Management of Acute Ischemic Stroke and Transient Ischemic Attack

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Learning Objectives

1. Evaluate risk factors associated with acute ischemic stroke (AIS) and assess stroke risk after transient ischemic attack (TIA).
2. Discuss reperfusion therapy and justify the expanded time window of alteplase for AIS in appropriate populations.
3. Evaluate ongoing controversies regarding medical management of TIA/AIS.
4. Formulate primary and secondary prevention plans using risk factors for patients with TIA/AIS.
5. Delineate future neuroprotective therapies and quality improvement measures for the management of AIS.

Introduction

Strokes are classified as ischemic or hemorrhagic cerebral vascular events. More than 85% of all strokes are ischemic, whereas about 15% are hemorrhagic (intracranial hemorrhage or subarachnoid hemorrhage). An acute ischemic stroke (AIS) and a transient ischemic attack (TIA) occur when bloodflow to a focal region of the brain is occluded. Although both are caused by the occlusion of cerebral vasculature, a TIA differs from a stroke in that a TIA is a temporary event that results in no permanent damage to the brain tissues. However, both TIA and AIS should be treated as medical emergencies because it is difficult to predict who will experience permanent neurologic injury, and "time is brain."

Traditionally, AIS has been attributed to arterial occlusions; however, a stroke may also result from a venous occlusion, which is termed a *cerebral venous thrombosis* (CVT). This type of stroke is uncommon (about 1% of AISs) and often under-recognized. Clinical features, risk factors, and treatments vary between arterial and venous strokes.

Since their inception in the early 1900s, the American Heart Association/American Stroke Association (AHA/ASA) have shaped best practices. The development of scientific guidelines and establishment of quality-of-care measures with Get With The Guidelines–Stroke program in 2003 allowed reporting of stroke outcomes in a large national database. The newest guidelines from AHA/ASA include management of CVT (2011), management of extravascular (carotid and vertebral) diseases (2011), and pediatric stroke management (2008). Other guidelines recently updated include early management of AIS (2007 and 2009), stroke prevention (2011), and evaluation of TIA (2009).

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS). Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–7.
- Rothwell PM, Algra A, Amarenco P. Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke. Lancet 2011;377:1681–92.
- Rhoney DH. Contemporary management of transient ischemic attack: role of the pharmacist. Pharmacotherapy 2011;31:193–213.
- International Stroke Conference. American Heart Association/American Stroke Association [homepage on the Internet]. Available at *http://www.strokeassociation.org/STROKEORG/Professionals/Professionals_UCM_308581_SubHomePage.jsp*. Accessed February 24, 2012.

Significant changes in the guidelines that may affect clinical pharmacists' daily practice include expansion of the time window for intravenous alteplase (from 3 hours to 4.5 hours in selected individuals), dabigatran for prevention of stroke in nonvalvular atrial fibrillation, use of antiplatelet agents for noncardioembolic stroke, and an enhanced role for statin therapy in individuals with atherosclerotic TIA/AIS regardless of coronary disease. This chapter provides updates on the prevention and management of TIA and AIS based on the new guidelines and literature.

EPIDEMIOLOGY

Prevalence and Economic Impact

The annual incidence of AIS in the United States is about 795,000; of these, 610,000 are estimated to be a first stroke, and 15% of these events are preceded by a TIA. Transient ischemic attack carries significant morbidity and mortality; 12% of those who suffer a TIA will die within 1 year. It is estimated that up to 50% of patients who experience a TIA do not report the event to their physicians.

Although the overall stroke mortality rate declined from 29.7% to 13.5% between 1995 and 2005, stroke is the No. 1 cause of long-term disability. It has been estimated that up to 30% of stroke survivors are permanently disabled. An additional 20% of survivors require institutional care at 3 months after the incident. As a result, AIS contributes significantly to both productivity loss and public health care costs in the United States. The direct and indirect costs of stroke in 2010 have been estimated at $73.3 billion, a significant increase from $58 billion in 2006.

Risk Factors

Recognizing stroke-related risk factors is important because preventive measures targeting these risk factors are vital in reducing stroke burdens. Important risk factors for both arterial and venous AIS are summarized in Box 1-1. Most AISs were of arterial origin, and risk factors for these strokes are outlined in the AHA/ASA 2011 guidelines.

Nonmodifiable risk factors remain unchanged since the 2006 guidelines, which associated African American race, male sex, older age, and family history of TIA/stroke with a higher incidence of first-ever AIS. Among modifiable risk factors, hypertension and atrial fibrillation are the most powerful predictors for first-ever and recurrent arterial AIS. The age-adjusted incidence of AIS triples in the presence of hypertension and increases 5-fold with atrial fibrillation.

Treatment of AIS secondary to CVT varies greatly from arterial AIS because of different risk factors. Cerebral venous thrombosis–related AIS is more prevalent in younger women. Predisposing conditions for CVT include inherited or acquired thrombophilias (e.g., cancer-related coagulation disorders). Risk factors are more aligned with other venous thrombosis disorders (e.g., deep venous thrombosis) and include antithrombin III, protein C and S deficiencies; antiphospholipid and anticardiolipin antibodies; and factor V Leiden and prothrombin G2021A mutations. Drugs associated with CVT include oral contraceptives, immunoglobulin, and recreational drugs such as ecstasy.

PATHOPHYSIOLOGY

An AIS results from interruption of bloodflow within the cerebral vasculature and can be caused by either thrombotic (atherosclerotic plaque formation) or embolic sources. About 50% of all AISs are atherosclerotic, which refers to in situ obstruction of an artery. Embolic AIS is caused by a thrombus traveling from elsewhere, resulting in a blockage of the cerebral artery. Cardiac embolism from atrial fibrillation is the most common cause of embolic AIS.

Autoregulation tightly maintains normal cerebral bloodflow at around 50–60 mL/100 g of brain tissue per minute. When the autoregulatory mechanism fails and cerebral bloodflow falls below 20 mL/100 g of brain tissue per minute, tissue death occurs. This part of the brain becomes necrotic, and the injury is irreversible. The area of minimally perfused tissue surrounding the infarct is composed of potentially viable tissues called the penumbra. Most acute stroke therapies aim to salvage the penumbra and prevent enlargement of necrotic tissue.

