Chapter 39: Stroke

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UPDATE SUMMARY

Update Summary

September, 2023

The following sections, tables, and figures were updated:

- Updated guidance regarding the use of tenecteplase for the treatment of acute ischemic stroke following publication of the NOR-TEST 2, part A study and updated recommendations from the European Stroke Organization.
  - Table 39-3
  - Pharmacologic Therapy/Acute Ischemic Stroke/Acute Treatment/Tenecteplase

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 13, Stroke.

KEY CONCEPTS

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1. Stroke can be either ischemic (87%) or hemorrhagic (13%), and the two types are treated differently.
2. Transient ischemic attacks (TIAs) require urgent intervention to reduce the risk of stroke, which is known to be highest in the first few days after TIA.
3. In patients with an ischemic stroke and a blood pressure (BP) <220/120 mm Hg without comorbid conditions requiring acute hypertensive treatment, the acute lowering of BP in the first 48 to 72 hours after stroke onset does not improve survival or the level of dependency; "permissive hypertension" (BP up to 220/120 mm Hg) is often allowed. In patients with intracranial hemorrhage and elevated systolic blood pressure (SBP) between 150 and 220 mm Hg, the acute lowering of SBP to lower than 140 mm Hg is safe and may improve functional outcomes.
4. Thrombectomy is strongly recommended for patients with anterior circulation arterial occlusion in the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) who are within 6 hours of symptom onset and may be considered in select patients within 6 to 24 hours of symptom onset.
5. In patients with ischemic stroke and 70% to 99% stenosis of the carotid artery, carotid endarterectomy or carotid stenting should be performed.
6. Early pharmacologic reperfusion (initiated less than 4.5 hours from symptom onset) with intravenous alteplase or tenecteplase has been shown to improve functional ability after ischemic stroke.
7. Antiplatelet therapy is the cornerstone of antithrombotic therapy for the secondary prevention of noncardioembolic ischemic stroke.
8. Oral anticoagulation is recommended for the secondary prevention of cardioembolic stroke in moderate- to high-risk patients.
9. Elevated blood pressure is very common in ischemic stroke patients, and treatment of hypertension in these patients is associated with a decreased risk of stroke recurrence.
10. Statin therapy is recommended for all ischemic stroke patients, regardless of baseline cholesterol, to reduce stroke recurrence.

BEYOND THE BOOK

BEYOND THE BOOK

Watch the video entitled "What is a stroke?" (https://youtu.be/QIAI6KOwKII) in Khan Academy. This 11-minute video provides an overview of stroke and is useful to enhance understanding of stroke pathophysiology.

INTRODUCTION

Stroke is the leading cause of disability among adults and the fifth leading cause of death in the United States, behind cardiovascular disease, cancer, unintentional injuries, and chronic lower respiratory diseases.[1] Although the incidence of stroke has been trending downward, approximately 795,000 strokes occur annually, contributing to nearly 148,000 deaths each year.[2] Aggressive efforts to organize stroke care at the local and regional levels and increased utilization of evidence-based recommendations and national guidelines may have contributed to improved outcomes.

EPIDEMIOLOGY

There are about 7.6 million stroke survivors in the United States, and stroke is the leading cause of adult disability, with women having worse outcomes than men.[2] Owing in part to the need for expensive posthospitalization rehabilitation and nursing home care, the annual cost of stroke in the United States is estimated to be nearly $50 billion.[2]

Not all groups have benefitted equally from advances in care and stroke prevention efforts. Black Americans have stroke rates that are 1.5 times higher than White Americans; rates are up to four times higher at younger ages.[2] Genome-wide studies provide some evidence that part of this racial disparity is genetic. However, age-adjusted death rates for stroke are still 1.6 times higher for Black men compared to White men and 1.3 times higher for Black women compared to White women.[2] In addition, geographic disparity in stroke incidence exists, such that many southeastern states in the United States have stroke mortality rates 30% to 40% higher than the national average.[2] Lastly, case fatality due to hemorrhagic stroke has not declined in the past decade, with 30-day rates remaining around 46%.[2]

ETIOLOGY

1 Stroke is subdivided into either ischemic or hemorrhagic types (87% and 13%, respectively).[2] Hemorrhagic stroke includes subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). SAH occurs when blood enters the subarachnoid space, which can occur due to trauma, rupture of an intracerebral aneurysm, or rupture of an arteriovenous malformation (AVM). ICH, however, occurs when bleeding occurs in the brain parenchyma itself, with the formation of a hematoma within the brain. Uncontrolled hypertension is the most common cause of ICH, but antithrombotic therapy, cerebral amyloid angiopathy, and some drugs of abuse are also associated with ICH.[3] Hemorrhagic stroke, though less frequent in occurrence, has significantly higher mortality than ischemic stroke and is dependent on the quality and availability of critical care. In high-income countries, the mortality rate is 25% to 30%, but it is 30% to 48% in low- and middle-income countries.[3]

Ischemic stroke is caused by occlusion within a cerebral artery or emboli from a more proximal source resulting in occlusion of a cerebral artery. Atherosclerosis of large arteries, either intracranial or extracranial, as well as small artery damage, can give rise to ischemic stroke. Emboli can also arise centrally from the heart in patients with atrial fibrillation, valvular heart disease, or other prothrombogenic heart problems and are responsible for approximately 25% of ischemic strokes. While large artery atherosclerosis, small artery disease, and cardioembolism comprise the majority of ischemic stroke mechanisms, the cause of stroke is undetermined in some cases.[2] Determining the stroke mechanism (eg, cardiogenic mechanism vs other causes) is important when selecting the most appropriate long-term pharmacotherapy in stroke patients.

Risk Factors

Risk factors for ischemic stroke can be described as nonmodifiable or modifiable, with some risk factors more well-documented than others. The main risk factors of ischemic stroke are listed in TABLE 39-1.[4] The risk of stroke doubles for each decade after 55 years of age. Men are at a higher risk of ischemic stroke than women at a younger age, but women have higher mortality and lifetime risk of ischemic stroke overall. Individuals who identify as Black, Asian-Pacific Islanders, or Hispanic have higher rates of death from ischemic stroke compared to those who identify as White.[4] Recommendations for ischemic stroke prevention focus on aggressive management of modifiable, well-documented risk factors.

TABLE 39-1

Risk Factors for Ischemic Stroke

Nonmodifiable Risk Factors • Age • Race • Sex • Low birth weight • Genetic factors
Modifiable, Well Documented • Cigarette smoking • Hypertension • Diabetes • Asymptomatic carotid stenosis • Dyslipidemia • Atrial fibrillation • Sickle cell disease • Poor diet • Obesity • Physical inactivity • Other cardiac diseases (coronary heart disease, heart failure, peripheral arterial disease)
Potentially Modifiable, Less Well Documented • Migraine • Metabolic syndrome • Drug and alcohol abuse • Inflammation and infection • Elevated lipoprotein (a) • Homocysteinemia • Patent foramen ovale • Sleep-disordered breathing

Data from Reference 4.

The most common modifiable, well-documented risk factors for ischemic stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and dyslipidemia. Hypertension is the most common risk factor, affecting up to one in three adults in the United States. Cardiac disease, including coronary artery disease, heart failure, left ventricular hypertrophy, and particularly atrial fibrillation, is also a very important risk factor. Atrial fibrillation increases an individual's risk of ischemic stroke to 5% to 20% per year, depending on concomitant comorbidities. Diabetes mellitus, dyslipidemia, and cigarette smoking contribute to atherogenic disease and increase the risk of ischemic stroke.[4]

PATHOPHYSIOLOGY

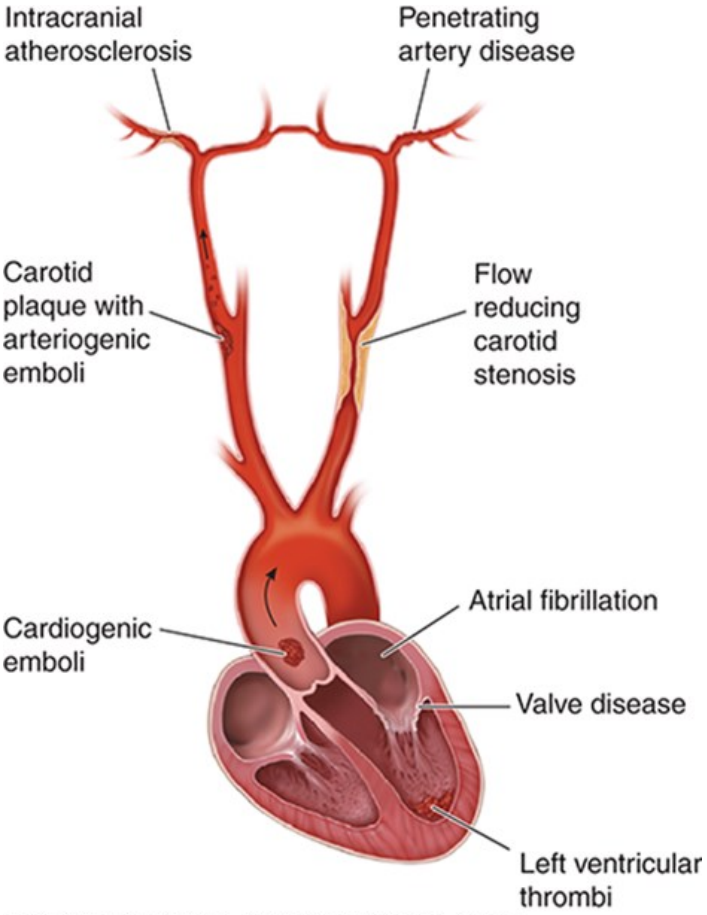
Ischemic Stroke

Ischemic stroke is the manifestation of neurologic deficits due to the occlusion of a cerebral artery, causing a reduction in cerebral blood flow and neuronal ischemia. The pathophysiologic mechanisms of ischemic stroke are depicted in Fig. 39-1. These arterial occlusions are most commonly due

to artery-to-artery emboli, cardiac sources of emboli, or vascular changes leading to occlusion of the cerebral artery itself. Cerebral blood flow is maintained at an average rate of 50 mL/100 g per minute over a wide range of blood pressure (mean arterial pressures of 50-150 mm Hg) by a process called cerebral autoregulation. Cerebral blood vessels dilate and constrict in response to changes in blood pressure, but this process can be impaired by atherosclerosis, chronic hypertension, and acute injury, such as stroke. Decreased cerebral blood flow due to arterial occlusion can lead to infarction of cerebral tissue. Surrounding a core area of infarct is tissue that is ischemic but may maintain membrane integrity. This area is called the *ischemic* penumbra.[5] This penumbra is the area of brain tissue that is potentially salvageable with urgent pharmacologic and endovascular interventions in acute ischemic stroke.

