Cerebrovascular Disease and Chronic Kidney Disease

14

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Before You Start: Facts You Need to Know

- Patients with low glomerular filtration rate (GFR) and/or albuminuria are at risk for both thrombotic and hemorrhagic events.
- In cases of CKD, endothelial dysfunction in brain arterioles, atherosclerotic changes of the large vessels, blood pressure elevation due to the activation of the renin-angiotensin system, and coagulation abnormalities probably underlie both hemorrhagic and ischemic stroke.
- Hypertension is the primary, manageable risk factor for both hemorrhagic and ischemic stroke.
- Hemorrhagic infarction is a major concern after thrombolytic therapy in CKD patients, because hemorrhagic transformation or cerebral microbleeds are more prevalent in these patients.
- Although CT is the gold standard for diagnosis of intracerebral hemorrhage, MRI (magnetic resonance imaging) gradient-echo sequences are also an effective way to delineate small or large hemorrhagic foci.

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14.1 Introduction

Several misconceptions exist about stroke. Stroke is not only a pure cerebral event (CVE) but also it is a primary or secondary devastating disease of the blood vessels of the brain. There is a presumed reason or cause for every stroke. Stroke is not one illness but it involves several diseases that lead to occlusion of arteries that deprive blood supply to certain parts of the brain or that predispose to bleeding into or around the brain. In the United States, nearly three fourths of a million individuals have a stroke, and 150,000 people die from stroke each year. In China, approximately 1.5 million people die each year because of stroke. Someone in the United States has a stroke every 45 sec., and every 3.1 min, someone dies of stroke. Stroke affects three times as many women as breast cancer and yet receives much less public attention. For a long time, stroke has been the third leading cause of death in most countries in the world, surpassed as a killer only by heart disease and cancer. Strokes are an even more important cause of prolonged disability.

Stroke is anything but a homogeneous entity. Disorders as different as rupture of a large blood vessel that causes flooding of the brain with blood and occlusion of a tiny artery with softening in a small but strategic brain site both qualify as strokes. These two pathologic caricatures of stroke subtypes are as divergent as grapes and watermelons, two very different substances that fit in the general category of fruit. Stroke refers

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to any damage to the brain or the spinal cord caused by an abnormality of the blood supply. The term stroke is typically used when the symptoms begin abruptly, whereas cerebrovascular disease is a more general term that carries no connotation as to the tempo of brain injury. Of course, many patients with severely diseased blood vessels have no injury to the brain tissue. A blood or cardiovascular abnormality precedes and subsequently leads to the brain injury. Recognition of the cardiac or cerebrovascular lesion or hematologic disorder before the brain becomes damaged offers clinicians a window of opportunity during which brain damage can be prevented. At times, even when brain injury has occurred, the patient is unaware of any symptoms, and neurologists may not be able to detect any abnormality on neurologic examination. Sophisticated neuroimaging techniques have taught clinicians that such "silent strokes" are common.

Diagnosis and treatment of stroke patients require a basic understanding of the anatomy, physiology, and pathology of the major structures involved—the brain and spinal cord, the heart and blood vessels that supply blood to these structures, and the blood itself. To be effective, clinicians caring for stroke patients must be intimately familiar with the appearance of the normal brain and the usual locations and course of arteries supplying the brain and spinal cord and veins that drain blood from these regions.

14.2 Mechanisms of Cerebrovascular Damage to Brain Tissue

There are two major categories of brain damage in stroke patients, namely, ischemia and hemorrhage. Bleeding damages the brain by cutting off connecting pathways and by causing localized or generalized pressure injury to brain tissue; biochemical substances released during and after hemorrhage also may adversely affect nearby vascular and brain tissues [1].

14.2.1 Ischemia

Ischemia can be further subdivided into three different mechanisms: thrombosis, embolism, and decreased systemic perfusion.

14.2.2 Thrombosis

The most common type of vascular pathology is atherosclerosis, in which fibrous and muscular tissues overgrow in the subintima, and fatty materials form plaques that can encroach on the lumen. Next, platelets adhere to plaque crevices and form clumps that serve as nidi for the deposition of fibrin, thrombin, and clot. Atherosclerosis affects chiefly the larger extracranial and intracranial arteries. Occasionally, a clot forms within the lumen because of a primary hematologic problem, such as polycythemia, thrombocytosis, or a systemic hypercoagulable state. The smaller, penetrating intracranial arteries and arterioles are more often damaged by hypertension than by atherosclerotic processes. Less common vascular pathologies leading to obstruction include (1) fibromuscular dysplasia, an overgrowth of medial and intimal elements that compromises vessel contractility and luminal size; (2) arteritis, especially of the Takayasu or giant-cell type; (3) dissection of the vessel wall, often with a luminal or extraluminal clot temporarily obstructing the vessel; and (4) hemorrhage into a plaque, leading to acute or chronic luminal compromise. At times, the focal vascular abnormality is a functional change in the contractility of blood vessels. Intense focal vasoconstriction can lead to decreased blood flow and thrombosis. Dilatation of blood vessels also alters local blood flow and clots often form in dilated segments.

14.2.3 Embolism

In embolism, material formed elsewhere within the vascular system lodges in an artery and blocks blood flow. Blockage can be transient or may persist for hours or days before moving distally. In

contrast to thrombosis, embolic luminal blockage is not caused by a localized process originating within the blocked artery. The material arises proximally, most commonly from the heart; from major arteries such as the aorta, carotid, and vertebral arteries; and from systemic veins. Cardiac sources of embolism include the heart valves and clots or tumors within the atrial or ventricular cavities. Artery-to-artery emboli are composed of clots, platelet clumps, or fragments of plaques that break off from the proximal vessels. Clots originating in systemic veins travel to the brain through cardiac defects such as an atrial septal defect or a patent foramen ovale, a process termed paradoxical embolism. Also, occasionally air, fat, plaque material, participate matter from injected drugs, bacteria, foreign bodies, and tumor cells enter the vascular system and embolize to brain arteries.

14.2.4 Decreased Systemic Perfusion

In decreased systemic perfusion, diminished flow to brain tissue is caused by low systemic perfusion pressure. The most common causes are cardiac pump failure (most often due to myocardial infarction or arrhythmia) and systemic hypotension (due to blood loss or hypovolemia). In such cases, the lack of perfusion is more generalized than in localized thrombosis or embolism and affects the brain diffusely and bilaterally. Poor perfusion is most critical in border zone or so-called watershed regions at the periphery of the major vascular supply territories.

14.2.5 Damage Caused by Ischemia

The three mechanisms of brain ischemia may lead to temporary or permanent tissue injury. Permanent injury is termed infarction. Capillaries or other vessels within the ischemic tissue may also be injured, so that reperfusion can lead to leakage of blood into the ischemic tissue, resulting in a hemorrhagic infarction. The extent of brain damage depends on the location and duration of the poor perfusion and the ability of collateral vessels to perfuse the tissues at risk. The systemic blood pressure, blood volume, and blood viscosity also affect blood flow to the ischemic areas.