CLASSIFICATION AND PROGNOSIS

As discussed, most AISs are arterial, and less than 1% involve the venous vasculature (CVT). However,

Box 1-1. Risk Factors for Primary Stroke Prevention

Nonmodifiable
- Age
- Family history of stroke or transient ischemic attack
- Genetic factors[a]
- Low birth weight
- Race/ethnicity
- Sex

Modifiable: Well Documented
- Asymptomatic carotid stenosis
- Atrial fibrillation
- Cigarette smoking
- Diabetes
- Dyslipidemia
- Hypertension
- Other cardiac conditions[b]
- Obesity
- Oral contraceptive use[c,d]
- Physical inactivity
- Postmenopausal hormone therapy
- Sickle cell disease
- Parameningeal/sinus infections[c]
- Pregnancy[c]

Modifiable: Less Well Documented
- Alcohol consumption (> 60 g/day)
- Drug abuse
- Elevated lipoprotein(a)
- Hypercoagulability[c,e]
- Hyperhomocysteinemia
- Inflammatory disease
- Metabolic syndrome
- Migraines with aura
- Sleep-disordered breathing

[a]Genetic factors include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Marfan syndrome, neurofibromatosis types I and II, and Fabry disease.
[b]Other cardiac conditions include coronary artery disease, congestive heart failure, and peripheral arterial disease.
[c]These are risk factors for cerebral venous thrombosis–related stroke.
[d]Oral contraceptive use is a risk factor for both arterial- and venous-related stroke.
[e]Hypercoagulability includes both acquired (e.g., trauma and cancer) and inherited (e.g., antiphospholipid antibodies; hyperhomocysteinemia; and protein C and S deficiency) conditions. This is a well-defined risk factor for venous thrombosis–related stroke, but it is a less well-defined risk factor for arterial stroke.

the mortality associated with acute CVT stroke is about 3% to 15% because of transtentorial herniation or complications associated with venous thromboembolism (VTE) such as pulmonary embolism. Therefore, the management of CVT generally involves immediate anticoagulation in contrast to arterial AIS, which requires thrombolytic therapy.

The classification of arterial AIS depends on the location of ischemia, mechanism of occlusion, and type of lesion. Thrombotic AIS, the most common, includes large artery atherosclerosis and penetrating small artery disease (lacunar infarcts). Cardiogenic embolic stroke, the second most common AIS, may be caused by atrial fibrillation, valvular disease, or patent foramen ovale. A small percentage of AISs are of either undetermined etiology or other causes. In a stroke of undetermined etiology (cryptogenic stroke), several risk factors can be identified but not the exact cause. Stroke of other determined etiology includes rare causes such as arterial dissections, drug-induced stroke, and prothrombotic states.

The outcome after an AIS depends largely on the timely presentation to a well-equipped and organized facility (i.e., certified stroke center) for emergency stroke workup and treatment. At greatest risk of dying are patients with higher National Institutes of Health Stroke Scale (NIHSS) scores (i.e., more than 15), advanced age, large vascular territory infarcts (e.g., middle cerebral artery occlusions), multilobar infarction, decreased consciousness, or hemodynamic instability. Symptomatic intracranial hemorrhagic (SICH) transformation may occur spontaneously in 5% of patients with AIS.

Evolution of TIA

The risk of developing AIS after a TIA is significantly higher than previously believed. It is estimated that the overall risk of AIS after a TIA is 5.2% at 7 days and 15% at 30 days. Of the 15%, one-fourth to one-half occur within 48 hours after the TIA.

The high risk of developing AIS after TIA is partly caused by the traditional time-based classification, in which TIA is defined as transient neurologic deficits lasting less than 24 hours. This definition is thought to delay appropriate therapy in some patients because one-third of individuals previously defined as having a TIA were found to have an AIS when evaluated by the newer and more sensitive neuroimaging tests. Therefore, the AHA/ASA endorsed a tissue-based definition of TIA in 2009. The definition of TIA now is "a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction."

With this change to a tissue-based definition, more aggressive use of neurodiagnostic tests and higher urgency for treatment are emphasized in TIA

management. In addition, several scoring systems have been validated to risk-stratify a patient's risk of AIS after TIA. These scoring systems include the age, blood pressure, clinical features, duration of symptoms (ABCD) system, the California system (age, diabetes, duration of episode, weakness, and speech impairment), and the age, blood pressure, clinical features, duration of symptoms, diabetes (ABCD2) system (Table 1-1). The ABCD2 score, which combines elements from the other two systems, has the best prognostic value in predicting stroke after TIA at 2, 7, 30, and 90 days. No randomized trials have evaluated the use of the ABCD2 score in assisting with triage decisions; however, AHA/ASA recommends inpatient management as a reasonable approach for patients with an ABCD2 score of 3 or more when presenting within 72 hours of a TIA.

Diagnosis

Physical examination remains an important first step in assessing patients with TIA/AIS. A short neurologic assessment helps identify the neurologic impairment and may predict the vessel involvement and location of the infarct. For example, a left hemispheric infarct may present with contralateral findings such as right-sided hemiparesis.

Two assessment tools are widely used to determine stroke deficits: the NIHSS and the modified Rankin Score (mRS). Either tool may be used by health care providers certified in this process. The NIHSS evaluates acute neurologic impairment using a scoring system of 0–42 points. Higher scores indicate more severe neurologic impairment; lower scores indicate less severe impairment. A score of 0 indicates the absence of impairment. Large strokes, including malignant middle cerebral artery infarctions, may decrease bloodflow to several vascular territories and result in higher NIHSS scores. Any baseline score other than 0 warrants neurologic workup. The mRS, which has a scoring range of 0–6 points, is often used to assess a patient's functional disability after AIS. Scores of 0–1 represent no to minimal disability, whereas scores of 5–6 represent severe disability or death.

The differential diagnosis of TIA/AIS includes ruling out hypoglycemia, seizure with postictal paralysis, hemorrhagic stroke, head trauma, brain abscess, encephalitis, migraine, and brain tumor. Laboratory tests should include blood glucose, serum electrolytes, complete cell blood count with platelet count, kidney function studies, prothrombin time, activated partial thromboplastin time, toxicology screen, oxygen saturation, and cardiac markers. Electrocardiography (ECG) should be obtained because atrial fibrillation and myocardial infarction may contribute to stroke.

Neuroimaging is an integral part of stroke management. Noncontrast-enhanced computed tomography

Table 1-1. The ABCD2 Scoring System to Predict Stroke After TIA

Criteria	Points
Age 60 years or older	1
Blood pressure of 140/90 mm Hg or higher	1
Clinical features	
Unilateral weakness	2
Speech impairment without weakness	1
Duration of symptoms	
60 minutes or more	2
10–59 minutes	1
Diabetes	1
Total score	Risk of AIS Within 2 days of TIA
6 or 7	High risk (8.1%)
4 or 5	Moderate risk (4.1%)
2 or 3	Low risk (1.3%)

ABCD2 = age, blood pressure, clinical features, duration of symptoms, diabetes; AIS = acute ischemic stroke; TIA = transient ischemic attack.

Information from Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007;369:283–92.

(CT) of the brain remains the current criterion standard and is useful in differentiating hemorrhagic stroke from AIS. It can also provide the clinician with information regarding the size, location, and vascular distribution of the infarct. Noncontrast imaging is preferred because CT with contrast provides no additional information and is potentially toxic to brain tissue during a primary or secondary hemorrhagic event. Other multimodal neuroimaging technologies are available that can further provide diffusion and perfusion mismatch information.