FIGURE 39-1

Pathophysiology of ischemic stroke. Diagram illustrating the three major mechanisms underlying ischemic stroke including occlusion of an intracranial vessel by an embolus that arises from a distant site (eg, cardiogenic embolus), in situ thrombosis of an intracranial vessel, typically affecting the small penetrating arteries, and hypoperfusion caused by flow-limiting stenosis of a major extracranial artery. *(Reproduced, with permission, from Smith WS, Johnston S, Hemphill J III. Ischemic stroke. In: Jameson J, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2018.)*



Insufficient oxygen supply in ischemic tissue leads to adenosine triphosphate (ATP) depletion and anaerobic metabolism. This results in an accumulation of intracellular lactate, sodium, and water, which may cause cytotoxic edema and eventual cell lysis. There is also an influx of intracellular calcium leading to activation of lipases and proteases that degrade proteins and release free fatty acids from cellular membranes. Additionally, excitatory amino acids, such as glutamate and aspartate, are released in ischemic tissue, which perpetuates neuronal damage and the production of damaging prostaglandins, leukotrienes, and reactive oxygen species. These processes occur within 2 to 3 hours from the onset of

ischemia and, ultimately, lead to cellular apoptosis and necrosis.[5]

Hemorrhagic Stroke

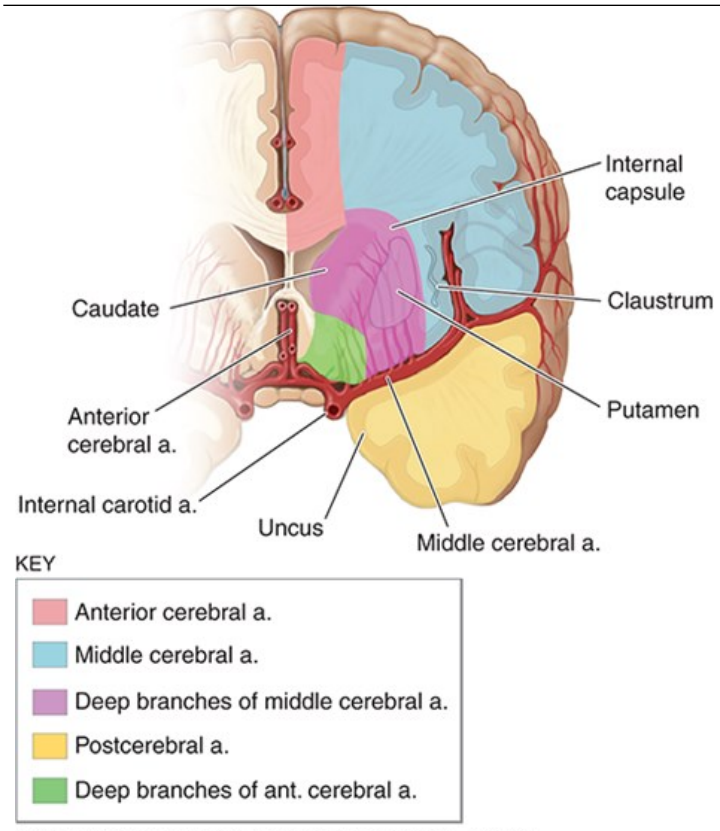
Hemorrhagic stroke causes neuronal damage by a variety of mechanisms and timelines. In patients with ICH, the hematoma causes primary injury and mechanical compression of the brain parenchyma itself. Early hematoma expansion, which may occur in up to 38% of patients within 3 hours of ICH onset, is associated with worsened functional outcomes and increased mortality. The highest rates of mortality are associated with a low Glasgow Coma Score (GCS) on presentation (GCS 3-4), ICH volume greater than 30 cc (mL), intraventricular extension, brain stem location, and age greater than 80.[6] Secondary mechanisms of injury in ICH patients are mediated by subsequent inflammatory response, cerebral edema, and damage from blood product degradation.[3]

CLINICAL PRESENTATION

The term stroke describes patients with an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction. The syndrome of arterial ischemia with transient symptoms (<24 hours) and without evidence of infarction is a transient ischemic attack (TIA). Appropriate patient history obtainment helps determine the nature of symptom onset and duration of neurologic dysfunction. The location of the central nervous system (CNS) injury and its reference to a specific arterial distribution in the brain are determined through neurologic examination and confirmed by imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI). The main arterial supply to the cerebral hemispheres is illustrated in Figs. 39-2 and 39-3. Vascular imaging with computed tomography angiography (CTA) can aid clinicians in determining the cause of stroke and whether urgent mechanical intervention is necessary.

FIGURE 39-2

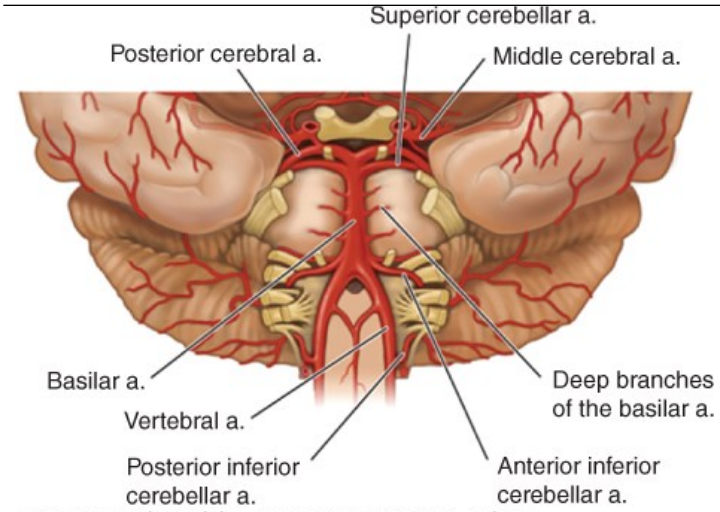
Diagram of a cerebral hemisphere in coronal section showing the territories of the major cerebral vessels branching from the internal carotid arteries. *(Reproduced, with permission, from Smith WS, Johnston S, Hemphill J III. Cerebrovascular diseases. In: Jameson J, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2018.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

FIGURE 39-3

Diagram of the posterior circulation, showing the intracranial vertebral arteries forming the basilar artery that gives off the anterior inferior cerebellar, superior cerebellar, and posterior cerebral arteries. The posterior inferior cerebellar artery arises from each of the vertebral segments. The majority of brainstem blood flow arises from numerous deep branches of the basilar artery that penetrate directly into the brainstem. *(Reproduced, with permission, from Smith WS, Johnston S, Hemphill J III. Cerebrovascular diseases. In: Jameson J, Fauci AS, Kasper DL, et al., eds. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw Hill; 2018.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

CLINICAL PRESENTATION: Stroke

General

- The patient may not be able to reliably report the history due to cognitive or language deficits. A reliable history may have to come from a family member or witness.

Symptoms

- The patient may complain of weakness on one side of the body, inability to speak, loss of vision, vertigo, and/or falling. Ischemic stroke is not usually painful, but some patients may complain of headache. Pain and headache, often severe, are more common with hemorrhagic stroke.

Signs

- The specific areas of neurologic deficit are determined by the area of the brain involved.
- Hemiparesis or monoparesis occurs commonly, as does a hemisensory deficit.
- Patients with vertigo and double vision are likely to have posterior circulation involvement.
- Aphasia is seen commonly in patients with anterior circulation strokes.
- Patients may also suffer from dysarthria, visual field deficits, and altered levels of consciousness.

Laboratory Tests

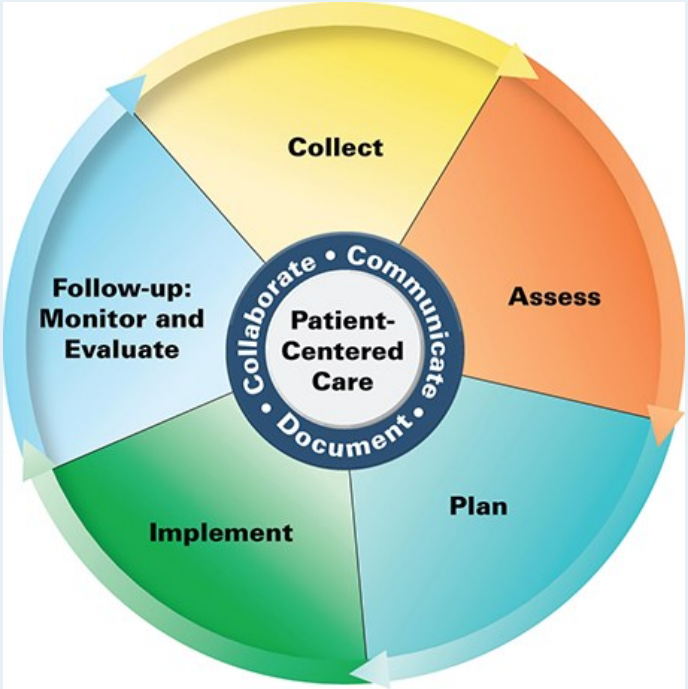
- In acute stroke, assessment of blood glucose, platelet count, and coagulation parameters (eg, prothrombin time, aPTT) are used to determine treatment eligibility.
- Tests for hypercoagulable states (protein C/S deficiency, antiphospholipid antibody) should be done only when the cause of the stroke cannot be determined based on the presence of well-known risk factors.