14.2.6 Hemorrhage

Hemorrhage can be further subdivided into four subtypes: subarachnoid, intracerebral, subdural, and epidural. These subtypes have different causes, pose different clinical problems, and have different managements.

14.2.7 Subarachnoid Hemorrhage

In subarachnoid hemorrhage, blood leaks out of the vascular bed onto the brain's surface and is disseminated quickly via the spinal fluid pathways into the spaces around the brain. Bleeding most often originates from aneurysms or arteriovenous malformations, but bleeding diatheses or trauma can also cause subarachnoid bleeding. The blood within the subarachnoid space often contains substances that promote vasoconstriction of the basal arteries that are bathed in cerebrospinal fluid.

14.2.8 Intracerebral Hemorrhage

The cause is most often hypertension, with leakage of blood from small intracerebral arterioles damaged by the elevated blood pressure. Bleeding diatheses, especially from the iatrogenic prescription of anticoagulants or from trauma, drugs, vascular malformations, and vasculopathies (such as cerebral amyloid angiopathy), can also cause bleeding into the brain. The degree of damage depends on the location, rapidity, volume, and pressure of the bleeding.

14.2.9 Subdural and Epidural Hemorrhages

These hemorrhages are almost always caused by head trauma. Subdural hemorrhages arise from

injured veins that are located between the dura mater and the arachnoid membranes. The bleeding is most often slow and accumulates during days, weeks, and even a few months. When a large vein is lacerated, bleeding can develop more rapidly over hours to days. Epidural hemorrhages are caused by tearing of meningeal arteries, most often the middle meningeal artery. Blood accumulates rapidly over minutes to hours between the skull and the dura mater. Both subdural and epidural hemorrhages cause symptoms and signs by compressing brain tissue and increasing intracranial pressure.

14.3 General Measures to Prevent Stroke

Prevention is the most effective way to avoid death or suffering from stroke. Successful preventive strategies are cost-effective because they eliminate the expenses of acute hospital care and rehabilitation. Prevention of stroke involves two different tactics. One consists of interventions applied to large segments of the population and includes health promotion and identification and treatment of common factors that increase the risk of either hemorrhagic or ischemic stroke (Box 14.1). These measures (e.g., control of hypertension) may have limited benefit for individual persons, but their aggregate effects are substantial when prescribed to large populations. The second approach involves the use of more expensive and potentially more dangerous therapies given to smaller groups of persons judged to be at the highest risk. *Primary prevention* includes therapies to forestall ischemic vascular events, including stroke, in either large populations or small high-risk groups of asymptomatic people. *Secondary prevention* implies the use of treatments to prevent stroke or other ischemic vascular event in persons who already have had symptoms. Secondary prevention of stroke can include treatment of a spectrum of people to include those without neurological symptoms. The symptomatic high-risk groups especially include those patients who have evidence of atherosclerosis, such as:

- Myocardial infarction
- Angina pectoris
- Claudication
- Amaurosis fugax
- Transient ischemic attack (TIA)
- Ischemic stroke

Box 14.1. Factors Associated with an Increased Risk of Stroke

Epidemiologic

Age—(Elderly > middle-aged or young adults > children)

Gender—(Men > women in each age group)

Race—(Blacks > Asians or Hispanics > Whites)

Geographic region—(Eastern Europe > Western Europe; Asia > Europe or North America)

Family history—(Stroke or heart disease < aged 60)

Other, *potentially modifiable*, *factors*:

- Diastolic or isolated systolic hypertension
- Diabetes mellitus, type 1 or type 2
- Hyperlipidemia (hypercholesterolemia)
- Elevated low-density lipoprotein (LDL) cholesterol or low high-density lipoprotein (HDL) cholesterol
- Hyperhomocysteinemia
- Smoking
- Alcohol abuse
- Drug abuse
- Oral contraceptive use
- Pregnancy
- Migraine headaches

14.3.1 Risk Factors for Stroke

The conditions or factors that predispose to or increase the risk of a cerebrovascular event are diverse (Table 14.1 and Boxes 14.2, 14.3, and 14.4). While some conditions that lay the groundwork for ischemic stroke also lead to brain hemorrhage, additional factors may promote intracranial bleeding. Some conditions that predispose to stroke are not modifiable. Advancing age is the single most common factor that predicts a high risk for stroke. Although stroke is much more common in

Table 14.1 Nonatherosclerotic vasculopathies causing ischemic stroke

Noninflammatory causes	Inflammatory causes	Infectious causes
Dissection	PAN	Syphilis
Fibromuscular dysplasia	Wegener granulomatosis	Herpes zoster
Moyamoya disease	SLE	Cysticercosis
Ehlers-Danlos syndrome tip4	RA	AIDS
Fabry disease	Scleroderma	Bacterial meningitis
Hyperhomocysteinemia	Sjögren syndrome	
Marfan syndrome	Takayasu syndrome	
Menkes disease	Temporal arteritis	
Amyloid angiopathy	Behçet disease	
	Ulcerative colitis	
	Sarcoidosis	
	Cogan syndrome	
	Kawasaki syndrome	
	Polymyositis	
	Dermatomyositis	

PAN polyarteritis nodosa, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *AIDS* acquired immunodeficiency syndrome

elderly people than in children or young adults, it also is an important disease in these latter groups. Approximately 3 % of ischemic strokes occur among people under the age of 45. The ratio of hemorrhagic stroke to ischemic stroke is higher in younger people than in the elderly. The causes of stroke also vary by age. Atherosclerosis and cardioembolism secondary to atrial fibrillation are the leading causes of ischemic stroke in the elderly, while the differential diagnosis of ischemic stroke etiologies is much broader in younger people. Similarly, cerebral amyloid angiopathy and chronic hypertension are leading causes of intracerebral hemorrhage in older persons, while vascular malformations and aneurysms are more common causes in younger adults [2].