Pharmacotherapy

The overall goals of management are to reduce neurologic injury, decrease mortality, and prevent long-term disability. Interventions are aimed at limiting the area of infarction and salvaging the penumbra, which is achieved primarily by removing the occlusion through reperfusion therapy.

Reperfusion strategies are time-sensitive; therefore, establishing protocols for emergency triage and managing patients with acute stroke are critical. The ASA-established goal is that patient evaluation and treatment decision should occur within 60 minutes (the golden hour) of the patient's arrival to the emergency

department. The established goal for neuroimaging from door-to-interpretation is 45 minutes, allowing 25 minutes for imaging and 20 minutes for interpretation. In addition to reperfusion therapy, acute management involves anticoagulation for CVT-related stroke, antiplatelet use, and blood pressure management.

After acute treatment, preventing and treating medical complications (e.g., VTE prophylaxis, fever, hyperglycemia, infection, hemodynamic instability) and initiating secondary stroke prevention are important. New information on reperfusion therapy, blood pressure management for both acute and secondary prevention, and antithrombotic therapy for secondary prevention are discussed in the following.

Reperfusion Therapy

Intravenous alteplase, administered within 3 hours of symptom onset, remains the gold standard and is the only class I level A reperfusion therapy recommended by AHA/ASA. Other reperfusion therapy includes either intra-arterial alteplase or mechanical thrombectomy alone or in combination with intravenous alteplase. The NIHSS and mRS scores are commonly used to assess the effectiveness of these interventions. A decrease in these scores indicates good outcomes, whereas an increase in scores indicates poor outcomes and diminished effectiveness.

Rationale for Use

The potential clinical gains from alteplase pertain to tissue reperfusion and attenuation of infarct growth, which depend on both the degree of irreversible damage and the presence and extent of ischemic penumbra. An ischemic penumbra is present in at least 80% of patients within 3 hours of stroke onset but diminishes with time. Patients who are excluded from intravenous alteplase may be considered for catheter-based interventions or intra-arterial thrombolytic therapy directly into the clot. Mechanical thrombectomy may be accomplished using devices for clot extraction and evacuation. Ultrasound-enhanced thrombolysis (sonothrombolysis) may be used in an attempt to alter the structure of the thrombus and accelerate thrombolysis with either intravenous or intra-arterial thrombolytic administration.

Intravenous Thrombolysis

Alteplase, a tissue plasminogen activator, is an enzyme with the ability to convert plasminogen to plasmin because of fibrin enhancement. At pharmacologic concentrations, it binds to fibrin within the thrombus, forming an active lytic complex. The recommended dose for AIS is 0.9 mg/kg (maximal dose of 90 mg) infused over 60 minutes. A bolus dose of 10% is administered over 1 minute, and the remainder is infused over 60 minutes.

The National Institute of Neurological Disorders and Stroke (NINDS) trial established the efficacy of intravenous alteplase when administered within 3 hours of stroke symptom onset; this was the basis for U.S. Food and Drug Administration (FDA) label approval for its use in AIS. Patients who received alteplase had significant improvements at 90 days as measured by four outcome scales: NIHSS score, mRS score, Barthel Index, and Glasgow Outcome Scale. Alteplase-treated patients were at least 30% more likely to have minimal or no disability at 90 days. In the 1990s after the NINDS trial, several large trials evaluated the optimal dose and window of opportunity for this agent, but the efficacy of alteplase was not shown outside the 3-hour time window.

The European Cooperative Acute Stroke Study-3 (ECASS-3) was conducted between 2003 and 2007 at 130 sites in 19 European countries. The results of this study suggest that certain patients may safely receive intravenous alteplase up to 4.5 hours after symptom onset. Patients with known risk factors for SICH (e.g., age older than 80, baseline NIHSS score greater than 25, any oral anticoagulant use regardless of international normalized ratio [INR], combination of prior stroke and diabetes) were excluded. Based on the ECASS-3 fndings, the AHA/ASA recommended expansion of the 3-hour time window for intravenous alteplase administration to 4.5 hours in certain patients (class 1 level B evidence). However, AHA/ASA emphasized the importance of administering alteplase within 3 hours when it is possible, because a greater benefit was seen when the drug was administered within 90 minutes of symptom onset versus 90–180 minutes and 180–270 minutes. These findings suggest that every effort should be made to ensure timely administration of alteplase.

Intra-arterial Thrombolysis

Intra-arterial thrombolysis with alteplase, with or without mechanical thrombectomy, remains a viable therapeutic alternative for patients who are excluded from receiving intravenous alteplase. Other patients who may benefit from this approach include those who present with large vessel disease with heavy clot burden (including malignant middle cerebral artery infarcts) and those whose recanalization after intravenous alteplase failed.

Advantages of endovascular therapies include expansion of the available treatment window to 6 hours, reduced or eliminated risk associated with systemic thrombolysis, higher rates of recanalization, and earlier recanalization. However, higher recanalization rates do not necessarily translate into better brain tissue perfusion or improved outcomes. Lack of perfusion may be caused by downstream embolizations from plaque showering, blockage of circulation caused by permanent vascular injury from the ischemic event, or tissue reperfusion injury. Disadvantages of an endovascular

approach include the need for a high level of expertise and specialized equipment, potential vascular perforation, delay in the initiation of thrombolysis, and risk of distal embolization.

Thrombectomy

Several devices are available for mechanically removing clots from large intracranial arteries; these devices are FDA label approved for use up to 8 hours after symptom onset. The use of diffusion-weighted magnetic resonance imaging (MRI) or CT perfusion studies may identify patients who are less likely to recanalize with intravenous alteplase alone and who may be candidates for these procedures. In addition, thrombectomy with or without intra-arterial thrombolysis may be a treatment option for patients with contraindications to intravenous alteplase or who have NIHSS scores greater than 25.

Complications and Cost-effectiveness

The most devastating complications associated with thrombolytic therapies remain SICH or death. The NINDS alteplase study reported that SICH occurred in 6.4% of patients treated with alteplase versus 0.6% of patients treated with placebo within 36 hours of symptom onset. Strict inclusion and exclusion criteria as established by AHA/ASA must be followed because several community-based hospital studies have noted that protocol violations can increase SICH by as much as 15.7%. The main deviations identified in the literature include uncontrolled hypertension, previous administration of alteplase, and administration outside the 3-hour window.

In the ECASS-3 trial, the SICH rate was 7.9% in the alteplase group and 3.5% in the placebo group using the NINDS definition of SICH. Although the incidence of SICH was significantly different between the two groups, it is similar to what was reported in the original NINDS trial and community studies. When SICH was defined as any intracranial hemorrhage resulting in neurologic deterioration or death, the SICH rate was 2.4% in the treatment group and 0.2% in the placebo group. In addition to protocol deviation, risk factors associated with SICH development include high baseline NIHSS scores, large clot burdens, location of stroke (MCA or multi-lobar stroke), and early hyperglycemia.