Other Diagnostic Tests

- CT scan of the head will reveal an area of hyperdensity (bright) in patients with hemorrhage and will be normal or hypodense (dark) in patients with infarction. It may take 24 hours before the CT scan will reveal the area of infarction.
- MRI of the head will reveal areas of ischemia with higher resolution, and an MRI with diffusion-weighted imaging (DWI) will reveal an evolving infarct within minutes of stroke onset.
- Vascular imaging with CTA is recommended in patients with endovascular treatment indications. CTA can identify both acute treatment candidacy as well as identify intracranial and extracranial arterial stenosis.
- An ECG can help determine whether the patient is presenting with atrial fibrillation.
- TTE can identify cardiac valve abnormalities or wall-motion abnormalities as sources of emboli to the brain. A “bubble study” in which a solution with tiny bubbles is injected intravenously can be done to look for an intra-arterial shunt indicating an atrial-septal defect or a patent foramen ovale. The bubbles can be seen moving through the heart chambers during the TTE.
- In patients unable to undergo CTA, carotid Doppler (CD) and transcranial Doppler (TCD) can be used to determine extracranial carotid artery stenosis and intracranial artery stenosis.

PATIENT CARE PROCESS

Patient Care Process for Acute Ischemic Stroke



Collect

- Patient characteristics (eg, age, sex, race)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current medications including nonprescription aspirin/nonsteroidal anti-inflammatory drug (NSAID) use, herbal products, dietary supplements, and prior antiplatelet and anticoagulant medication use
- Medication allergies
- Symptoms (time of onset, duration)
- Objective data
    - Blood pressure (BP), heart rate, respiratory rate, height, weight
    - Labs including hemoglobin, platelets, serum creatinine, activated partial thromboplastin time (aPTT), prothrombin time, blood glucose, troponin
    - Noncontrast computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or computed tomography angiography (CTA) may be needed
    - Neurologic examination (eg, National Institutes of Health Stroke Scale [NIHSS] score)
    - Electrocardiogram (ECG) and, in some patients, transthoracic echocardiogram (TTE)

Assess

- Hemodynamic stability (eg, systolic blood pressure [SBP] <110 mm Hg, diastolic blood pressure [DBP] <185 mm Hg, if a candidate for tissue

plasminogen activator candidate; otherwise, BP less than 220/120 mm Hg; O_2-sat >94% [0.94]; temperature <38°C [100.4°F])

- Blood glucose (<60 mg/dL [3.7 mmol/L] or >180 mg/dL [10.0 mmol/L] should be treated)
- Presence of active bleeding and/or bleeding risk factors (Table 39-6)
- Patient's candidacy for tissue plasminogen activator treatment (Table 39-2) or thrombectomy
- Presence of dysphagia (swallowing disorder)

Plan

- Aspirin within 24 to 48 hours unless contraindicated; delay for 24 hours if the patient has been given tissue plasminogen activator
- Antiplatelet drug therapy regimen including specific medication(s), dose, frequency, and duration OR oral anticoagulant, if the patient has atrial fibrillation (see Table 39-2)
- Evaluation for carotid endarterectomy or carotid stenting
- Prophylaxis for venous thromboembolism, if immobile
- Nutritional plan; if the patient has dysphagia, nutrition via nasogastric tube or percutaneous gastrostomy tube
- Treat and manage stroke risk factors (Table 39-2) (eg, BP control, dyslipidemia, diabetes)
- Monitoring parameters including efficacy (eg, stroke symptoms) and safety (eg, signs and symptoms of bleeding [all antiplatelets and oral anticoagulants], headache [dipyridamole]); frequency and timing of follow-up
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Self-monitoring for stroke recurrence, the occurrence of bleeding, and when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, physical therapist, occupational therapist, behavioral health, dietician)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Improvement of stroke symptoms; neurological examination
- Presence of adverse drug reactions (eg, bleeding [all medications], gastrointestinal upset [aspirin], headache [dipyridamole], cerebral edema, seizures)
- Patient adherence to treatment plan using multiple sources of information
- Adherence to recommended follow-up appointments (eg, neurology, physical therapy)
- Assess for poststroke depression

**Collaborate with patient, caregivers, and other healthcare professionals.*

TREATMENT

Desired Outcomes

The goals of treatment of acute stroke are to (a) minimize the ongoing neurologic injury in the acute setting to reduce mortality and long-term disability, (b) prevent complications secondary to immobility and neurologic dysfunction, and (c) prevent stroke recurrence. Primary prevention of stroke is described in the Chapter 30 (Hypertension), Chapter e31 (Acute Hypertensive Crisis), and Chapter 32 (Dyslipidemia).[4]

General Approach to Treatment

2 3 Patients with presumed acute stroke should have a CT scan performed urgently to identify the type of injury (eg, ischemic or hemorrhagic), provided respiratory and cardiac indices are stable. Ischemic stroke patients presenting within hours of symptom onset should be evaluated for pharmacologic and mechanical reperfusion therapy. Patients with TIA require urgent assessment and intervention to reduce the risk of stroke, which is highest in the first few days after TIA.[4]

In the absence of comorbid conditions, in patients with an acute ischemic stroke and uncontrolled hypertension with a BP <220/120 mm Hg, acutely lowering BP in the first 48 to 72 hours does not prevent death or improve the level of dependency. Therefore, “permissive hypertension” is often part of routine care in these patients. However, for patients who are candidates for alteplase or those with comorbid conditions, such as aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy, treatment of acute hypertension may be required. If BP is treated, the use of short-acting and easily titrated agents, such as labetalol or nicardipine/clevidipine, is preferred. See Chapter e31, Acute Hypertensive Crisis. Table 39-2 outlines current recommendations regarding the management of arterial hypertension in patients with acute ischemic stroke. In patients with ICH and elevated BP, the acute lowering of SBP to 140 mm Hg has been shown to be safe and may improve functional outcomes.[6]

TABLE 39-2

Blood Pressure Treatment Guidelines in Stroke

Recommendation	Class (Strength) of Recommendation[a]	Level (Quality) of Evidence[b]
Ischemic Stroke with Alteplase Treatment		
• Pre-alteplase: lower BP to SBP <185 mm Hg and DBP <110 mm Hg • Post-alteplase: maintain SBP <180 mm Hg and DBP <105 mm Hg for 24 hours	I	B-NR
Ischemic Stroke Without Alteplase Treatment		
• Treatment benefit uncertain/not recommended unless BP >220/120 mm Hg • If comorbid conditions (eg, acute coronary event, acute heart failure, aortic dissection, symptomatic intracranial hemorrhage, preeclampsia/eclampsia) are present that require acute lowering of BP, lowering BP by 15% is probably safe)	IIb I	C-EO C-EO
Ischemic Stroke with Mechanical Thrombectomy Without Fibrinolytic Treatment		
• It is reasonable to maintain BP ≤185/110 mm Hg before the procedure	IIb	C-EO
Intracranial Hemorrhage		
• Treatment is reasonable for ICH patients with SBP >220 mm Hg • For ICH patients with SBP 150-220 mm Hg, acute lowering of SBP to 140 mm Hg is safe	IIb I	C A
Pharmacologic Options for Blood Pressure Lowering in Acute Stroke		
• Labetalol 10-20 mg IV over 1-2 minutes; may repeat • Nicardipine 5 mg/hr IV, titrate up by 2.5 mg/hr every 5-15 minutes, maximum 15 mg/hr • Clevidipine 1-2 mg/hr IV, titrate by doubling the dose every 2-5 minutes, maximum 21 mg/hr • Other agents to consider: hydralazine, enalaprilat, nitroprusside IV infusion, labetalol IV infusion	IIb	C-EO

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GLP1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

Data from References 6 and 7.

[a]Class (strength) of recommendation: I, strong; IIa, moderate; IIb, weak; III, no benefit (moderate); 3, harm (strong).

[b]Level (quality) of evidence: A, high-quality evidence from more than 1 randomized clinical trial, meta-analyses of high-quality randomized clinical trials, or one or more randomized clinical trials corroborated by high-quality registry studies; B-R (randomized), moderate-quality evidence from one or more randomized clinical trials or meta-analyses of moderate-quality randomized clinical trials; B-NR (nonrandomized), moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies; C-LD (limited data), randomized or nonrandomized observational or registry studies with limitations or design or execution, meta-analyses of such studies, or physiological or mechanistic studies in human subjects; C-EO (expert opinion), consensus of expert opinion based on clinical experience.

Once the patient is out of the hyperacute phase (eg, first 24 hours), management is focused on preventing the worsening of stroke, minimizing complications, and secondary prevention. The acute phase of the stroke includes the first week after the event.[4]

Nonpharmacologic Therapy

Ischemic Stroke

4 To reperfuse ischemic brain tissue, endovascular intervention and thrombectomy is recommended by the American Heart Association (AHA)/American Stroke Association (ASA) since 2015 based on data from several clinical trials.[7] Thrombectomy is strongly recommended for patients with anterior circulation arterial occlusion in the ICA or the M1 segment of the MCA who are within 6 hours of symptom onset and may be considered in select patients within 6 to 24 hours of symptom onset. Patients with ICA and M1 MCA arterial occlusions and symptom onset within 24 hours may be candidates for endovascular intervention if imaging studies suggest a significant area of salvageable penumbra is present. The benefit of mechanical thrombectomy is less clear in patients with posterior circulation occlusions and should be considered in a case-by-case basis.[7] The availability of this mechanical intervention for stroke has greatly increased the importance of early vascular diagnostic imaging followed by rapid transfer to centers with interventional capabilities and escalation of care in patients with these emergent large vessel occlusions.

