectomy or surgical decompression as a life-saving procedure. Acute hemorrhagic stroke patients need to have an immediate evaluation by the neurologist and neurosurgeon to determine the need for surgical intervention. This procedure is usually done after medical management procedures such as hyperosmolar therapy with IV mannitol or hyperventilation have failed. A meta-analysis of 12 prospective randomized controlled trials of neurosurgical intervention in spontaneous intracerebral hemorrhage shows a strong trend toward reduced mortality (0.85; 95% CI, 0.71 to 1.02). However, in the setting of dominant hemisphere infarction, a significant morbidity effect on language and dominant extremities should be considered. The patients' wishes should be considered and discussed thoroughly with their next of kin or legal guardian.

Acute Hemorrhagic Stroke Patients Who Do Not Require Neurosurgical Intervention

See Figure 19.4 for an algorithm for stabilization and monitoring of acute hemorrhagic stroke patients who do not need surgical intervention on the initial evaluation.

Anticonvulsants

Seizure prophylaxis is recommended for up to 1 month after ICH and should be discontinued in the absence of seizures. The 30-day risk of clinically evident seizures after ICH is about 8%. Convulsive status epilepticus may be seen in 1% to 2% of patients, and the risk or epilepsy is 5% to 20%.

Written Protocol and Telemedicine for Assessment and Initial Care of Stroke Patients

The narrow time window, as well as the relationship between time to treatment and outcome, has led to the development of a number of strategies (e.g., clinical pathways, standing orders) to be able to administer treatment drug as soon as possible.

In the ED without a stroke center facility, ED physicians can evaluate patients for eligibility to receive IV-tPA. Consultation

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Neurology

STROKE

A Practical Approach

James D. Geyer, MD
Camilo R. Gomez, MD

Stroke: A Practical Approach is a unique source of practical information for frontline providers of care for stroke patients. With a focus on patient management – from stroke prevention through acute stroke management, through chronic care – this title offers how-to guidance on implementing diagnostic and treatment protocols. Each chapter incorporates a bulleted list of key learning points; an evidence-based rationale for why the diagnostic and treatment recommendations work; a step-by-step approach to clinical application; practical recommendations from the authors; a critical pathway; and a bibliography. Also included in the text is an entire chapter on building a stroke team from EMT education to the emergency department — of interest to hospital managers who are interested in being considered as a JCAHO-certified stroke center.

Highlights include:

- Bulleted list of key learning points
- An evidence-based rationale for why the diagnostic and treatment recommendations work
- Step-by-step approach to clinical application
- Practical recommendations from the authors
- A critical pathway

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