Despite the benefits and low incidence of complications of intravenous alteplase for stroke, the drug remains underused. Before 2005, financial disincentives to the use of alteplase existed. No additional reimbursement was made to physicians or hospitals despite a substantial increase in time and hospital-associated costs to care for these patients. In 2005, Medicare reimbursement to hospitals increased by $6000 (to almost $12,000) per patient with stroke when thrombolysis was administered, thereby providing an incentive for intravenous alteplase

use. This occurred after studies showed the drug to be both cost-effective and cost saving.

One study showed a per-patient savings of $600 because of decreased rehabilitation and nursing home costs. Another analysis found that the increase in hospitalization costs of $1.7 million associated with intravenous alteplase was outweighed by a decrease in rehabilitation costs of $1.4 million and nursing home costs of $4.8 million per 1000 eligible treated patients. The estimated impact on long-term outcomes was 564 quality-adjusted life-years saved over 30 years per 1000 patients. Of interest, only 2% of patients with AIS in this analysis received intravenous alteplase. This study concluded that increasing the treatment group to 4%, 6%, 8%, 10%, 15%, or 20% would realize cost savings (in millions) of $15, $22, $30, $37, $55, and $74, respectively, in the United States.

Acute Medical Management

In addition to reperfusion therapy, management during the acute phase of cerebral ischemia centers around general supportive care (airway protection and circulation) and management of acute complications (e.g., fever, blood glucose, elevated blood pressure, VTE prophylaxis, seizures).

Fever is common after brain injuries and is often not attributable to infection. Several mechanisms are suggested as the cause of fever immediately after AIS, including increased sympathetic response, inflammatory response, and/or damage to the thermoregulatory centers. Fever can lead to poorer outcomes because of the production of proinflammatory cytokines, free radicals, and excitatory neurotransmitters, which cause further tissue injury. A meta-analysis found that fever was associated with prolonged intensive care unit stay, higher mortality, and worse functional outcomes as measured by the Glasgow Outcome Scale. However, the definition of fever varied greatly from study to study, ranging from 99.5°F to 102°F (37.5°C–39.0°C).

Although the negative impact of fever after acute neurologic injury is established, it is unclear whether any benefit is associated with aggressive management of temperature. This is likely because of a lack of clear definition of fever, various methods to control temperature, and unknown duration of aggressive management. The current AHA/ASA guidelines recommend maintenance of normothermia (less than 100.4°F or 38°C) with proper source control (i.e., treating any existing infection) and antipyretic drugs. Induced hypothermia for fever management is not recommended because of insufficient data.

Both hypo- and hyperglycemia should be addressed promptly. The brain lacks the capacity to store necessary nutrients such as glucose; therefore, a constant supply is essential to maintain cellular function. In addition to mimicking stroke-like symptoms, hypoglycemia

may exacerbate cerebral injury. Maintaining euglycemia is an easy and important step in AIS management. Hyperglycemia has been suggested to increase the risk of hemorrhagic transformation after thrombolytic therapy. In addition, hyperglycemia is associated with poor neurologic outcomes. However, controversy exists on the optimal threshold to treat patients with AIS and the appropriate glycemic goal.

Data suggest that the traditional glucose concentration of 200 mg/dL is too high and that less than 110 mg/dL is too low during the acute phase of injury. Therefore, targeting glucose concentrations of 80–110 mg/dL in patients with AIS may subject the brain cells to hypoglycemia. The Treatment of Hyperglycemia in Ischemic Stroke (THIS) trial tested the feasibility and tolerability of aggressive glucose control (less than 130 mg/dL) versus usual care (less than 200 mg/dL) and found no significant adverse events associated with aggressive management. However, no difference in clinical outcomes was noted between the two treatment groups. The recent AHA/ASA guidelines reflect the inconsistency in the literature, stating that a blood glucose concentration greater than 140–185 mg/dL should be the trigger for treatment. No specific glycemic goal was recommended.

Acute hypertension occurs in about 80% of patients after AIS regardless of medical history, and determination of acute treatment and goal blood pressure is multifactorial. Treatment approaches for elevated blood pressure during the acute phase (within 24–48 hours of onset) are based on whether the patient is a candidate for thrombolytic therapy. For patients who are candidates, aggressive blood pressure management is recommended with a goal systolic/diastolic blood pressure of less than 180/105 mm Hg (Figure 1-1).

The decision about when and how aggressively to treat high blood pressure in patients not receiving thrombolytics remains controversial. Aggressive treatment during the acute phase is argued to avoid hemorrhagic transformation, cerebral edema, and increased intracranial pressure. However, aggressively lowering blood pressure is feared to precipitate further cerebral ischemia because of a lack of perfusion, and many patients have blood pressure decreases without intervention.

Limited studies have evaluated the feasibility and efficacy of acute blood pressure reduction immediately after AIS. Two prospective trials evaluated the use of angiotensin receptor blockers within 30 hours of AIS onset. Of interest, opposite findings were reported, although the study designs were similar. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) trial found that acute use of candesartan significantly decreased cardiovascular events with minimal adverse events compared with placebo, whereas the Scandinavian Candesartan Acute Stroke Trial (SCAST) failed to show any benefit regarding vascular events or functional outcomes. Because of conflicting findings,

the recommendation for blood pressure management in patients who are not candidates for thrombolytic therapy is to treat systolic blood pressure greater than 220 mm Hg or diastolic blood pressure greater than 120 mm Hg. Several questions regarding acute blood pressure management remain, such as the optimal target blood pressure, how quickly to lower blood pressure, and the appropriate antihypertensive agents to use in these patients.

Effective VTE prophylaxis measures after AIS include early mobilization, nonpharmacologic measures (compression stockings), and pharmacologic therapies (unfractionated heparin and low-molecular-weight heparin). The compression devices should only be used alone if anticoagulant prophylactic therapy is contraindicated. Although the 2007 AHA/ASA guidelines recommend early use of either unfractionated heparin or low-molecular-weight heparin after AIS for VTE prevention in patients without contraindications, some recent data suggest that low-molecular-weight heparin produces a greater reduction in the VTE incidence than unfractionated heparin without an increase in bleeding. The Prevention of Venous Thromboembolism after Acute Ischemic Stroke (PREVAIL) investigators reported that enoxaparin was associated with a 43% relative risk reduction compared with unfractionated heparin. A recent meta-analysis found that low-molecular-weight heparin was associated with reduction in any VTE as well as proximal VTE compared with unfractionated heparin. Subcutaneous enoxaparin 40 mg/day was the most commonly studied treatment option and was safely initiated within 48 hours of stroke onset.