Large infarcts of the MCA are often devastating and, in patients without recanalization via pharmacologic or mechanical intervention, are associated with high rates of morbidity and mortality. Decompressive hemicraniectomy is a surgical procedure that can be done to reduce intracranial pressure, typically due to cerebral edema, and can reduce mortality and improve functional outcomes. In patients under 60 years of age with unilateral MCA infarcts and significant cerebral edema, surgical intervention with decompressive craniectomy has been shown to reduce mortality by almost 50% and improve favorable neurologic outcomes at 1 year. This surgical intervention can be considered for patients over the age of 60, but the likelihood of favorable neurologic outcomes is less robust. In patients with cerebellar infarction and significant swelling, surgical decompression can be lifesaving. For all ischemic stroke patients, coordinated care with a multidisciplinary approach to assessment and early rehabilitation is effective in reducing overall disability due to stroke.[7]

5 For the secondary prevention of ischemic stroke, carotid endarterectomy of an ulcerated and/or stenotic carotid artery is a very effective way to reduce stroke incidence and recurrence in patients with 70% to 99% stenosis if performed in centers with low operative morbidity and mortality.[8] Carotid stenting is a less invasive alternative that can be effective in reducing recurrent stroke risk when combined with aspirin and clopidogrel therapy.[8] However, it is associated with a higher periprocedural stroke rate.[8]

A patent foramen ovale (PFO) occurs when the septum between the right and left atria fails to close after birth. A PFO is present in 20% to 25% of adults, but in patients with stroke from unknown causes, 40% to 50% have a PFO.[9] The PFO can be closed surgically. People who benefit most from this surgery are 18 to 60 years of age with nonlacunar ischemic strokes of undetermined cause.[8]

Other nonpharmacological approaches for secondary stroke prevention include diet modification, exercise, smoking cessation, avoidance of environmental tobacco smoke, moderation of alcohol consumption, and avoidance of stimulants such as amphetamines and cocaine. A Mediterranean-type diet and, in patients with hypertension, reducing sodium intake is recommended. Exercise plans should take any mobility considerations into account. Alcohol consumption should be no greater than two drinks per day for men or one drink per day for women.[8]

Hemorrhagic Stroke

SAH often arises from a ruptured intracranial aneurysm or AVM, and intervention as early as possible with either surgical clipping or endovascular coiling of the vascular anomaly reduces the risk of rebleeding and improves mortality.[6] For patients with cerebellar ICH and neurologic deterioration, brainstem compression, and/or hydrocephalus from ventricular obstruction, early surgical intervention and hematoma removal is recommended. For patients with cerebral ICH, the usefulness of surgical hematoma evacuation or the use of minimally invasive clot evacuation is not well established. Ventricular drainage with an extraventricular drain (EVD) is reasonable in patients with hydrocephalus causing decreased consciousness.[6]

Temperature Management

Fever worsens outcomes in patients with both hemorrhagic and ischemic stroke types. Identification of the source of fever and management is recommended to maintain patients within normothermia ranges. Pharmacologic and nonpharmacologic interventions can be considered and applied. Data are limited to support induced hypothermia; it should be done only in a controlled, clinical trial setting.[6,7]

Pharmacologic Therapy

Ischemic Stroke

Acute Treatment

The stroke council of the ASA has created and published guidelines that address the management of acute ischemic stroke.[7] For acute treatment, the only two pharmacologic agents with class I recommendations are alteplase, initiated within 4.5 hours of stroke onset, and aspirin, started within 24 to 48 hours of stroke onset (Table 39-3).[7]

TABLE 39-3

Recommendations for Pharmacotherapy of Ischemic Stroke

Acute Treatment of Ischemic Stroke[7]		
Recommendation	**Class (Strength) of Recommendation[a]**	**Level (Quality) of Evidence[b]**
Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with the remainder given over 1 hour in selected patients		
• Within 3 hours of onset	I	A
• Between 3 and 4.5 hours of onset	I	B-R
Tenecteplase 0.25 mg/kg IV bolus (maximum 25 mg) may be a reasonable alternative to alteplase for patients who are also eligible to undergo mechanical thrombectomy	IIb	B-R
European Stroke Organisation Recommendation: For patients who are eligible for intravenous thrombolysis, tenecteplase 0.25mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg.	Strong	Moderate
Aspirin 160-325 mg daily started within 48 hours of onset	I	A
Aspirin 81 mg daily and clopidogrel 75 mg daily for 21 days may be effective in reducing recurrent stroke in patients who do not receive IV alteplase and present with minor, non-cardioembolic stroke (NIHSS ≤3)	I	A
Ticagrelor is not recommended over aspirin for the treatment of patients with minor acute stroke	III	B-R
Acute Treatment of Spontaneous Intracerebral Hemorrhage[6]		
Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets	I	C
Prophylactic antiseizure medication is not recommended	III	B

Secondary Prevention of Ischemic Stroke[7,10]			
Stroke Etiology	**Recommendation**	**Class (Strength) of Recommendation[a]**	**Level (Quality) of Evidence[b]**
Noncardioembolic	Antiplatelet therapy[7]		
	• Aspirin 50-325 mg daily	I	A
	• Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	I	A
	• Clopidogrel 75 mg daily	I	A
Cardioembolic (especially atrial fibrillation)	Anticoagulant therapy[7]		
	• Vitamin K antagonist (warfarin) (INR = 2-3)	I	A
	• Apixaban 5 mg twice daily	I	A
	• Dabigatran 150 mg twice daily	I	A
	• Edoxaban 60 mg daily	I	A
	• Rivaroxaban 20 mg daily	I	A
Atrial fibrillation without moderate to severe mitral stenosis or a mechanical heart valve	Apixaban, dabigatran, endoxaban, or rivaroxaban is preferred over warfarin	I	B-R
Risk Factor	**Recommendation**	**Class (Strength) of Recommendation[a]**	**Level (Quality) of Evidence[b]**
LDL cholesterol >100 mg/dL (2.59 mmol/L) with no known coronary heart disease, and no major cardiac sources of embolism	Atorvastatin 80 mg daily	I	A
Patients with atherosclerotic disease	Statins and ezetimibe, if needed; goal LDL cholesterol <70 mg/dL (1.81 mmol/L)	I	A
Very high risk (stroke + another major ASCVD or stroke + multiple high-risk conditions)[c] already taking statins at	Proprotein convertase subtilisin/kexin type 9 inhibitor therapy	IIa	B-NR

maximally tolerated dose and ezetimibe, but who still have LDL-cholesterol >70 mg/dL (1.81 mmol/L)			
Fasting triglycerides 135-499 mg/dL (1.53-5.64 mmol/L) and LDL cholesterol 41-100 mg/dL (1.06-2.59 mmol/L) who are on moderate- or high-intensity statin therapy, with HbA1c <10% (86 mmol/mol), and no history of pancreatitis, atrial fibrillation, or severe heart failure	Icoaspent ethyl 2 g twice daily	IIa	B-R
Fasting triglycerides ≥500 mg/dL (5.65 mmol/L)	Identify and address causes of hypertriglyceridemia; implement a very low-fat diet, avoid refined carbohydrates and alcohol; omega-3 fatty acids; fibrate therapy, if needed to prevent acute pancreatitis	IIa	B-NR
BP >130/80	BP reduction, goal <130/80 mm Hg	I	B-R
Patients who smoke	Smoking cessation with or without drug therapy	I	A
Men who drink >2 alcoholic drinks per day or women who drink >1 alcoholic drink per day	Reduce or eliminate alcohol consumption	I	B-NR
Patients who use stimulants and patients with infective endocarditis in the context of intravenous drug use	Cessation of use of substance	I	C-EO
Diabetes - treatment goal	Goal HbA1c ≤7% (53 mmol/mol)	I	A
Diabetes - drug therapy selection	Treatment with glucose-lowering agents with proven cardiovascular benefit (metformin + GLP1 receptor agonist therapy or sodium-glucose cotransporter 2 inhibitor) regardless of baseline HbA1C	I	B-R
Prediabetes, particularly with BMI ≥35 kg/m^2, <60 years, women with a history of gestational diabetes	Metformin 850 mg twice daily	IIb	B-R

[a]Class (strength) of recommendation: I, strong; IIa, moderate; IIb, weak; III, no benefit (moderate); 3, harm (strong).

[b]Level (quality) of evidence: A, high-quality evidence from more than 1 randomized clinical trial, meta-analyses of high-quality randomized clinical trials, or one or more randomized clinical trials corroborated by high-quality registry studies; B-R (randomized), moderate-quality evidence from one or more randomized clinical trials or meta-analyses of moderate-quality randomized clinical trials; B-NR (nonrandomized), moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies; C-LD (limited data), randomized or nonrandomized observational or registry studies with limitations or design or execution, meta-analyses of such studies, or physiological or mechanistic studies in human subjects; C-EO (expert opinion), consensus of expert opinion based on clinical experience.

[c]Very high risk of future ASCVD events includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. Major ASCVD events are history of ischemic stroke, acute coronary syndrome within the past 12 months, history of myocardial infarction, symptomatic peripheral arterial disease. High-risk conditions include: age ≥65 years; heterozygous familial hypercholesterolemia; history of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events; diabetes; hypertension; chronic kidney disease; current smoking.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; GLP1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LDL, low-density lipoprotein; NIHSS, National Institutes of Health Stroke Scale.

Alteplase

6 Early pharmacologic reperfusion (initiated less than 4.5 hours from symptom onset) with IV alteplase has been a mainstay of acute pharmacologic treatment to improve functional ability after ischemic stroke as compared to no intervention.[7] Alteplase, or recombinant tissue plasminogen activator (rt-PA), is a fibrinolytic agent that exhibits a moderate binding preference for fibrin and facilitates the conversion of plasminogen to plasmin, leading to the degradation of fibrin clots. Alteplase has a short half-life (approximately 4 minutes). The total dose for acute ischemic stroke is 0.9 mg/kg (maximum 90 mg), 10% administered as an intravenous (IV) bolus over 1 minute, and the remaining 90% given as an IV infusion over 60 minutes.[7]

The first large trial demonstrating the effectiveness of IV alteplase in the treatment of ischemic stroke was published in 1995. A subsequent study demonstrated improved functional outcomes at 3 months in patients with acute ischemic stroke treated with alteplase between 3 and 4.5 hours of stroke symptom onset when compared with placebo (52.4% vs 45.2%).[7] Based on these data, the AHA/ASA guidelines extended the window for alteplase from 3 hours to up to 4.5 hours from symptom onset. However, there may be diminished benefit of alteplase in patients presenting within 3 to 4.5 hours from symptom onset and severe stroke (NIHSS>25 or evidence of more than one-third of MCA territory infarct on initial imaging).[7] Consequently, delays in alteplase therapy should be minimized and early administration prioritized since this approach is associated with improved outcomes.