Box14.2. Cardiac Causes of Embolization to the Brain

Atrial Fibrillation

Left Ventricle or Intraventricular Lesions

- Dilated cardiomyopathy
- Recent myocardial infarction (MI), anterior in particular
- Ventricular aneurysm (post-MI)
- Akinetic segment (post-MI)
- Mural or intraventricular thrombus

Left Atrium, Intra-atrial, or Interatrial Lesions

- Atrial septal aneurysm
- Atrial septal defect
- Patent foramen ovale
- Atrial turbulence
- Atrial thrombus
- Myxoma

Valvular Lesions

- Mechanical or bioprosthetic valve
- Congenital valvular abnormality
- Rheumatic mitral stenosis
- Mitral valve prolapse
- Infective endocarditis
- Nonbacterial thrombotic endocarditis (marantic)
- Libman-Sacks endocarditis
- Mitral annulus calcification
- Calcific aortic stenosis
- *Cardiac Procedures*
- Coronary artery bypass surgery
- Cardiac catheterization
- Percutaneous transluminal coronary angioplasty
- Percutaneous transluminal valvuloplasty
- Intra-aortic balloon pump procedure

Box 14.3. Atherosclerotic Causes of Ischemic Stroke

- Atherosclerosis of the aortic arch
- Extracranial large-artery atherosclerosis:
  - Origin of the internal carotid artery
  - Origin of the vertebral artery
  - Subclavian artery
- Intracranial larger-artery atherosclerosis:
  - Distal portion of internal carotid artery
  - Proximal portion of middle cerebral artery
  - Distal portion of vertebral artery
  - Middle portion of the basilar artery
  - Disseminated atherosclerosis
- Fusiform aneurysm:
  - Basilar artery
  - Internal carotid artery
- Small-artery disease (lipohyalinosis/microatheroma)

Box14.4. Hematologic or Coagulation Disorders Causing Ischemic Stroke

- Polycythemia rubra vera
- Sickle-cell disease
- Essential thrombocytosis
- Thrombotic thrombocytopenic purpura
- Heparin-induced thrombocytopenia
- Antithrombin III deficiency
- Protein C or S deficiency
- Deficiency of factors V, VII, XII, or XIII
- Heparin cofactor II deficiency
- Dysfibrinogenemias
- Antiphospholipid/anticardiolipin antibodies
- Nephrotic syndrome
- Malignancy
- Pregnancy
- Oral contraceptives
- Dehydration

14.3.2 Modifiable Risk Factors

Some of the interventions to prevent stroke are aimed primarily at slowing the course of atherosclerosis, preventing fracture of an atherosclerotic plaque, or stabilizing the arterial endothelium. Many therapies are aimed at controlling risk factors or conditions that promote development of advanced atherosclerotic conditions. Attention to these risk factors is critical when making decisions about the primary or secondary prevention of stroke.

14.3.2.1 Hypertension

Hypertension is the primary manageable risk factor for both hemorrhagic and ischemic stroke. Regardless of age, the presence of diastolic arterial hypertension greatly increases the likelihood of stroke. Among older persons, isolated systolic hypertension also promotes stroke. The relationship between hypertension and stroke is much closer than the association between an elevated blood pressure and coronary artery disease. Hemorrhagic stroke also complicates chronic hypertension and acute hypertensive crises, including eclampsia. A number of antihypertensive agents are available. The selection of medications is made on a case-by-case basis and involves consideration of factors such as concomitant diseases.

In most cases, β-blockers or oral diuretic agents are prescribed initially. Patients with concomitant symptomatic heart disease often are treated with β-blockers or calcium channel blocking medications. Recent evidence suggests that some of the newer angiotensin-converting enzyme (ACE) inhibitors may have additional potential benefits for stroke prevention. These agents may have some efficacy in stabilizing the vascular endothelium, which in turn might lower the risk of thromboembolism. In one trial, the ACE inhibitor ramipril was found to reduce the risk of stroke in asymptomatic high-risk patients, especially those with diabetes mellitus. The medication was given in conjunction with other measures to prevent stroke. Patients with hypertension secondary to renal artery stenosis usually are not treated with an ACE inhibitor.

14.3.2.2 Diabetes Mellitus

Diabetes mellitus promotes both atherosclerotic large-artery and small-artery disease of the brain. Stroke is a common complication in both younger, insulin-dependent diabetic patients and

older persons with type 2 diabetes. Diabetic patients may have more severe strokes, and hyperglycemia also may exacerbate the severity of the neurologic impairments. Current recommendations advise careful control of diabetes mellitus and elevated blood glucose concentrations.

14.3.2.3 Hypercholesterolemia

Hyperlipidemia encourages early development of atherosclerosis. Hyperlipidemia is a likely important factor for stroke secondary to atherosclerosis, especially in middle-aged adults. Patients with ischemic stroke should be evaluated for the presence of hyperlipidemia. If the blood levels cannot be assayed within the first 24–48 h after stroke, the test should be delayed until the patient is convalescent. The cholesterol levels might be falsely low during the acute stage of stroke.

14.3.2.4 Smoking

Cessation of smoking probably is the single most cost-effective strategy to lower the risk of either hemorrhagic or ischemic stroke. Smokers have an increased risk of atherosclerosis. Even passive exposure to smoking has been implicated. Smoking also potentiates the use of oral contraceptives in young women. In addition, smoking adds to the risk of intracranial bleeding, including rupture of saccular aneurysms.

14.3.2.5 Other Potential Risk Factors

Other potential risk factors for stroke include:

- Migraine
- Use of oral contraceptives
- Obesity
- Excessive alcohol consumption
- Drug abuse
- Sleep disorders (including sleep apnea)

Excessive consumption of alcohol has been associated with an increased risk of intracranial bleeding. Elevated blood levels of homocysteine may augment the development of atherosclerosis and associated thrombosis. Supplementing the diet with folic acid, vitamin B12, and pyridoxine will lower homocysteine levels and might be helpful in preventing ischemic events. Inflammation also may play a role in the course of atherosclerosis.

14.3.3 Patients at Highest Risk

Persons with the following conditions are at the highest risk for ischemic stroke:

- Atrial fibrillation (AF)
- Asymptomatic stenosis of the carotid artery
- Amaurosis fugax
- TIA
- Previous ischemic stroke

14.3.3.1 Atrial Fibrillation

Atrial fibrillation (AF) is the primary cardiac abnormality associated with ischemic stroke. It is the most important risk factor for stroke in persons older than 75, especially in women. AF complicates a number of cardiac diseases and the presence of the arrhythmia is associated with an increased risk of cardioembolism. The most common cardiac diseases complicated by AF are:

- Coronary artery disease
- Hypertensive heart disease
- Cardiomyopathies
- Rheumatic heart disease
- Prosthetic cardiac valves

Persons younger than 60 years old who have AF and no other cardiac disorder (lone AF) appear to have a relatively low risk for stroke. Thus, the importance of AF is as an abetting factor leading to the formation of intra-atrial thrombi in a patient with another heart disease. Both people with chronic, sustained AF and those with an intermittent arrhythmia are at risk, and embolization can complicate intermittent or new-onset AF. The risk of embolization is relatively low during the first 2–3 days after the start of AF. Many patients do not have symptoms corresponding to the onset of the arrhythmia and the time the AF began becomes inferential. Thus, determining the onset of AF is problematic. Either electrical or pharmacologic cardioversion can be associated with embolization, and therefore, anticoagulation is prescribed for several weeks before and after correction of the arrhythmia. Several factors identify those persons with AF who are at greatest risk for embolization:

- Prior stroke or TIA
- Aged >75 years, especially women
- History of hypertension or systolic blood pressure >160 mmHg

- Diabetes mellitus
- Coronary artery disease
- Congestive heart failure
- Left ventricular dysfunction

14.3.3.2 Asymptomatic Cervical Stenosis or Bruit

Severe asymptomatic stenosis of the extracranial portion of the internal carotid artery can be detected after a physician auscultates a cervical bruit. Besides being a marker for a high risk for stroke, an asymptomatic carotid stenosis also forecasts an increased risk of myocardial infarction or vascular death. The risk of ipsilateral stroke in patients with narrowing >60 % appears to be approximately 2 % per year. The chance of stroke probably correlates with the severity of the arterial narrowing; patients with high-grade stenosis are assumed to be at the greatest risk. Doing carotid endarterectomy to treat an asymptomatic lesion at the same time as a major cardiovascular operation is not recommended because the chances for serious complications are excessively high.

14.3.3.3 Transient Ischemic Attack/ Amaurosis Fugax

Patients with ischemic symptoms of the brain or eye have the greatest risk of ischemic stroke. In general, the risk is highest among patients with a previous stroke, higher among patients with a TIA, and high in patients with amaurosis fugax. Amaurosis fugax (transient monocular blindness) is an episode of painless visual loss in one eye that is secondary to retinal ischemia. Amaurosis fugax usually is associated with atherosclerotic disease of the ipsilateral internal carotid artery. Global symptoms, including confusion, wooziness, light-headedness, and loss of consciousness, usually are not due to a TIA. The symptoms of a TIA usually involve weakness, numbness, or incoordination and represent a loss of normal neurologic activity. Positive neurologic symptoms, such as scintillating visual phenomena, seizure activity, or involuntary movements, rarely are due to transient brain ischemia. A migration or march of symptoms from one body part to another is uncommon with a TIA. The pattern of symptoms of a TIA in the vertebrobasilar circulation (binocular visual loss, diplopia, vertigo, unilateral or bilateral weakness, numbness, heaviness or clumsiness, ataxia, dysarthria, dysphagia, hearing loss, drop attack) differs from the pattern of symptoms in the carotid territory (ipsilateral monocular visual loss-amaurosis fugax, contralateral weakness, numbness, heaviness, or clumsiness, dysarthria, aphasia) [3].

14.4 Immediate Evaluation of Patients with Suspected Stroke

Early differentiation of ischemic stroke from hemorrhagic stroke is especially important because it influences acute treatment and subsequent care. A limited number of rapidly performed diagnostic tests are required, while extensive testing to determine the cause of stroke can be done after admission to the hospital. These diagnostic tests should be performed on an urgent basis because timing is critical (Box 14.5).

Box 14.5. Emergent Diagnostic Tests for Evaluation of a Patient with Suspected Stroke

- Computed tomography (CT) of the brain without contrast
- Electrocardiogram (ECG)
- Chest x-ray (if hypoxia or acute lung disease suspected)
- Complete blood count and platelet count
- Prothrombin time/international normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)
- Blood glucose
- Serum chemistries, including electrolytes
- Cervical spine x-ray (if the patient is unresponsive and trauma is possible)
- Arterial blood gases (if hypoxia is suspected)
- Cerebrospinal fluid (CSF) examination (if subarachnoid hemorrhage is suspected but no blood or mass effect is seen on CT)

Brain imaging (computed tomography [CT]) is the most important diagnostic test because it is the most reliable way to differentiate hemorrhagic stroke from ischemic stroke (Box 14.6). Clinical presentations of the two types of cerebrovascular disease are sufficiently similar to make the diagnosis of brain hemorrhage or infarction problematic when using only the history and physical examination. Patients should not be treated with anticoagulants or thrombolytic agents until CT has helped exclude the presence of intracranial hemorrhage.

Because of the strong relationship between heart disease and stroke and because of the critical nature of early cardiopulmonary complications and their effect on emergent management and outcomes, an electrocardiogram (ECG) and chest x-ray are important as initial diagnostic tests. The coagulation tests also screen for the presence of an underlying hematologic (coagulation) disorder that could lead to either ischemic or hemorrhagic stroke. The tests also can influence decisions about use of thrombolytic agents to treat acute ischemic stroke. Examination of the cerebrospinal fluid (CSF) is an important study to search for bleeding if the patient's clinical findings suggest SAH. A lumbar puncture is not necessary if the CT has demonstrated hemorrhage.

Box 14.6. Sequence of Vascular Imaging Tests with Acute Stroke

- Imaging of the brain should be performed first (CT or MRI)
- Consider vascular imaging if:
  - Results would alter acute management
  - Patient has unexplained symptoms suggesting brain stem dysfunction
  - Acute intra-arterial intervention is planned
  - Patient has SAH or unexplained intraparenchymal hemorrhage
- Sequence:
  - If available, do CTA after CT
  - If MRI is performed, do MRA
  - If available, consider ultrasonography
  - DSA can be done if other tests are unavailable or if they give inconclusive results

Abbreviations: CT, computed tomography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SAH, subarachnoid hemorrhage

14.4.1 Subsequent Diagnostic Evaluation

Magnetic resonance imaging (MRI) is more sensitive than CT in detecting small ischemic lesions, particularly in the posterior fossa. MRI also can be used to assess the presence of an underlying arterial or venous occlusion. In addition, advances in MRI technology allow evaluation of perfusion, diffusion, and metabolic studies of the brain. The role of MRI in emergent evaluation will likely increase. In particular, mismatches between perfusion and other imaging sequences might become a key early diagnostic finding in determining eligibility for emergent stroke care. The recent development of gradient-echo T2-weighted magnetic resonance imaging (MRI) has enabled the highly accurate detection of prior cerebral microbleeds (CMBs), which might indicate a higher risk of future intracerebral hemorrhage (ICH) and be a marker of cerebral small-vessel disease in the general population. The cerebral vasculature can be examined by several diagnostic tests (Table 14.2). Arteriography (digital subtraction angiography [DSA]) is the preferred method for evaluation of patients with intracranial hemorrhage. Because early surgery often is recommended for those with ruptured aneurysms, DSA is performed as an emergent procedure for persons with SAH. Imaging of the heart usually is recommended because of the high prevalence of cardiac disease that can be the source of emboli in people with ischemic stroke. Transthoracic and transesophageal echocardiography (TTE and TEE) are the two most commonly ordered cardiac tests. If another likely cause for stroke, such as a carotid artery dissection, is found or if the results of cardiac imaging are not likely to alter

Table 14.2 What can be imaged in patients with acute stroke?