Seizures may occur after AIS; however, the overall incidence is relatively low. Cortical involvement and large infarction are risk factors for developing seizures. Currently, there are no data showing the benefit of routine seizure prophylaxis in AIS. The use of prophylactic antiepileptic drugs is therefore not recommended in patients who suffer an AIS, but treatment should be initiated if a patient experiences seizures after AIS.

Stroke Prevention

Preventive strategies in AIS management involve goal setting, interventions, and monitoring of outcomes. Primary prevention involves lifestyle modifications such as smoking cessation, blood pressure management, lipid management, and treatment of cardiac conditions such as atrial fibrillation. Secondary prevention measures are similar to primary prevention regarding risk factor control; however, more specific recommendations exist regarding blood pressure management, antiplatelet use for noncardioembolic stroke, and anticoagulation for cardioembolic stroke.

Primary Prevention

Both blood pressure and lipid management remain vital components of primary stroke prevention. Blood
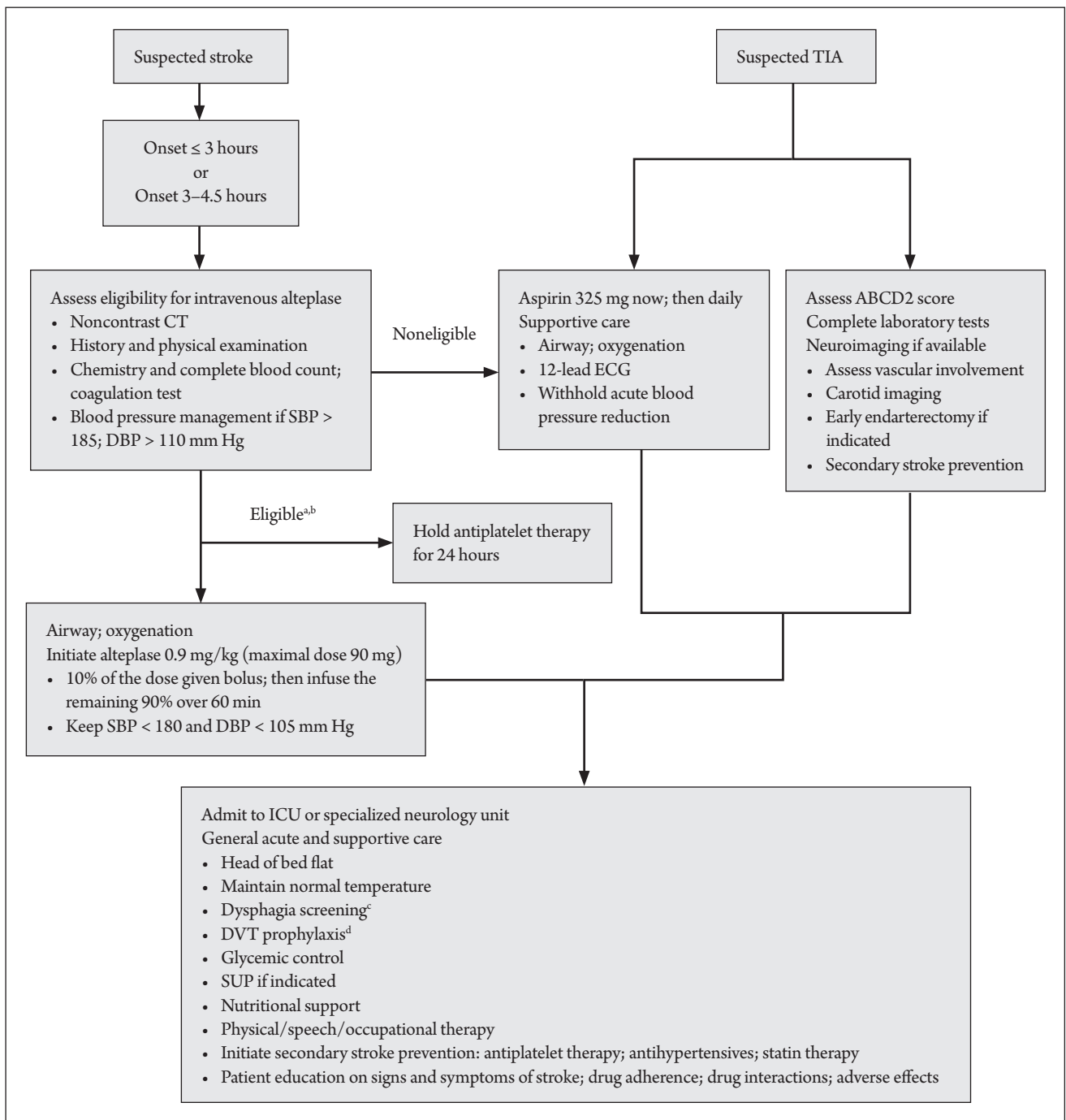
Figure 1-1. Management of acute ischemic stroke.

[a]Eligibility for intravenous alteplase in patients with onset within 3 hours: negative for hemorrhagic stroke or history of hemorrhagic stroke; no head trauma, stroke, myocardial infarction in the past 3 months; no gastrointestinal or urinary tract hemorrhage in the past 21 days; no major surgery in the previous 14 days; blood pressure not > 185/110 mm Hg; not taking oral anticoagulant or INR ≤ 1.7; platelet count ≥ 100,000/mm^3; blood glucose ≥ 50 mg/dL.
[b]Additional eligibility criteria for intravenous alteplase in patients with onset between 3 hours and 4.5 hours: age < 80 years; no history of stroke and diabetes; not taking oral anticoagulants regardless of INR; no significant symptomatic improvement within 30 minutes; NIHSS score < 25.
[c]All patients should be kept NPO immediately after stroke until dysphasia screening is performed.
[d]All patients with stroke may receive mechanical VTE prophylaxis. The current guidelines do not address the timing of initiating pharmacologic VTE prophylaxis.
ABCD2 = age, blood pressure, clinical features, duration (symptoms), diabetes rating scale; CT = computed tomography; DBP = diastolic blood pressure; DVT = deep venous thrombosis; ECG = electrocardiograhy; ICU = intensive care unit; INR = international normalized ratio; min = minutes; NIHSS = National Institutes of Health Stroke Scale; NPO = nothing by mouth; SBP = systolic blood pressure; SUP = stress ulcer prophylaxis; TIA = transient ischemic attack; VTE = venous thromboembolism.

pressure reduction was associated with a 32% risk reduction in stroke incidence across all age groups. Specific pharmacologic therapy and blood pressure goals are consistent with the Joint National Committee (JNC) 7 recommendations. In patients with dyslipidemia, a statin is recommended for primary stroke prevention. Studies of other lipid-lowering agents (e.g., niacin, fibric acid derivatives) have not shown efficacy in stroke risk reduction. The recommended lipid goal in AIS prevention mirrors the National Cholesterol Education Program guidelines.