Alteplase use is associated with a high risk for bleeding, including ICH. Therefore, adherence to the guideline-recommended protocol is essential for achieving a positive outcome and minimizing the risk. This protocol can be summarized as (a) stroke team activation, (b) brain imaging study (eg, CT scan), (c) treatment as early as possible within 4.5 hours of symptom onset, (d) meeting inclusion and exclusion criteria (TABLE 39-4), (e) administration of alteplase 0.9 mg/kg total dose (maximum dose of 90 mg), 10% given as a bolus over 1 minute and the remaining 90% given as an IV infusion over 1 hour, (f) avoidance of antithrombotic therapy (anticoagulant or antiplatelet) for 24 hours after alteplase, and (g) close patient monitoring for BP, neurologic status, and hemorrhage. Endovascular intervention is not a contraindication to alteplase and patients eligible for alteplase should receive pharmacologic treatment in addition to mechanical thrombectomy.[7]

TABLE 39-4

Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

Inclusion Criteria
• Age ≥18 years • Clinical diagnosis of ischemic stroke with neurologic deficit • Time of symptom onset well established to be <4.5 hours from treatment initiation
Contraindications
• History of intracranial hemorrhage • History of ischemic stroke within the prior 3 months • Symptoms/imaging consistent with subarachnoid hemorrhage or acute intracerebral hemorrhage • Current use of direct thrombin inhibitors or direct factor Xa inhibitors in prior 48 hours • Use of treatment-dose low molecular weight heparin in prior 24 hours • Infective endocarditis • Intra-axial, intracranial neoplasm • Aortic arch dissection • Active internal bleeding or coagulopathy (platelets <100,000/mm^3 [100 × 10^9/L], INR>1.7, aPTT>40s, PT>15s) • Severe head trauma in prior 3 months • Gastrointestinal malignancy or bleeding within the prior 21 days
Warnings/Use Clinical Judgment
• Unruptured/unsecured AVM or aneurysm >10 mm • Major surgery or nonhead trauma • History of bleeding diathesis • Extensive regions of clear hypoattenuation on initial CT scan

aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; CT, computed tomography; INR, international normalized ratio; PT; prothrombin time.

Data from Reference 7.

Tenecteplase

Tenecteplase is a modified form of tissue plasminogen activator with protein substitutions that yield a higher degree of fibrin specificity and a longer half-life than alteplase. Unlike alteplase, tenecteplase can be administered as a single, rapid IV bolus dose. While tenecteplase is FDA-approved for the management of patients with acute ST-elevation myocardial infarction, use for ischemic stroke remains off-label. Tenecteplase has been studied in a variety of acute ischemic stroke populations and is specifically mentioned in the 2019 update to the AHA/ASA guidelines, which state tenecteplase 0.25 mg/kg (maximum 25 mg) may be considered an alternative to alteplase for patients who are also eligible to undergo mechanical thrombectomy (class IIb recommendation).[7] The AHA/ASA 2019 guideline update also includes a recommendation for consideration of tenecteplase 0.4 mg/kg (maximum 40 mg) as an alternative to alteplase for patients receiving thrombolysis with an NIHSS of 7 or less. More recently, an investigation studying the dose of tenecteplase 0.4 mg/kg was stopped early due to safety concerns[11]. Further commentary regarding the specific dose of tenecteplase and its place in therapy compared to alteplase is expected to change in the next guideline revision from the AHA/ASA based on these data. Acknowledging this new

data, in 2023, the European Stroke Organisation published updated guidelines regarding the use of tenecteplase, stating tenecteplase 0.25 mg/kg (maximum 25 mg) can be used as a safe and effective alternative to alteplase 0.9 mg/kg, with a recommendation against the use of tenecteplase at a dose of 0.4 mg/kg.[12]

Aspirin

Early aspirin therapy, within 24 to 48 hours from symptom onset, should be given to patients with acute ischemic stroke in the absence of aspirin allergy or other contraindications. For patients receiving alteplase, aspirin, and other antithrombotics are generally held for 24 hours after alteplase administration to reduce the risk of hemorrhage.[7]

Early use of aspirin in ischemic stroke patients is recommended by the AHA/ASA guidelines to reduce the long-term risk of death and disability.[7] Data regarding the acute use of non-aspirin antiplatelet agents in the acute stroke phase, apart from combination therapy regimens, are limited. However, using an alternative antiplatelet agent in patients with acute ischemic stroke who have a severe allergy or contraindication to aspirin may be reasonable.[7]

Aspirin exerts its antiplatelet effect by irreversibly inhibiting cyclooxygenase (COX)-1, which, in platelets, prevents the conversion of arachidonic acid to thromboxane A2 (TXA2), a powerful vasoconstrictor and stimulator of platelet aggregation. The onset of the antiplatelet effect of aspirin is less than 60 minutes, and platelets remain impaired for their life span (5-7 days) after exposure to aspirin.[13] Aspirin also inhibits COX-2 in a dose-dependent manner, leading to decreased prostacyclin (PGI2) activity in vascular smooth muscle.[14] There is probably a point at which lower doses of aspirin do not completely block TXA2, and studies indicate that the lowest effective dose may be in the range of 75 mg/day.[14] Upper gastrointestinal (GI) discomfort and bleeding are the most common adverse effects of aspirin and have been shown to be dose-related. The risk of major bleeding is 43% higher in patients treated with aspirin compared to patients not receiving aspirin. The risk of bleeding is dose-dependent and increases with increasing age; therefore, the upper limit of the aspirin dose is between 300 mg and 325 mg.[7]

Some patients either have or develop high on-treatment platelet reactivity (“aspirin resistance”) and can require higher doses or twice daily dosing to achieve the desired antiplatelet effect.[15] Several factors contribute to this effect, including aging, diabetes, hyperlipidemia, smoking, chronic kidney disease, and drug-drug interactions (eg, nonsteroidal anti-inflammatory drugs).[16] Genetic polymorphisms, including those influencing activity of COX-1, COX-2, glycoprotein IIb/IIIa receptors, and adenosine diphosphate (ADP) receptors, may contribute to aspirin resistance.[17] Despite the growing evidence linking aspirin resistance to worse outcomes in patients with stroke, routine testing for aspirin resistance is not recommended.

Blood Pressure Management

In general, patients with acute ischemic stroke commonly present with elevated or normal BP. However, hypotension and hypovolemia, if present, should be corrected to maintain systemic perfusion and end-organ function. For patients with elevated BP who are otherwise eligible for alteplase, the treatment of hypertension to a goal SBP of less than 185 mm Hg and diastolic BP of less than 110 mm Hg is recommended before thrombolytic administration. While data are limited, it is also reasonable to maintain blood pressure less than 185/110 mm Hg for patients undergoing mechanical thrombectomy. For patients not requiring IV thrombolytic therapy or endovascular intervention, “permissive hypertension,” allowing BP to rise as high as 220/120 mm Hg for the first 48 to 72 hours, is often implemented as early initiation of antihypertensive therapy does not prevent death or dependency. For patients with comorbid conditions requiring BP lowering, a reduction of 15% is reasonable. See Table 39-3 for a summary of these recommendations and pharmacotherapeutic options.[7] When treating hypertension in acute ischemic stroke, it is typical to use IV drugs with a faster time to onset and the ability to titrate to patient response. Calcium channel blocker infusions, such as nicardipine and clevidipine, are often preferred. Labetalol can be administered as an IV bolus dose or as a continuous infusion. In patients with refractory hypertension, there may be a role for last-line agents such as sodium nitroprusside to achieve BP goals.

Therapeutic Anticoagulation

The use of therapeutic anticoagulation (eg, unfractionated heparin or low-molecular-weight heparin) is not routinely recommended in the early phase of acute ischemic stroke treatment. The clinical benefit of therapeutic anticoagulation in the setting of nonocclusive intraluminal thrombus in acute stroke is limited. Restricted use on a case-by-case basis or in a clinical trial setting may be considered. Anticoagulation for non-stroke indications (eg,

venous thromboembolism prophylaxis or treatment) must be weighed against the risk of hemorrhagic conversion in patients with acute ischemic stroke.[7] Patients with immobility after stroke should receive either mechanical or pharmacologic venous thromboembolism prophylaxis. Drug selection, dosing, and timing of pharmacologic venous thromboembolism prophylaxis will depend on patient factors and concomitant treatment for stroke.

Secondary Prevention

7 Antiplatelet therapy is the cornerstone of antithrombotic therapy for the secondary prevention of ischemic stroke and should be used in noncardioembolic strokes. Aspirin, extended-release dipyridamole plus aspirin, clopidogrel, and ticagrelor are all recommended for secondary stroke prevention.[4] In patients with atrial fibrillation, oral anticoagulation with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin is recommended for secondary stroke prevention.[4] Other pharmacotherapy recommended for secondary prevention of stroke includes treatment of hypertension and statin therapy. Current recommendations regarding the acute treatment and secondary prevention of stroke are given in Table 39-2.

Antiplatelet Agents

All patients who have had an acute ischemic stroke or TIA should receive long-term antithrombotic therapy for secondary prevention.[4] In patients with noncardioembolic stroke, this will be some form of antiplatelet therapy. In a comprehensive meta-analysis, antiplatelet therapy reduced the odds of a second stroke by 16% to 41% in patients with previous stroke.[18] While aspirin is the antiplatelet agent with the most data supporting its use, there is also evidence to support using clopidogrel and the combination product extended-release dipyridamole plus aspirin as alternative first-line agents for secondary stroke prevention.[8] For patients already taking aspirin at the time of a noncardioemoblic ischemic stroke or TIA, there is no evidence that increasing the dose of aspirin is more effective at preventing additional strokes.[8]

Clopidogrel

Clopidogrel exerts its antiplatelet effect by inhibiting the ADP pathway of platelet aggregation through antagonism of the purinergic receptor P2Y, G-protein coupled 12 ($P2Y_{12}$) receptor.[14,19] This effect causes an alteration of the platelet membrane and interference with the membrane–fibrinogenic interaction leading to a blocking of the platelet glycoprotein IIb/IIIa receptor. In the absence of a loading dose, the maximal antiplatelet effect is delayed for 3 to 7 days.