Imaging test	Imaging results
CT	Brain tissue, CSF space, skull, brain tissue perfusion
MRI	Brain tissue, CSF space, brain tissue proton diffusion and perfusion, brain function
CTA	Blood vessels in neck or brain (arteries and veins)
MRA	Same as CTA
DSA	Same as CTA
US	Same as CTA
TDU	Same as CTA
SPECT	Brain tissue perfusion
PET	Brain tissue perfusion, brain metabolism
MRS	Brain metabolism

Abbreviations: *CSF* cerebrospinal fluid, *CT* computed tomography, *CTA* computed tomographic angiography, *DSA* digital subtraction angiography, *MRA* magnetic resonance angiography, *MRI* magnetic resonance imaging, *MRS* magnetic resonance spectroscopy, *PET* positron emission tomography, *SPECT* single photon emission computed tomography, *TDU* transcranial Doppler ultrasound, *US* duplex ultrasound

management, these tests could be avoided. On the other hand, echocardiography can be informative in young people with ischemic symptoms or those who have other evidence suggesting a cardiac source for embolization. In general, TTE has a low yield in detecting cardiac abnormalities; it is most likely to find abnormalities in the left ventricle. The test should be ordered if a mural thrombus following a myocardial infarction or a left ventricular aneurysm or an akinetic left ventricular segment is suspected.

14.5 Emergent Medical Management

Acute cardiovascular and cerebrovascular events have several similarities. These life-threatening conditions usually are of arterial origin and accompanied by complications that add to morbidity and mortality. Complications of stroke can occur at any time during the acute illness, but they are most common during the first 24–48 h. Both acute coronary artery occlusion and acute occlusion of an artery to the brain can be treated with emergent administration of thrombolytic agents. Both conditions can be treated successfully and outcomes can be improved. Like management of those persons with acute heart disease, modern stroke care requires urgent treatment.

14.5.1 Fever

Fever is uncommon during the first day after stroke. It can result from complications, such as aspiration pneumonia, or be a marker of an infectious cause of stroke, such as endocarditis. People with intracranial bleeding often have an elevated temperature secondary to disturbances of the thermoregulatory center in the hypothalamus. An elevated temperature can be found in patients with intracranial hemorrhage, and its presence is a poor prognostic sign. An elevated temperature can potentiate the effects of acute ischemia. Measures to lower the temperature in febrile patients are encouraged.

14.5.2 Cardiac Complications

While heart disease is a leading cause of stroke, cardiac disorders are important, potentially life-threatening complications of cerebrovascular events. Myocardial ischemia, cardiac failure, and pulmonary edema are potential complications of intracranial hemorrhage. Acute myocardial injury and secondary arrhythmias are potential causes of sudden death in patients with major strokes. Cardiac monitoring to detect abnormal rhythms should be part of the initial observation of all patients with possible stroke. If serious arrhythmias are detected, medications should be prescribed using the rules of advanced cardiac life support.

14.5.3 Arterial Hypertension

During the first hours after stroke, most patients have an elevated blood pressure. Both acutely elevated and low blood pressures are associated

with poor outcomes after stroke. The degree of hypertension is associated with the severity of neurological impairments; in general, blood pressures are highest among those patients with the most severe strokes. The high blood pressure can also be a compensatory mechanism to maintain adequate perfusion to the brain. Cerebrovascular autoregulation is lost in the ischemic bed and blood flow becomes pressure dependent. The brain may need an elevated blood pressure to limit the scope of the ischemic injury, and sudden lowering of the blood pressure might result in worsening of the neurologic signs. Information is lacking about what level of blood pressure is too high in the setting of acute stroke or about the best response to the finding of arterial hypertension. The best approach lies in not lowering the blood pressure too steeply or too rapidly. Rather, the blood pressure should be measured at frequent intervals and treatment responses should be based on sustained elevations of arterial hypertension.

For patients with ischemic stroke, the values that should lead to treatment are systolic >220 mmHg or mean >130 mmHg. The aim is to cautiously lower the blood pressure by approximately 15 % during the first 24 h after stroke. Parenteral agents can be given to rapidly lower arterial pressures in more urgent situations (Table 14.3). The current guidelines for the use of thrombolytic agents for treatment of acute ischemic stroke recommend that the medications not be used when a patient's systolic blood pressure is >185 mmHg or diastolic blood pressure is >110 mmHg. Lowering the blood pressure can be attempted so that recombinant tissue-plasminogen activator (rt-PA) can be administered. Given the

Table 14.3 Approach to elevated blood pressure in acute ischemic stroke

Blood pressure level (mmHg)	Treatment
Not eligible for thrombolytic therapy	
Systolic <220 or diastolic <120	Observe unless other end-organ involvement, e.g., aortic dissection, acute myocardial infarction, pulmonary edema, and hypertensive encephalopathy. Treat other symptoms of stroke such as headache, pain, agitation, nausea, and vomiting. Treat other acute complications of stroke, including hypoxia, increased intracranial pressure, seizures, or hypoglycemia
Systolic >220 or diastolic 121–140	Labetalol 10–20 mg IV over 1–2 min. May repeat or double every 10 min (maximum dose 300 mg) or nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by 2.5 mg/h every 5 min to maximum of 15 mg/h, aim for a 10–15 % reduction of blood pressure
Diastolic >140	Nitroprusside 0.5 ug/kg/min IV infusion as initial dose with continuous blood pressure monitoring, aim for a 10–15 % reduction of blood pressure
Eligible for thrombolytic therapy	
Pretreatment	
Systolic >185 or diastolic >110	Labetalol 10–20 mg IV over 1–2 min. May repeat x 1 or nitropaste 1 –2 in.
	If blood pressure is not reduced and maintained at desired levels (systolic <185 and diastolic <110), do not administer rt-PA
During and after treatment	
1. Monitor BP	Check BP every 15 min for 2 h, then every 30 min for 6 h, and then every hour for 16 h
2. Diastolic >140	Sodium nitroprusside 0.5 ug/kg/min IV infusion as initial dose and titrate to desired blood pressure
3. Systolic >230 or diastolic 121–140	Labetalol 10 mg IV over 1–2 min, may repeat or double labetalol every 10 min to a maximum dose of 300 mg or give the initial labetalol bolus and then start a labetalol drip at 2–8 mg/min or nicardipine 5 mg/h IV infusion as initial dose; titrate to desired effect by increasing 2.5 mg/h every 5 min to maximum of 15 mg/h. If BP is not controlled by labetalol, consider sodium nitroprusside
4. Systolic 180–230 or diastolic 105–120	Labetalol 10 mg IV over 1–2 min. May repeat or double labetalol every 10–20 min to a maximum dose of 300 mg or give the initial labetalol bolus and then start a labetalol drip at 2–8 mg/min

Source: Adams et al. [18]

current relatively short window of time for the safe and effective use of rt-PA, management of arterial hypertension becomes problematic in the setting of acute stroke. In most instances, time will not be sufficient to determine if the blood pressure is stabilized at acceptable levels before rt-PA is given. The potential risks of exacerbating brain ischemia by lowering the blood pressure also may counteract any benefits from treating with rt-PA. The possibility of an elevated blood pressure increasing the risk of hemorrhagic transformation of the infarction after rt-PA treatment requires that monitoring and control of the blood pressure be aggressive during and following the use of the agent (Box 14.7).