In patients with atrial fibrillation, therapy with either aspirin or oral anticoagulation (warfarin) is recommended for primary AIS prevention. Using an antiplatelet drug versus an anticoagulant is based on the risk stratification for AIS in patients with atrial fibrillation. The congestive heart failure, hypertension, age, diabetes, stroke/TIA (CHADS$_2$) score is the most commonly used tool for stroke risk assessment. A score of 2 or greater indicates high risk of AIS in patients with atrial fibrillation, and warfarin is recommended for stroke prevention in this population. In low-risk patients with atrial fibrillation, warfarin was not found more effective than aspirin when hemorrhagic complications were considered. In patients with moderate risk of stroke (CHADS$_2$ score of 1), treatment decisions should consider benefits as well as bleeding risk, drug adherence, and ability to monitor anticoagulation therapy.

Concerns with warfarin therapy include a narrow therapeutic window, drug-drug and drug-food interactions, need for frequent monitoring, and increased bleeding risk; these contribute to underuse of the agent even when it is indicated. Dabigatran, a new oral direct thrombin inhibitor, was approved for prevention of stroke secondary to nonvalvular atrial fibrillation. In the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study, dabigatran was associated with a 34% relative risk reduction in stroke or VTE compared with warfarin. Although the risk of major bleeding was similar between groups, intracranial bleeding was significantly lower in the dabigatran group than in the warfarin group. The

AHA/ASA issued a 2011 advisory recommending dabigatran as an alternative to warfarin for preventing strokes in patients with nonvalvular atrial fibrillation. Warfarin remains the drug of choice in patients with prosthetic heart valves or valvular disease.

Although the U.S. Preventive Services Task Force (USPSTF) recommends aspirin for the prevention of cardiovascular disease, its benefit in stroke prevention is not clearly established. Several large trials in high-risk patients have failed to show a benefit against stroke when aspirin was compared with placebo. The Women's Health Study showed a 24% stroke risk reduction in women younger than 45 years. Although the reduction was not statistically significant, the benefit of aspirin was more consistently shown in those 65 years or older.

Based on current evidence, aspirin is only recommended for prevention of cardiovascular disease in high-risk patients (defined as having a 10-year risk of 6% to 10% with a low risk of hemorrhagic complications). Specific to primary AIS prevention, low-dose aspirin (81 mg/day or 100 mg every other day) is recommended by AHA/ASA and USPSTF in high-risk women 55–79 years old without contraindications. Table 1-2 summarizes the role of aspirin in primary stroke prevention.

Secondary Prevention

In patients who are ineligible for thrombolytic therapy, aspirin 325 mg is the only antiplatelet agent recommended for acute treatment (i.e., within 24–48 hours of AIS). Other antiplatelet agents (e.g., clopidogrel, aspirin/dipyridamole extended release) have not been studied in the acute phase. Nevertheless, aspirin, clopidogrel, and aspirin/dipyridamole extended release remain the cornerstone of secondary prevention after noncardioembolic stroke.

Aspirin alone results in a 15% relative risk reduction of vascular events compared with placebo; clopidogrel has been associated with about a 9% relative risk reduction compared with aspirin; and aspirin/dipyridamole extended release reduces AIS risk by 23% compared with aspirin. Although aspirin/dipyridamole extended

Table 1-2. USPSTF Recommendations Regarding Aspirin for Primary Stroke Prevention

Population and Age (years)	Recommendation	Level of Evidence[a]
Men < 45	Recommend against use	D
Men 45–70	Potential benefit for reduction of MI	A
Women < 55	Recommend against use	D
Women 55–79	Potential benefit for reduction in AIS	A
Men/Women > 80	Current evidence insufficient for recommendation	I

[a]A = high certainty that the net benefit is substantial; D = no net benefit and possible harm outweighs benefit; I = current evidence is insufficient to assess balance of benefits and harms.

AIS = acute ischemic stroke; MI = myocardial infarction; USPSTF = U.S. Preventive Services Task Force.

release appears to be more effective than aspirin alone, all three agents are recommended as first line by AHA/ASA for secondary prevention on the basis of cost, patient-specific comorbidities, allergies, and tolerance.

The combination of aspirin and dipyridamole immediate release has not been studied and therefore cannot be recommended as an alternative to aspirin/dipyridamole extended release. Based on available data, the combination of aspirin and clopidogrel for stroke prevention alone is not recommended unless patients have other comorbidities such as coronary stents; this dual antiplatelet therapy was associated with an increase in hemorrhagic complications. Another challenge the clinician may face is the patient who develops AIS while on an antiplatelet agent. Currently, there are no data supporting that changing to a different antiplatelet agent reduces the stroke risk.

In 2009, the FDA issued a clinical advisory about the potential suboptimal response to clopidogrel secondary to coadministration of proton pump inhibitors. The concern stems primarily from a randomized trial evaluating platelet function in patients receiving both omeprazole and clopidogrel; results showed a significant decrease in the platelet inhibitory effect of clopidogrel. The mechanism for decreased antiplatelet effect was thought to be a drug interaction between clopidogrel and omeprazole. Clopidogrel is a prodrug that requires activation through hepatic metabolism; this metabolism is primarily by CYP2C19, which is also responsible for omeprazole metabolism. Coadministration may decrease clopidogrel activation by competitive binding to CYP2C19. Of interest, newer proton pump inhibitors such as pantoprazole and lansoprazole do not appear to have the same effect on clopidogrel because of less competition for CYP2C19. All studies evaluated platelet function as a surrogate marker for clinical outcomes, so the clinical implications of an interaction of combined clopidogrel and proton pump inhibitors are unclear at this time. However, the use of pantoprazole or lansoprazole with clopidogrel appears to be safe.

Acute full anticoagulation within 24 hours of AIS is not routinely recommended for secondary stroke prevention; however, the practice continues to be debated for patients with cardioembolic stroke or CVT-related stroke. In these patients, anticoagulation can be achieved with unfractionated heparin, low-molecular-weight heparin, or warfarin if the benefit outweighs the risk of hemorrhage. Dabigatran has not been evaluated immediately after noncardioembolic AIS but has been studied for secondary stroke prevention in patients with atrial fibrillation. A subgroup analysis of the RE-LY trial found that in patients with a history of stroke or TIA, dabigatran was associated with a nonsignificant decrease in the rate of recurrent stroke or systemic embolism compared with warfarin at 2 years. However, intracranial bleeding was significantly less in the dabigatran-treated group. The

definitive role of dabigatran for secondary stroke prevention needs further evaluation.