Clopidogrel is a prodrug and requires activation by the cytochrome P450 isoenzyme 2C19 (CYP2C19) to achieve its antiplatelet effect. There are polymorphisms of various alleles encoding for this enzyme, with *1 being the wild type, *17 leading to increased metabolism, and *2 and *3 causing decreased metabolism. Thus, individuals with one copy of *2 or *3 are classified as intermediate metabolizers, and those with two copies of *2 or *3 or one copy of each (*2/*3) are termed poor metabolizers, leading to diminished antiplatelet activity.[20] Poor metabolizers are found in about 2% of Caucasians, 4% of African Americans, and 14% of Chinese.[20] Consequently, the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy both suggest pharmacogenetic testing prior to using clopidogrel.[20] However, current AHA/ASA guidelines for acute treatment of stroke do not suggest doing so.[8] Medications that inhibit CYP2C19 may also reduce the antiplatelet activity of clopidogrel. Omeprazole and esomeprazole both inhibit CYP2C19, and their use should be avoided in patients taking clopidogrel. Opioids slow gastric emptying, delaying and decreasing absorption, leading to reduced antiplatelet activity and, potentially, decreased efficacy.[21]

In a study of patients with atherothrombotic disorders (eg, ischemic stroke, myocardial infarction, or peripheral arterial disease), clopidogrel was slightly more effective than aspirin in preventing vascular events and had a similar incidence of adverse effects.[22] The tolerability of clopidogrel 75 mg/day is at least as good as medium-dose (325 mg/day) aspirin, and there is less GI bleeding.[22] Clopidogrel is associated with an increased risk of diarrhea and rash, but discontinuation rates due to adverse effects are similar to those with aspirin 325 mg/day (5.3% and 6%, respectively).[22]

Extended-Release Dipyridamole Plus Aspirin

Dipyridamole, in high doses, is thought to inhibit phosphodiesterase, increasing intracellular cyclic adenosine monophosphate (cAMP) and cyclic

guanosine monophosphate (cGMP), leading to inhibition of platelet activation.[14] Early studies of the role of dipyridamole in stroke prevention failed to show a benefit over aspirin alone. However, 25% of the patients who received a combination of dipyridamole and aspirin discontinued the therapy early, many due to adverse drug reactions. The discontinuation due to headache was more than threefold higher (10%) than the aspirin-alone group (3%).[23] Another study demonstrated similar efficacy in preventing recurrent stroke between the combination of extended-release dipyridamole and aspirin and clopidogrel.[24] However, clopidogrel was better tolerated with less bleeding and headache. Despite carefully educating and coaching patients on managing headache, discontinuation due to headache was six times higher in the extended-release dipyridamole plus aspirin group (5.9% vs 0.9%) compared to clopidogrel.[24] The extended-release formulation of dipyridamole is important in that it allows twice-daily administration. The use of immediate-release dipyridamole in combination with regular aspirin, in order to reduce cost, is unproven and should be discouraged.

Ticagrelor

Ticagrelor is a direct-acting $P2Y_{12}$ receptor inhibitor.[19] Ticagrelor (loading dose of 180 mg then 90 mg twice daily for 90 days) was compared to aspirin (300 mg loading dose then 100 mg daily 90 days) in a large clinical trial of patients with noncardioembolic stroke not treated with alteplase.[25] Ticagrelor did not demonstrate superiority to aspirin in this trial.[25] However, in a subgroup analysis of patients with an atherosclerotic cause of stroke, there was a 32% lower risk of secondary stroke within 90 days in patients treated with ticagrelor.[26] Despite this subgroup analysis, ticagrelor is not FDA-approved for secondary stroke prevention.

Dual Antiplatelet Therapy

The combination of two or more antiplatelet medications for secondary stroke prevention may be an option for select patients (Table 39-5). The combination of clopidogrel and aspirin has been the most studied dual antiplatelet strategy. A systematic review determined that short-term use of dual antiplatelet therapy (≤90 days) was associated with a significantly lower risk of recurrent stroke without an accompanying risk of major bleeding.[27] However, in longer-term studies (>90 days), the dual therapy was not associated with a reduced number of strokes but did increase the risk of major bleeding. Therefore, use of dual antiplatelet therapy with aspirin and clopidogrel for longer than 90 days is not recommended.[8]

TABLE 39-5

Dual Antiplatelet Recommendations for Patients with Noncardioembolic Ischemic Stroke or TIA

Patient Sub-type	Recommendation	Class (Strength) of Recommendation[a]	Level (Quality) of Evidence[b]
Minor stroke (NIHSS score ≤3)orhigh-risk TIA (ABCD2 score ≥4)[c]	Aspirin and clopidogrel should be initiated within 7 days (ideally within 12-24 hours). Continue for 21-90 days followed by single-agent antiplatelet therapy	I	A
Recent (<30 days) minor stroke or TIA attributable to 70-99% stenosis of a major intracranial artery	Aspirin and clopidogrel 75 mg daily for up to 90 days followed by single-agent antiplatelet therapy	IIa	B-NR
Recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery	Ticagrelor 90 mg twice a day may be added to aspirin for up to 30 days	IIb	B-NR

[a]Class (strength) of recommendation: I, strong; IIa, moderate; IIb, weak; III, no benefit (moderate); III, harm (strong).

[b]Level (quality) of evidence: A, high-quality evidence from more than 1 randomized clinical trial, meta-analyses of high-quality randomized clinical trials, or one or more randomized clinical trials corroborated by high-quality registry studies; B-R (randomized), moderate-quality evidence from one or more randomized clinical trials or meta-analyses of moderate-quality randomized clinical trials; B-NR (nonrandomized), moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies or meta-analyses of such studies; C-LD (limited data), randomized or nonrandomized observational or registry studies with limitations or design or execution, meta-analyses of such studies, or physiological or mechanistic studies in human subjects; C-EO (expert opinion), consensus of expert opinion based on clinical experience.

[c]The ABCD2 score is a clinical prediction rule used to determine the risk for stroke soon after a TIA. Score 1 point each for age ≥60 years, blood pressure ≥140/90 mm Hg, speech disturbance, unilateral weakness, 10-59 minute duration, diabetes and 2 points for duration ≥60 minutes.

NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Data from Reference 8.

Ticagrelor (180 mg loading dose then 90 mg twice daily for 30 days) in combination with aspirin (300-325 mg loading dose then 75-100 mg daily) has been compared to aspirin alone in patients with mild-moderate noncardioembolic stroke.[28] Fewer patients in the dual therapy group had stroke or death in the first 30 days compared to the aspirin-only group. However, the overall level of disability was not different between the groups, and the incidence of severe bleeding, including ICH, was increased in the dual therapy group. A subgroup analysis of patients at higher risk for recurrent stroke found rates of stroke and death were lower in the combination therapy group compared to aspirin alone, while no difference in severe bleeding was observed between the groups.[29] Consequently, the use of ticagrelor and aspirin together for secondary stroke prevention is only recommended for patients with minor stroke or TIA with more than 30% stenosis of an ipsilateral major intracranial artery; combination therapy should be limited to a duration of 30 days.[8]

The positive results of dual antiplatelet therapy led researchers to investigate triple antiplatelet therapy. One trial compared the combination of aspirin, sustained-release dipyridamole, and clopidogrel to a “guideline group” which received either clopidogrel or aspirin and sustained-release dipyridamole. This trial was stopped early because of a doubling of the risk of major bleeding in the triple therapy group. There was no difference in the risk of recurrent stroke between the groups.[30] Therefore, the use of triple antiplatelet therapy is not recommended.[8]

Oral Anticoagulants

Oral anticoagulation is the treatment of choice for the prevention of stroke in patients with atrial fibrillation and atrial flutter.[4,31] Patients with atrial fibrillation and a recent history of stroke or TIA are among the highest risk groups for stroke recurrence. However, there is a significant risk of bleeding with anticoagulation. Thus, a stroke risk stratification tool known as CHA_2DS_2-VASc has been developed to determine the patient's risk of stroke (see Chapter 40 "The Arrhythmias"). CHA_2DS_2-VASc scores greater than zero for men and 1 for women should receive oral anticoagulation therapy.[4] Several risk stratification tools have been developed to evaluate bleeding and determine bleeding risk. HAS-BLED is a simple tool that is widely used.[32] A HAS-BLED score >2 indicates a high risk for bleeding and should be accompanied by more intensive patient monitoring (Table 39-6).

TABLE 39-6

HAS-BLED Score for Assessing Bleeding Risk with Oral Anticoagulants

HAS-BLED Symbol	Risk Factor	Score
H	**H**ypertension (SBP >160 mm Hg)	1
A	**A**bnormal renal or liver function	1
S	Prior **S**troke	1
B	Prior major **B**leeding or **B**leeding predisposition	1
L	**L**abile INRs (in therapeutic range <60% of time)	1
E	**E**lderly (age >65 years)	1
D	**D**rugs of abuse or excessive alcohol use	1

HAS-BLED score >2 associated with clinically relevant and major bleeding.

SBP, systolic blood pressure, INR, international normalized ratio.

Data from References 4 and 32.

In patients with atrial fibrillation, adjusted-dose warfarin reduces stroke risk by 62% when compared to placebo and by 36% when compared to aspirin.[33] When using warfarin, targeting an international normalized ratio (INR) of 2 to 3 prevents stroke with the lowest bleeding risk; therefore, a target INR of 2 to 3 is recommended for the secondary prevention of stroke.[4,7,31] In settings of atrial fibrillation with mechanical heart valves or moderate to severe mitral stenosis, warfarin should be used.[8]

Direct-acting oral anticoagulants (DOAC), including direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, edoxaban, and apixaban), have significant advantages over warfarin in terms of ease of dosing and less food and drug interactions. In addition, all four agents have been shown to be as effective, and in some cases, superior to warfarin in reducing stroke risk with reduced rates of serious hemorrhage.[31]

Before using a DOAC, the patient's renal function must be evaluated and the dose adjusted if significant renal impairment is present (TABLE 39-7). Patients with creatinine clearance less than 15 mL/min (0.25 mL/s) or who require hemodialysis, either warfarin or apixaban, are preferred.[31] Additionally, edoxaban should not be given to patients with creatinine clearances above 95 mL/min because the risk of stroke is increased compared to warfarin.[31] There is limited information on the use of these agents in patients with a body mass index over 40 kg/m^2.[34] However, emerging data suggest that apixaban and rivaroxaban may be the best options for patients with a body weight over 120 kg or body mass index over 40 kg/m^2.[35]

TABLE 39-7

Direct-acting Oral Anticoagulant Dosing Adjustments Required for Renal Impairment.