Box 14.7. Treatment of Increased Intracranial Pressure Following Acute Stroke

General Prophylaxis

- Control fever, agitation, nausea and vomiting, hypoxia, hypercarbia
- Modest fluid restriction (approximately 1.5–2.0 l/day)
- Avoid potentially hypo-osmolar intravenous fluids (5 % dextrose/water)
- Elevate the head of the bed to augment venous drainage

Acute Interventions

- Intubation to protect the airway and to permit hyperventilation
- Goal to lower pCO2 to approximately 30 mmHg
- Mannitol 0.5 g/kg given in a 20 % solution over approximately 20–30 min:
  - Can repeat 0.25 g/kg every 6 h as needed
  - Usual maximal daily dose is 2 g/kg
  - Replace lost fluids
- Furosemide, 20–40 mg given intravenously
- Monitor intracranial pressure
- Drainage of CSF via a ventricular catheter
- Corticosteroids (dexamethasone or methylprednisolone) are not recommended

Surgical Procedures

- Evacuation of a hematoma
- Resection of infarcted brain
- Craniectomy with removal of a large section of skull

Abbreviations: *CSF* cerebrospinal fluid, *pCO2* partial pressure of carbon dioxide

14.5.4 Hypoglycemia and Hyperglycemia

Approximately one third of patients with stroke have hyperglycemia detected upon admission. Persistent hyperglycemia during the first 24 h predicts expansion of stroke and poor outcomes. The hyperglycemia may be a manifestation of underlying diabetes or it may be a secondary stress reaction. Treatment of hyperglycemia should be a component of emergent management.

14.5.5 Seizures

Seizures complicate approximately 5 % of strokes but status epilepticus is uncommon. Frequent seizures can intensify the brain injury from stroke, and they are a neurologic emergency in their own right. Seizures are most numerous in patients with subarachnoid hemorrhage (SAH) or cortical infarctions secondary to embolism. Phenytoin is the most commonly prescribed agent. Short-acting benzodiazepines can be given to patients who are having active seizures. Prophylactic administration of anticonvulsants to those patients who have had a recent stroke, but who have not had a seizure, is not recommended.

14.5.6 Increased Intracranial Pressure (ICP)

Patients with multilobar infarction or large hemorrhages of the cerebral hemisphere are at high risk for severely elevated ICP. A high ICP can worsen brain ischemia by reducing cerebral

blood flow and cerebral perfusion pressure. In addition, pressure gradients between compartments within the cranial vault can lead to herniation and secondary brain injury. Elevations of ICP usually result from brain edema of the mass effect of the vascular lesion. In addition, large strokes in the posterior fossa or hemorrhages with ventricular or SAH can be complicated by acute hydrocephalus. The mass effects of the brain hematoma or acute hydrocephalus secondary to blockage of CSF pathways by clots mean that marked rises in ICP during the first hours after stroke are largely a problem in patients with hemorrhagic stroke. Usually, the course of brain edema and increased ICP is slower in patients with ischemic stroke; the symptoms evolve over the first 2–4 days in people with large hemispheric infarctions. Those with large hematomas or infarctions in the cerebellum or brain stem can develop signs of increased ICP rapidly. In this situation, the mass effects of the vascular lesion can cause both hydrocephalus and brain stem compression. Signs of herniation, such as unilateral oculomotor nerve (III) palsy, appear late in the course. Management of increased ICP after stroke includes both prophylactic and urgent treatment (Box 14.7). Osmotic therapy (saline, mannitol, or glycerol) is given to patients with signs of clinically significant brain edema and elevated ICP following stroke. Mannitol is administered intravenously over a 20-min period in a dose of 0.5 g/kg. Subsequent doses can be given every 4–6 h. The usual maximal daily dose is 2 g/kg. The ICP usually drops within 20 min of starting the infusion and effects will persist for approximately 4–6 h. A hyperosmolar state is a potential complication of repeated use of mannitol. In order to lessen the risk of this side effect, intravenous fluids can be administered to compensate for losses that are occurring. The level of monitored ICP can be used to time subsequent doses of mannitol. In patients with secondary hydrocephalus, drainage of CSF can be achieved via an intraventricular catheter. Removal of a small amount of fluid often can lower ICP dramatically. Continuous CSF drainage can be done, especially in patients with SAH. Repeated lumbar punctures can be performed if a patient does not have a mass; the only likely situation is severe SAH without a focal hematoma. Hypothermia also has been used to treat increased ICP following stroke.

14.6 Characteristics of Stroke in CKD Patients

14.6.1 Stroke Subtypes

CKD is an independent risk factor for ischemic, as well as hemorrhagic, stroke. In a population-based cohort study, the relative risk for ischemic stroke was 4.3–10.1 and that for hemorrhagic stroke was 4.1–6.7, respectively, in dialysis patients [4]. Even in the patients with a mild level of glomerular dysfunction, the risk for stroke appears to be increased. Recently, our group also demonstrated that CKD is associated with recurrent ischemia but not with hemorrhagic transformation in acute stroke patients [5]. A recent study with 20,386 participants without previous stroke has revealed that the incidence of stroke symptoms increased in patients with a lower estimated GFR (eGFR) and a higher level of albuminuria [6]. The impact of CKD on the stroke subtype may be different depending on gender. In 539,287 Swedish men and women free of previous stroke, the hazard ratios of renal dysfunction for ischemic stroke were 1.09, 1.24, and 2.27 for those with a mildly, moderately, and severely decreased GFR, respectively. This trend was observed in both genders. In contrast, hemorrhagic stroke was only related to renal dysfunction in females: 1.39, 1.70, and 3.46 for a mildly, moderately, and severely decreased GFR [7]. In a study of 12,222 Japanese men and women living in four communities, CKD increased the risk of hemorrhagic stroke, especially for males, but that of ischemic stroke for females. In that study, it was concluded that the gender difference was due to the differences in the prevalence of alcohol drinkers [8]. Therefore, CKD may have a gender-specific association with ischemic and hemorrhagic stroke, but this may differ according to the presence of other risk factors or in different ethnic groups.

14.6.2 Subtypes of Ischemic Stroke

Atherosclerosis is progressive in CKD patients. The prevalence of intracranial artery calcification was shown to be high in acute ischemic stroke patients with a reduced GFR [9]. Another study reported that proteinuria was an independent risk factor for ischemic stroke due to thrombotic arterial occlusion in patients with non-insulin-dependent diabetes mellitus [10]. A reduced GFR and increased excretion of albumin are factors closely associated with increased permeability or vulnerability of the small vessels, independent of other risk factors. These changes are causative of white matter lesions, cerebral microbleeds, and lacunar infarction. Recent studies showed that patients with a reduced GFR had more frequent lacunar strokes, as assessed by MRI. Cerebral microbleeds were also shown to be associated with proteinuria and with the level of microalbuminuria. The prevalence of atrial fibrillation is high in patients with late-stage CKD, ranging from 7 to 27 % in various studies. The hypercoagulable state deteriorates in parallel with the severity of renal dysfunction. Go et al. [11] reported that in patients with atrial fibrillation, proteinuria and a lower eGFR increased the risk of thromboembolism, independent of other known risk factors. Albuminuria or proteinuria is a surrogate for an increased permeability of the brain vasculature and thus implies an increased susceptibility to hemorrhagic transformation after infarction. A recent study showed that albuminuria was an independent predictor for hemorrhagic transformation following acute ischemic stroke, even after adjustment for possible confounding factors. Albuminuria was shown to be associated with parenchymal hemorrhage [12].

14.7 Clinical Outcomes in Stroke Patients with CKD

14.7.1 Functional Outcomes

CKD is associated with the functional outcomes in patients with acute stoke. Ovbiagele et al. [13] investigated the association between proteinuria or a low eGFR and functional activities in patients with an acute ischemic stroke without known CKD. They found that the clinical outcomes were poorer in relation to proteinuria, but not to a low GFR. It has been shown that in patients with lacunar stroke, the progression of neurological symptoms occurred more often in those with albuminuria. Albuminuria was an independent predictor of the neurological progression in patients with a lacunar stroke, and the progression was associated with a worse outcome at 90 days. Recent studies showed that patients with microalbuminuria showed a more severe neurological deficit and presented more decreased levels of consciousness. In cases of hemorrhagic stroke, moderate-to-severe CKD was associated with a larger hematoma volume. However, another study showed that, in patients with intracerebral hemorrhage, proteinuria and a low eGFR were not linked to the patient being discharged directly to home [14].

14.7.2 Mortality

A recent study showed that CKD was also significantly associated with in-hospital mortality after stroke, regardless of the stroke subtypes, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. This association was more pronounced in patients with a younger age and in females. A low GFR or proteinuria, or both, have been suggested to be involved in the short-term mortality after stroke. In patients with ischemic stroke, both proteinuria and a lower eGFR were predictive factors for the 30-day mortality. The mechanism by which CKD is associated with poor outcomes after stroke is unknown. In patients with ischemic stroke, acute kidney injury tended to occur in those with a reduced GFR after acute stroke and was associated with short-term survival. Since baseline kidney function was an independent predictor for acute kidney injury, poor functional outcomes may be partially mediated by acute kidney injury [11–14].

14.8 Management of Acute Stroke in CKD Patients

14.8.1 Tissue-Plasminogen Activator

It still remains controversial as to whether tissue-plasminogen activator is beneficial or detrimental to the clinical outcomes after ischemic stroke complicated by CKD. Hemorrhagic infarction is a major concern after thrombolytic therapy in CKD patients, because hemorrhagic transformation or cerebral microbleeds are more prevalent in these patients. Agrawal et al. [15] reported that an eGFR <60 ml/min/1.73 m^2 was not associated with an increased risk of symptomatic intracranial hemorrhage, poor functional outcomes, or in-hospital death in patients receiving thrombolytic therapy. They concluded that the clinical outcomes after the use of thrombolytic therapy were similar between those with and without CKD. However, another recent study has shown contradictory results, thus suggesting that a reduced eGFR was associated with early intracerebral hemorrhage and poor outcomes after 3 months in patients treated with tissue-plasminogen activator [16].

14.8.2 Anticoagulation Therapy

In patients with CKD, a variety of factors, including the treatments being administered, affects the coagulation and fibrinolytic states, leading to thrombosis and/or hemorrhage. The use of warfarin is associated with an improved survival in dialysis patients with atrial fibrillation. In high-risk patients with stage 3 CKD, an adjusted dose of warfarin was suggested to be effective to reduce the risk of ischemic stroke and systemic embolism. Anticoagulation therapy with warfarin targeting an INR between 2.0 and 3.0 is probably effective in CKD patients with atrial fibrillation to reduce the risk of thromboembolic stroke without increasing major bleeding. However, the efficacy and optimal intensity of anticoagulation to prevent early recurrence after cardioembolic stroke in CKD patients with atrial fibrillation are currently unknown.

14.9 Management of Symptomatic Carotid Stenosis in CKD Patients

CKD carries an increased risk for cardiovascular disease (CVD) including cerebrovascular events (CVE). There are multiple etiologies for CVE, and among them extracranial carotid artery disease accounts for approximately 25 % of ischemic strokes. It has been shown that carotid revascularization by carotid endarterectomy and carotid artery angioplasty and stenting can decrease the risk of CVE in appropriately selected population with carotid artery disease. Both these techniques of carotid revascularization have been shown to be safe and clinically effective in many large multicentered randomized clinical trials. However, most of these large trials have predominately excluded the patients with kidney failure. Most of the evidence for the management of carotid disease in CKD is based on small clinical trials and expert opinions. There is an urgent need to conduct large clinical trials in patients with CKD to enable better understanding and to improve techniques of various carotid revascularization therapies in CKD patients. A recent study showed that *individuals who have symptomatic moderate- to high-grade carotid stenosis and also have CKD benefit from and tolerate carotid endarterectomy. How this compares with the use of carotid stenting or with the use of maximal medical therapy in an era of statin use and good BP management is still unclear and warrants further study*.

14.10 Secondary Prevention

Secondary prevention includes the treatment of patients who have had ischemic symptoms, including prior ischemic stroke, transient ischemic attack (TIA), or amaurosis fugax. These persons have a much higher risk of stroke than any other population, and of these groups, those patients with previous ischemic stroke have the highest risk. Because persons with ischemic cerebrovascular disease also are at high risk for symptomatic coronary artery disease, prophylactic measures should include

interventions to prevent or treat any ischemic heart disease. Fortunately, most medications that are effective in lowering the risk of ischemic stroke also lower the risk of myocardial infarction and vascular death. Still, one must remember that none of the measures to prevent stroke or other serious ischemic events will be uniformly successful. Rather, these therapies lower risks.