Direct-acting Oral Anticoagulant	Usual Oral Dosing for Stroke Prevention in Atrial Fibrillation	Dosing Adjustments
Apixaban	5 mg twice daily	2.5 mg twice daily in patients with at least two high-risk characteristics below:Age ≥80 years Body weight ≤60 kg Serum creatinine ≥1.5 mg/dL (133 µmol/L)
Dabigatran	150 mg twice daily	75 mg orally twice daily if creatinine clearance 15-30 mL/min (0.25-0.50 mL/s)
Edoxaban	60 mg daily	30 mg orally daily if creatinine clearance is 15-50 mL/min (0.25-0.83 mL/s)
Rivaroxaban	20 mg daily with food	15 mg orally daily with evening meal if creatinine clearance is ≤50 mL/min (0.83 mL/s)

The timing of oral anticoagulant initiation has been in question due to the risk of hemorrhagic conversion of the infarcted area. Guidelines suggest for patients with a low risk of hemorrhagic conversion; anticoagulation can begin 2 to 14 days after the stroke. However, in patients with a high risk of hemorrhagic conversion, waiting at least 14 days is recommended.[8]

Blood Pressure Management

9 Elevated BP is very common in ischemic stroke patients, and treatment of hypertension in these patients is associated with a decreased risk of stroke recurrence.[8] Current guidelines have the following recommendations for BP control after ischemic stroke to prevent future strokes:

- Adults with previously treated hypertension who experience a stroke or TIA should be restarted on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events.
- For adults with hypertension who experience a stroke or TIA, treatment with a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin II receptor blocker is useful.
- Adults not previously treated for hypertension who experience a stroke or TIA and have an average BP of 130/80 mm Hg or higher should be prescribed antihypertensive treatment a few days after the index event to reduce the risk of recurrent stroke and other vascular events.
- For adults who experience a stroke or TIA, a BP goal of less than 130/80 mm Hg is recommended.[8,36]

Cholesterol Management

10 Statin therapy has been shown to reduce the risk of stroke by approximately 30% in patients with coronary artery disease and elevated plasma lipids.[8] Patients with ischemic stroke without known heart disease but who have LDL cholesterol over 100 mg/dL (2.59 mmol/L) should be given atorvastatin 80 mg daily to reduce the risk of stroke recurrence.[8] Patients with ischemic stroke or TIA who have atherosclerotic cardiovascular disease (ASCVD) should be given lipid-lowering therapy with a high-intensity statin (and ezetimibe, if necessary) to reach a goal of LDL cholesterol of less than 70 mg/dL (1.81 mmol/L).[8] In very high-risk patients (multiple major atherosclerotic cardiovascular events or one major atherosclerotic cardiovascular event and multiple high-risk conditions) who are taking maximally tolerated statins and ezetimibe with LDL cholesterol ≥70 mg/dL (1.81 mmol/L), a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor may be considered.[8]

Hypertriglyceridemia has recently been recognized as a risk factor for ASCVD but lowering triglycerides with extended-release niacin or fibrates has not been shown to change cardiovascular outcomes. In contrast, adding icosapent ethyl 2 g twice daily to statin therapy has been shown to reduce major adverse cardiovascular events, including stroke, in patients with fasting triglycerides of 135 to 499 mg/dL (1.53 to 5.64 mmol/L) and LDL cholesterol of 41 to 100 mg/dL (1.06 to 2.59 mmol/L).[37] Therefore, icosapent ethyl is recommended for these patients with provided they have HbA1c <10% (86 mmol/mol) and no history of pancreatitis, atrial fibrillation, or severe heart failure.[8] When patients have fasting triglycerides of 500 mg/dL (5.65 mmol/L) or more, non-pharmacologic efforts to reduce them should be initiated along with fibrate therapy, if needed.[8]

Hemorrhagic Stroke

Acute Treatment

The stroke council of the AHA/ASA published guidelines on the management of spontaneous ICH in 2015.[6] While the usefulness of pharmacologic interventions is limited in this stroke type, the management of hypertension and reversal of coagulopathy in anticoagulant-associated ICH should be considered.

Blood Pressure Management

Hypertension in patients with hemorrhagic stroke increases the risk of hematoma expansion. For patients with ICH presenting with an SBP above 220 mm Hg, aggressive lowering of BP with continuous IV infusion medications is reasonable. Clinical trials have demonstrated that acute lowering of SBP to a goal of 140 mm Hg is safe and may be effective at improving functional outcomes.[6] For patients with SAH due to aneurysm rupture, targeting an SBP less than 160 mm Hg is reasonable in the time period from symptom onset to aneurysm obliteration.[6] Refer to Table 39-3 for a summary of these recommendations and pharmacologic treatment options.

Anticoagulation Reversal

When ICH occurs in a patient on anticoagulants, the use of reversal agents to correct the medication-induced coagulopathy should be considered. For patients on warfarin with elevated INR, reversal with vitamin K, typically IV, in combination with a four-factor prothrombin complex concentrate is recommended. Fresh frozen plasma can be used in place of a prothrombin complex concentrate, if necessary, but is not preferred.[6] Idarucizumab may be considered for reversing the effect of dabigatran specifically.[38] Factor Xa inhibitors, such as rivaroxaban and apixaban, may be reversed with andexanet alfa[39] (Table 39-8).

TABLE 39-8

Selected Anticoagulant Reversal

Drug	First-Line Reversal Recommendation	Alternate Treatment
Warfarin	Vitamin K 10 mg IV ×1 -and- 4-Factor Prothrombin Complex Concentrate (4PCC) INR 2 to <4: 25 units/kg, max 2,500 units INR 4-6: 35 units/kg, max 3,500 units INR >6: 50 units/kg, max 5,000 units	Vitamin K 10 mg IV ×1 -and- Fresh Frozen Plasma (FFP) 10-15 mL/kg
Dabigatran	Idarucizumab 5 gm IV ×1	Hemodialysis 4PCC 50 units/kg
Rivaroxaban ≤10 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Rivaroxaban >10 mg or unknown dose	If <8 hours since last dose or unknown time andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban ≤5 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban >5 mg or unknown dose	If <8 hours since last dose or unknown time Andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Edoxaban	Andexanet alfa not studied	4PCC 50 units/kg

FFP, fresh frozen plasma; IV, intravenous; 4PCC, 4-factor prothrombin complex concentrate; INR, international normalized ratio.

EVALUATION OF THERAPEUTIC OUTCOMES

Patients with acute stroke should be monitored intensely for the development of neurologic worsening (recurrence or extension of stroke), complications (venous thromboembolism or infection), and adverse effects from pharmacologic or nonpharmacologic interventions. The most common reasons for deterioration in a stroke patient are (a) extension of the original lesion—ischemic or hemorrhagic—in the brain, (b) development of cerebral edema and elevated intracranial pressure, (c) hypertensive emergency, (d) infection (urinary and respiratory most common), (e) venous thromboembolism (deep vein thrombosis and pulmonary embolism), (f) electrolyte abnormalities and cardiac rhythm disturbances (can be associated with brain injury), and (g) recurrent stroke.

The approach to monitoring drug therapy in patients hospitalized with an acute stroke is summarized in Table 39-9. The plan should be customized for

individual patients based on the etiology of the stroke, their comorbidities, and ongoing disease processes.

TABLE 39-9

Monitoring Stroke Therapy in Hospitalized Patients

Drug	Adverse Effect	Monitoring Parameters	Comments
Alteplase and tenecteplase	Bleeding	Neurologic examination, blood pressure	Every 15 minutes × 1 hour; every 30 minutes × 6 hours; every 1 hour × 17 hours; every shift after
Aspirin	Bleeding		Daily
Clopidogrel	Bleeding		Daily
Extended-release dipyridamole plus aspirin	Headache, bleeding		Daily
Ticagrelor	Bleeding, bradycardia, dyspnea	Heart rate, respiratory rate	Bleeding daily, heart rate and respiratory rate as clinically indicated
Direct-acting oral anticoagulants	Bleeding		Daily
Warfarin	Bleeding	PT/INR, hemoglobin, hematocrit	Daily

INR, international normalized ratio; PT, prothrombin time.

For survivors of noncardioembolic strokes, approximately 3% to 4% per year will experience another stroke. One-third to one-half of these strokes occur while patients are on antiplatelet therapy to prevent stroke.[40] None of these agents reduces stroke risk to zero; some of the most important causes of breakthrough strokes are nonadherence, inappropriate dosing, reduced absorption, increased metabolism, drug-drug interactions, and genetic polymorphisms.[40] The healthcare practitioner is in a position to impact several of these factors. Nonadherence can have a root cause in a lack of understanding of therapy, adverse effects of the therapy, or the number of medications on discharge, among other factors.