14.11 Medications to Prevent Thromboembolism

Several therapies that prevent thromboembolism are of proven usefulness in preventing stroke in high-risk patients (Box 14.8). Decisions about the prescription of medications to prevent thromboembolism are based on several factors including:

- Presumed vascular territory
- Likely cause of the ischemic symptoms
- Previous use of medications or prior surgery
- Contraindications for any specific intervention
- Wishes of the patient

14.11.1 Oral Anticoagulants

Warfarin or one of its derivatives is the usual oral anticoagulant that is prescribed for long-term stroke prophylaxis. As antagonists of vitamin K, these agents reduce plasma levels of the active factors II, VII, IX, and X and proteins C and S. Oral anticoagulants are of established utility for treatment of deep-vein thrombosis and for prevention of cardioembolic stroke. Patients with cardiac diseases associated with a high risk for thromboembolism should receive long-term anticoagulant therapy unless a specific contraindication exists. Hemorrhage is the most frequent adverse experience resulting from the use of oral anticoagulants; the leading fatal complication is intracranial hemorrhage [17].

Box 14.8. Therapies That Prevent Thromboembolic Stroke

Anticoagulants

- Warfarin

Antiplatelet-Aggregating Agents

- Aspirin
- Aspirin and dipyridamole
- Clopidogrel
- Ticlopidine

Surgical Interventions

- Carotid endarterectomy
- Other reconstructive operations
- Endovascular procedures

14.11.2 Antiplatelet Agents

14.11.2.1 Aspirin

Aspirin interferes with platelet function and thromboxane A2 production by irreversible acetylation and inactivation of cyclooxygenase. It has little effect on platelet adhesion or aggregation at high sheer stress. Aspirin is the most commonly prescribed medication for the primary or secondary prevention of ischemic stroke in patients with arterial diseases. Meta-analyses show that aspirin is effective in preventing stroke, myocardial infarction, and vascular death in high-risk men and women regardless of age. Presence of hypertension or diabetes mellitus does not affect responses to treatment. Aspirin also is used as an alternative to oral anticoagulants for those persons with cardiac sources of thromboembolism, such as AF, who cannot take warfarin. Aspirin can be started safely within the first days after stroke. Aspirin is recommended for the prevention of stroke for most high-risk patients with arterial diseases. It is the usual choice for the medical prevention of arterial thromboembolism for patients with symptoms in either the carotid or vertebrobasilar circulation. Aspirin alone, in a daily dose of 325 mg, is effective in preventing thromboembolism in people with AF, and it is recommended for treatment of those patients who cannot tolerate oral anticoagulants.

14.11.2.2 Dipyridamole and Aspirin/Dipyridamole

Dipyridamole has reversible effects on platelet aggregation through its inhibition of

phosphodiesterase. In addition, the medication causes vasodilation. Dipyridamole has few side effects, with headache being the most bothersome complaint. Some patients with unstable angina pectoris might not tolerate the medication. Bleeding complications are few. No trial has directly compared the efficacy of clopidogrel or the combination of aspirin and extended-release dipyridamole in preventing stroke among high-risk patients. The combination of low-dose aspirin plus extended-release dipyridamole is an important option for management when a patient has a TIA or stroke.

14.11.2.3 Clopidogrel

Clopidogrel is a potent antiplatelet agent that blocks adenosine diphosphate (ADP)-induced platelet aggregation. Its usual daily dose is 75 mg. Some groups have used a "loading dose" of approximately 300 mg of clopidogrel to start treatment in order to rapidly achieve maximal effects on platelet aggregation. The need for this tactic when treating patients with stroke is not clear. Because it is pharmacologically similar to ticlopidine, it can also be associated with gastrointestinal symptoms and allergic reactions. However, unlike ticlopidine, the risk of neutropenia is relatively low. In addition, patients undergoing cerebrovascular angioplasty and stenting often are prescribed the medication for a period that usually lasts 6–8 weeks after the procedure. Clopidogrel can be considered a treatment alternative in a patient who has recurrent symptoms despite use of aspirin or in a patient in which treatment with aspirin is contraindicated.

14.12 Surgical Procedures

Several surgical procedures are available to treat patients with extensive intracranial or extracranial cerebrovascular disease. The goals of these operations are to either remove a source for thromboembolism or to improve flow to a vulnerable area of the brain. Carotid endarterectomy (CEA) is the most widely performed operation for prevention of stroke [17].

14.12.1 Carotid Endarterectomy

Carotid endarterectomy is of proven utility for prevention of stroke in patients with symptomatic high-grade stenosis (>50 %) of the origin of the internal carotid artery. The role of the operation for prevention of stroke in patients with an asymptomatic stenosis >60 % is more controversial than its use in patients who have had an ipsilateral TIA or ischemic stroke, but recent evidence suggests that CEA can be recommended for carefully selected patients. The advantage of surgical treatment increases in patients with marked narrowing of the carotid artery (>70 % stenosis). The benefit of surgery in patients with very severe narrowing (99+ % stenosis) is not as clear. The presence of severe ulceration in addition to a high-grade stenosis increases the potential advantage to be derived from CEA. Patients with occlusion of the internal carotid artery and those with an intraluminal thrombus usually are not treated with operation.

14.12.1.1 Extracranial-Intracranial Arterial Anastomoses and Other Operations

Superficial temporal artery-middle cerebral artery anastomosis (extracranial-intracranial [EC/IC] bypass) was tested in a large clinical trial. Patients with occlusion of the internal carotid artery and stenoses of the middle cerebral artery were treated. Although operatively treated patients did very well, their outcomes were not superior to those of patients who were treated medically. As the result, EC/IC bypass has been abandoned other than for exceptional cases, such as those people who have moyamoya disease [17].

14.12.1.2 Angioplasty and Placement of Arterial Stents

Angioplasty, with or without stent placement, is being used to treat patients with stenotic lesions in the intracranial or extracranial arteries. The use of this procedure is controversial. In particular, the utility of angioplasty and stenting as an alternative to CEA is not known. While preliminary studies suggest that angioplasty and stenting

are a feasible way to manage stenotic lesions of the arteries perfusing the brain, there are concerns about the safety and long-term efficacy of these procedures. One trial demonstrated that endarterectomy and angioplasty were roughly equal in safety, although recurrent stenosis was more common with the endovascular procedure. Most of the patients did not have stents. Additional studies currently are under way.

Before You Finish: Practice Pearls for the Clinication

- Individuals who have symptomatic moderate- to high-grade carotid stenosis and also have CKD benefit from and tolerate carotid endarterectomy.
- In high-risk patients with stage 3 CKD, an adjusted dose of warfarin was suggested to be effective to reduce the risk of ischemic stroke and systemic embolism.
- CKD has significantly associated with in-hospital mortality after stroke, regardless of the stroke subtypes, ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.

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