CONCLUSION

Treatment of stroke requires a team approach to provide an accurate diagnosis to guide treatment and select therapies proven to improve outcomes. Careful patient selection for pharmacologic and nonpharmacologic therapies is paramount. Monitoring treatment helps assure the goals of therapy are met.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADP	adenosine diphosphate
AHA	American Heart Association

aPTT	activated partial thromboplastin time
ATP	adenosine triphosphate
AVM	arteriovenous malformation
ASA	American Stroke Association
ASCVD	atherosclerotic cardiovascular disease
BP	blood pressure
cAMP	cyclic adenosine monophosphate
CD	carotid Doppler
cGMP	cyclic guanosine monophosphate
COX	cyclooxygenase
CNS	central nervous system
CT	scan computed tomography
CTA	computed tomography angiography
CYP2C19	cytochrome P450 isoenzyme 2C19
DBP	diastolic blood pressure
DCI	delayed cerebral ischemia
DOAC	direct-acting oral anticoagulants
DWI	diffusion-weighted imaging
ECG	electrocardiogram
EVD	external ventricular drainage
FFP	fresh frozen plasma
GCS	Glasgow Coma Scale
GI	gastrointestinal
GLP1	glucagon-like peptide 1
HgA1c	hemoglobin A1c
ICA	internal carotid artery

ICH	intracerebral hemorrhage
INR	international normalized ratio
IPC	intermittent pneumatic compression
IV	intravenous
LDL	low-density lipoprotein
MCA	middle cerebral artery
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	modified Rankin score
NIHSS	National Institutes of Health Stroke Scale
NSAID	nonsteroidal anti-inflammatory drug
NVAF	nonvalvular atrial fibrillation
PFO	patent foramen ovale
P2Y12	purinergic receptor P2Y, G-protein coupled 12
PCC	prothrombin complex concentrate
PCSK9	proprotein convertase subtilisin/kexin type 9
PGI2	prostacyclin
PT	prothrombin time
SAH	subarachnoid hemorrhage
SBP	systolic blood pressure
TCD	transcranial Doppler
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TTE	transthoracic echocardiography
TXA2	thromboxane A2

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SELF-ASSESSMENT QUESTIONS

1. A cardioembolic stroke is a type of _____ stroke.
   A. Hemorrhagic
   B. Ischemic
   C. Lacunar
   D. Cerebellar
2. Which of the following pairs correctly matches the type of hemorrhagic stroke to one of its potential causes?
   A. Intracerebral hemorrhage: the rupture of an intracerebral aneurysm
   B. Intracerebral hemorrhage: trauma
   C. Subarachnoid hemorrhage: the rupture of an arteriovenous malformation
   D. Subarachnoid hemorrhage: uncontrolled hypertension
3. RT is a 77-year-old man who presents to the emergency department with symptoms of an ischemic stroke. Past medical history includes hypertension, hypothyroidism, benign prostatic hypertrophy, and hypercholesterolemia. What are RT's stroke risk factors?
   A. Age, hypertension, and hypercholesterolemia
   B. Age, sex, hypertension, hypothyroidism, and hypercholesterolemia
   C. Age, sex, hypertension, and hypercholesterolemia
   D. Sex, hypothyroidism, benign prostatic hypertrophy, and hypercholesterolemia
4. Which of the following is *not* a symptom of an acute stroke?
   A. Inability to speak

B. Loss of vision

C. Weakness on one side of the body

D. Whole body numbness

5. Who is the best candidate for carotid stenting to reduce recurrent stroke?

A. A 65-year-old female with 50% stenosis of the ipsilateral internal carotid artery

B. A 65-year-old male with 75% stenosis of the ipsilateral internal carotid artery

C. A 75-year-old male with 50% stenosis of the ipsilateral internal carotid artery

D. A 75-year-old female with 75% stenosis of the ipsilateral internal carotid artery

6. BN is an 84-year-old male who presents to the emergency department with acute ischemic stroke symptoms. Symptoms began 2 hours ago. Current blood pressure is 176/98 mm Hg and glucose is 110 mg/dL (6.1 mmol/L). A computed tomography (CT) scan of the head that shows no bleeding. The patient is currently taking aspirin 81 mg daily and lisinopril 10 mg daily. He has no medication allergies. Is BN a candidate for alteplase?

A. Yes.

B. No, his symptoms began too long ago.

C. No, he is too old.

D. No, he is taking aspirin.

7. KC is a 65-year-old woman who presents to the emergency department with acute ischemic stroke symptoms. Symptoms began 6 hours ago. Current blood pressure is 170/96 mm HG and her glucose is 104 mg/dL (5.8 mmol/L). A computed tomography (CT) scan of the head that shows no bleeding. The patient is currently taking hydrochlorothiazide 25 mg daily and is allergic to aspirin (oral facial edema). Is KC a candidate for alteplase?

A. Yes.

B. No, her symptoms began too long ago.

C. No, she is too old.

D. No, she is taking hydrochlorothiazide.

8. ST is a 68-year-old woman who presented with an ischemic stroke 2 days ago. The patient received alteplase and the neurological deficits improved. Prior to the stroke, the patient was taking no medications. The patient is allergic to aspirin (hives and shortness of breath). Which of the following agents should ST receive to prevent recurrent strokes?

A. Aspirin

B. Clopidogrel

C. Clopidogrel plus aspirin

D. Extended-release dipyridamole plus aspirin

9. FR is a 58-year-old man who has had atrial fibrillation for 5 years. The patient was maintained on aspirin 325 mg daily. Four days ago, the patient sustained an ischemic stroke. What is the best choice of therapy for FR to prevent recurrent stroke?

A. Aspirin

B. Clopidogrel

C. Extended-release dipyridamole plus aspirin

D. Rivaroxaban

10. JC is a 79-year-old 150 kg man who recently sustained an ischemic stroke. During the workup, the patient was found to have atrial fibrillation. Blood pressure is 145/90 mm Hg. Serum creatinine is 4.5 mg/dL (398 µmol/L) (creatinine clearance 28 mL/min [0.47 mL/s]) and BMI is 50 kg/m^2. Which of the following oral anticoagulants is most appropriate for JC?

A. Apixaban 5 mg daily

B. Edoxaban 30 mg daily

C. Dabigatran 150 mg twice daily

D. Warfarin adjusted to a target INR of 2 to 3

11. What is the HAS-BLED score for JC from question 10?

A. 1

B. 2

C. 3

D. 4

12. RG is a 74-year-old man who is being discharged from the hospital after a mild stroke. Blood pressure has stabilized at 156/98 mm Hg. Low-density lipoprotein cholesterol is 110 mg/dL (2.84 mmol/L). On which of the following regimens should RG be placed?

A. Atorvastatin 40 mg daily

B. Hydrochlorothiazide 25 mg daily plus rosuvastatin 20 mg daily

C. Lisinopril 5 mg daily

D. Lovastatin 40 mg daily plus losartan 50 mg daily

13. Which of the following is an appropriate monitoring parameter for a patient given alteplase?

A. Bleeding

B. Blue discoloration of the skin

C. Headache

D. Tongue swelling

14. BC is a 58-year-old man with atrial fibrillation who sustained an ischemic stroke and was placed on warfarin. Which of the following is an appropriate monitoring plan for BC?

A. Check blood glucose daily

B. Check blood pressure three times daily

C. Monitor INR for a target of 2 to 3

D. Monitor tyramine-containing food consumption

15. MP is a 66-year-old woman who sustained an ischemic stroke and was discharged on clopidogrel 75 mg daily plus aspirin 81 mg daily for 21 days. Which of the following will help decrease the patient's chance of recurrent stroke?

A. Follow-up regarding adherence

B. Frequently monitoring her blood pressure

C. Frequently monitoring her weight

D. Screening for depression

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** The two major types of stroke are ischemic and hemorrhagic. Ischemic strokes are often the result of large artery atherosclerosis, small artery disease, or cardioembolism. These three subtypes are the most common etiologies of ischemic strokes. See "Etiology" section for further description.

2. **C.** Subarachnoid hemorrhage occurs when blood enters the subarachnoid space, which can occur due to trauma, rupture of an intracerebral aneurysm, or rupture of an arteriovenous malformation. Intracerebral hemorrhage, however, occurs when bleeding occurs in the brain parenchyma itself, with the formation of a hematoma within the brain. Uncontrolled hypertension is the most common causative factor for intracerebral hemorrhage, but antithrombotic therapy, cerebral amyloid angiopathy, and some drugs of abuse are also associated with intracerebral hemorrhage. See "Etiology" section for further description.

3. **C.** The nonmodifiable stroke risk factors are age, race, sex, low birth weight, and genetic factors. The most common modifiable, well-documented risk factors for ischemic stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and dyslipidemia. See "Risk Factors" section for a comprehensive review.

4. **D.** Symptoms of acute stroke include weakness on one side of the body, inability to speak, loss of vision, vertigo and/or falling and occasionally headache. Stroke symptoms tend to involve only one side of the body. See the Clinical Presentation box for a review of stroke presentation.

5. **B.** In patients younger than 70 years with 70% to 99% stenosis of an ipsilateral internal carotid artery, carotid stenting can be performed. See "Nonpharmacologic Therapy" section for more details.

6. **A.** This patient is within the 4.5-hour window for alteplase administration, his blood pressure is <180/110 mm Hg, and he has no intracranial bleeding. Patients can be maintained on aspirin and receive alteplase. Please see and Table 39-2 for blood pressure management and criteria for alteplase use in the setting of acute stroke.

7. **B.** This patient is not within the 4.5-hour window for alteplase administration. Please see Table 39-4 for criteria for alteplase use in the setting of acute stroke.

8. **B.** This patient is allergic to aspirin; thus, it should not be a component of her therapy. Please see "Antiplatelet Agents" section for further discussion of the antiplatelet agents.

9. **D.** Oral anticoagulation is the treatment of choice for the prevention of stroke in patients with atrial fibrillation. Choice of agent may include warfarin, dabigatran, rivaroxaban, edoxaban, and apixaban. Please see "Oral Anticoagulant" section for more details on choosing between these agents.

10. **D.** The direct-acting oral anticoagulant doses need to be adjusted for patients with renal dysfunction. There is limited information on the use of these agents in patients with a body mass index over 40 kg/m^2. Therefore, warfarin would be the better choice for this patient. See "Oral Anticoagulant" section for more details of dosing these agents in decreased renal functioning.

11. **B.** This patient would receive points for a history of stroke and his age (>65 years). See Table 39-7 for HAS-BLED scoring.

12. **B.** This patient will require blood pressure lowering because his blood pressure is >140/90 mm Hg. He will also require high-intensity statin therapy because he is less than 75 years old. See "Blood Pressure Management" and "Statins" sections for additional review of this topic.

13. **A.** It is appropriate to monitor bleeding in a patient given alteplase. See Table 39-9 for additional monitoring parameters for hospitalized patients with ischemic stroke.

14. **C.** Target INR for patients with atrial fibrillation who are given warfarin is 2.5. See Table 39-2.

15. **A.** Some of the most important causes of breakthrough strokes are nonadherence, inappropriate dosing, reduced absorption, increased metabolism, drug-drug interactions, and genetic polymorphisms. Monitoring blood pressure, weight, or mood are unlikely to decrease future strokes. See "Evaluation of Therapeutic Outcomes" section.