In secondary stroke prevention, antihypertensive therapy is recommended regardless of baseline blood pressure after the first 24 hours after symptom onset. On the basis of the Perindopril Protection Against Recurrent Stroke (PROGRESS) study, a thiazide diuretic with or without an angiotensin-converting enzyme inhibitor is recommended for secondary stroke prevention. Other agent classes such as calcium channel blockers or β-adrenergic blockers have been evaluated with variable results. After the PROGRESS trial, several large randomized studies, including the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS), the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), and the Telmisartan Randomized Assessment Study in ACE iNtolerant subjects with Cardiovascular Disease (TRANSCEND) trial, evaluated the role of angiotensin receptor blockers with or without angiotensin-converting enzyme inhibitors for stroke/TIA prevention. None of these studies was able to show a statistically significant reduction in recurrent stroke associated with the use of angiotensin receptor blockers. The current consensus is that reducing blood pressure is the most important factor in stroke prevention. Drug selection should be based on patient-specific factors and comorbidities.

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study further solidified the role of statin therapy for secondary stroke prevention in patients with low-density lipoprotein cholesterol greater than 100 mg/dL and without coronary heart disease. A significant risk reduction in nonfatal and fatal stroke was observed in the atorvastatin group compared with placebo. The treatment also resulted in a 12% relative risk reduction in ischemic stroke. Therefore, statin therapy is recommended for secondary stroke prevention, including in patients without coronary heart disease. The goal low-density lipoprotein cholesterol concentration has been lowered in the guidelines from 100 mg/dL to less than 70 mg/dL or a 50% reduction from the baseline.

Future Therapies

During the past decades, many neuroprotectants have shown great promise in animal trials but no benefit in studies of humans.

Magnesium, which was associated with reduced infarction size in animal ischemic stroke models, has been examined as a neuroprotectant in subarachnoid hemorrhage. The proposed mechanisms of magnesium therapy include N-methyl-d-aspartate receptor inhibition, reduction in glutamate production, and decreased calcium influx during ischemic injury by blockage of voltage-dependent calcium channels. The Intravenous

MAGnesium Efficacy in Stroke (IMAGE) trial was the first randomized study to evaluate how magnesium infusion given within 12 hours of stroke onset affected mortality and disability at 90 days. More than 60% of the studied population suffered an ischemic stroke, and the primary outcome did not differ between magnesium and placebo. Although not significant, the mortality rate was slightly higher in the magnesium group than in the placebo group. The Field Administration of Stroke Therapy - Magnesium (FAST-MAG) trial group reported the safety and feasibility of magnesium administration by paramedics within 2 hours of stroke onset in a pilot study. A large phase III trial evaluating the efficacy of field administration of magnesium is ongoing to further investigate its role in functional outcomes after AIS.

Minocycline is a tetracycline derivative that improves neuron survival and decreases cerebral ischemia volume in animal models. A pilot human study evaluated oral minocycline 200 mg/day for 5 days in AIS (given 6–24 hours after onset). The NIHSS score at 90 days compared with baseline was used to evaluate efficacy. Although there was a significant improvement in the NIHSS score at days 7 and 30 compared with baseline (1.8 vs. 7.5, respectively), the clinical significance is unclear because the NIHSS score on admission was low. The Minocycline to Improve Neurologic Outcome (MINO) study is under way to evaluate the tolerability and safety of four escalating doses in patients with AIS.

Albumin has also been explored as a neuroprotectant after AIS. The Albumin in Acute Stroke (ALIAS) Part 1 trial showed a trend toward favorable neurologic outcomes with albumin therapy compared with saline in patients who received thrombolysis. These findings set the stage for the ALIAS Part 2 trial, which will evaluate the effect of albumin initiated within 5 hours of stroke onset on neurologic outcomes at 90 days.

Finally, hypothermic therapy has generated great interest because of improved neurologic outcomes associated with therapeutic hypothermia after cardiac arrest. The theoretical benefit with hypothermia is to suppress cerebral metabolism and alleviate further neuronal injury after AIS. Two pilot studies, Cooling Acute Ischemic Brain Damage (Cool AID) 1 and 2, showed that hypothermia (target temperature 32°C–33°C) in conjunction with thrombolytic therapy is feasible in patients with major AIS; however, efficacy and safety data are lacking. Several clinical trials are under way to evaluate the role of moderate-mild hypothermia (locally or systemically) in AIS management.

QUALITY IMPROVEMENT

Many measures have been evaluated and are recommended by AHA/ASA to improve overall stroke care. Studies suggest that a dedicated stroke center and specialized stroke unit contribute to earlier recognition as well as more aggressive management, increased use of thrombolytic therapy, and decreased hospital length of stay and mortality. Electronic communication methods have gained recognition and acceptance in stroke management. Several studies suggest that telemedicine improves the use of thrombolytic therapy in rural areas and lowers rates of hemorrhagic complications. This is an important development in AIS management because primary stroke centers and/or specialists are unavailable in many areas.

Another area of focus in stroke care is a multimodal approach for secondary stroke prevention. One study evaluated the effect of a combination of five key interventions (i.e., blood pressure control, antiplatelet therapy, statin use, dietary modification, and exercise) in secondary prevention and found an 80% risk reduction in all vascular events at 5 years. This emphasizes the importance of a multimodal approach in the long-term management of patients who suffer a TIA or stroke.

Pharmacists can be an integral part of public education and stroke awareness. Studies have shown that pharmacist involvement in the community significantly improves both adherence to secondary prevention therapies and patient quality of life. In addition, pharmacists have an important role in reducing drug errors, as advocated in a recent scientific statement from AHA. As part of the multidisciplinary team, pharmacists contribute to reduction in drug errors, improved patient safety, and reduced hospital mortality.

CONCLUSION

Ischemic stroke is the leading cause of long-term disability and imposes significant financial burdens on both the individual and society. The high risk associated with recurrent stroke after TIA, plus a better understanding of the disease from advanced imaging techniques, have placed increased urgency and emphasis on TIA management similar to the secondary prevention after AIS.

The ABCD2 score is a simple and useful prognostic tool to estimate a patient's risk of subsequent stroke after a TIA. Another significant change in the acute management of AIS is the expanded time window (from 3 hours to 4.5 hours) for administering intravenous alteplase after stroke symptom onset in selected patients. Because timely use of thrombolytic therapy is associated with the greatest benefit, every effort should be made to treat as early as possible. Finally, aggressive stroke prevention employing several modalities is the best measure to improve outcomes and reduce stroke burden.

ANNOTATED BIBLIOGRAPHY

1. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from

the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Stroke 2007;38:1655–711.

The 2007 guidelines incorporated three main changes to recommendations: (1) intra-arterial alteplase criteria, to establish the qualifications of physicians who can perform intra-arterial interventions; (2) dysphagia screening for all patients with AIS and the need to provide hydration and nutrition through nasogastric, nasoduodenal, or gastric tubes while undergoing efforts to restore swallowing in patients with impaired swallowing; and (3) transfer of patients at increased risk of malignant brain edema to a facility with neurosurgical support if the hospital does not have access to neurosurgery. For the first time, the guidelines added specific criteria for primary and comprehensive stroke centers. Emergency medical service should transfer stroke patients to the closest primary or comprehensive stroke center, not just the closest hospital. This comprehensive document covers topics from out-of-hospital care to emergency department management, as well as prevention and treatment of immediate complications.

2. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 2009;40:2276–93.

This guideline provides a detailed epidemiology of TIA, in addition to revising the definition of TIA by removing the arbitrary 24-hour time restriction. The traditional definition contributed to the underuse of time-sensitive reperfusion strategies by delaying the time to neuroimaging. It is estimated that one-third of patients were misclassified as having a TIA rather than AIS once neuroimaging techniques were employed. The new definition of a TIA is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. This new scientific statement emphasizes urgent neurodiagnostic testing including CT or MRI to differentiate patients with TIA from patients with AIS. The article also discusses the pros and cons associated with the new tissue-based definition. Of note, with this change in TIA definition, readers must be mindful when evaluating studies involving patients with TIA in the future.

3. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:1158–92.

This guideline discusses diagnosis, management, and treatment of CVT, an uncommon form of stroke usually affecting young individuals. Risk factors align with other venous thromboses rather than arterial strokes and include acquired risks (e.g., surgery, trauma, pregnancy, puerperium, cancer, exogenous hormones) as well as genetic risks such as inherited thrombophilias. An uncommon cause is infection in parameningeal locations such as ear, sinus, mouth, face, and neck. Common clinical manifestations include headache, increased intracranial pressure, papilledema, and seizures leading to rapid neurologic deterioration. About 30% to 40% of patients may present with intracranial hemorrhage; because this has important treatment implications, it is critical that CVT be identified as the cause. Initial anticoagulation with intravenous weight-based heparin or low-molecular-weight heparin, followed by vitamin K antagonists regardless of the presence of intracranial hemorrhage, is reasonable. Partial or complete recanalization rates range from 47% to 100% with anticoagulation alone. The guideline provides a comprehensive review of venous-related stroke.

4. Hacke W, Kaste M, Bluhmki E, Brozman M, Davalos A, Guidetti D, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317–29.

The ECASS-3 trial provided insight into which patients might benefit from intravenous alteplase outside the traditional 3-hour time window (up to 4.5 hours). The exclusion criteria used in the NINDS trial were used with several additions: severe stroke (NIHSS score of 25 or greater), combination of previous stroke and diabetes, and age 80 years or older. Of the 418 patients in the extended intravenous alteplase window, the median time for administration was 3 hours 59 minutes. The primary efficacy end point was disability, dichotomized as a favorable outcome (mRS 0–1) or an unfavorable outcome (mRS 2–6) at 90 days. Most patients had a favorable outcome with alteplase; 52.4% of participants in the treatment group reached the primary end point of an mRS score of 0–1 at 90 days compared with 45.2% in the placebo group. The per-protocol group showed similar efficacy. The rate of spontaneous intracranial hemorrhage in the ECASS-3 trial (using the same definition as in the NINDS trial) was 7.9% compared with 6.4% in the NINDS. However, when the definition of spontaneous intracranial hemorrhage was updated to "any hemorrhage with neurologic deterioration when combined with an NIHSS score 4 points greater than either the baseline value or the lowest value in the first 7 days, or death," the SICH rate was 2.6% in the treatment arm compared with 0.2% in the placebo arm. It is estimated that for patients receiving

intravenous alteplase, 1 of every 14.3 patients will have a favorable outcome, and 1 of every 34 will have an adverse effect. This study provided the basis for the new recommendations regarding thrombolytic therapy by the AHA/ASA.

5. del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/ American Stroke Association. Stroke 2009;40:2945–8.

This AHA/ASA scientific advisory addresses the issue of expanding the time window for the use of intravenous alteplase for AIS treatment to 4.5 hours, based on the ECASS-3 study results. This consensus statement indicated it would be appropriate to use intravenous alteplase in selected patients presenting with symptom onset within a 4.5-hour window, provided that the same inclusion/exclusion from the ECASS-3 were applied because there is no evidence that benefit can be accrued for patients who were not tested in the trial. However, the AHA/ASA emphasized that these results should not be interpreted as "there is plenty of time" to prepare for the use of intravenous alteplase in a patient who arrives in the hospital within 3 hours from stroke onset. It has been clearly established that the benefits of intravenous alteplase in AIS are strongly time-dependent, with early treatment yielding the largest benefit. The magnitude of the benefit declines progressively from the first 90 minutes to the 3-hour period to the 4.5-hour period. The consensus statement strongly discouraged practitioners from using the expanded time window as rationale to relax the triage of patients with AIS who may be within the 3-hour time window. The greater benefit is associated with earlier use of intravenous alteplase, and every effort should be made to ensure that happens.

6. Diener HC, Sacco RL, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al; Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study group. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. Lancet Neurol 2008;7:875–84.

This multicountry randomized trial evaluated the efficacy of both antiplatelet agents and angiotensin receptor blockers in secondary stroke prevention. The study was designed in a 2 x 2 factorial fashion to compare aspirin/dipyridamole extended release 25 mg/200 mg two times/day, clopidogrel 75 mg/day, telmisartan 80 mg/day, and placebo. Patients were compared four ways: aspirin/dipyridamole with telmisartan, aspirin/ dipyridamole with placebo, clopidogrel and telmisartan, and clopidogrel and placebo. Overall, there was no difference in recurrent stroke or functional outcomes among the four treatment groups. It is unclear whether the finding of nonsignificance was caused by both

antiplatelet and antihypertensive being equally efficacious in improving functional outcomes or because of lack of effect. Two subgroup analyses of antiplatelet therapies and telmisartan were published separately to further evaluate the efficacy of each intervention on preventing recurrent stroke.

7. Yusuf S, Diener HC, Sacco RL, Cotton D, Ounpuu S, Lawton WA, et al; PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008;359:1225–37.

This separate analysis of the PRoFESS trial focused on the effect of blood pressure treatment on recurrent stroke. More than 20,000 patients were randomized to receive either telmisartan 80 mg or placebo with a median time of 15 days from stroke onset. The mean treatment duration was 2.5 years. Other blood pressure drugs were allowed, including angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, and β-adrenergic blockers, but there was no difference in the proportion of patients using concomitant drugs between the two groups. The recurrent stroke rate was 8.7% in the telmisartan group compared with 9.2% in the placebo group (p=0.23). When recurrent stroke and cardiovascular events were evaluated after 6 months, there was a significant reduction in the composite events in favor of telmisartan. This finding suggests that telmisartan has a potential cerebrovascular protective effect in the long term. The study failed to demonstrate ARB effectiveness in secondary stroke prevention.

8. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. N Engl J Med 2008;359:1238–51.

This is the second subgroup analysis of the PRoFESS trial focusing on antiplatelet therapy in secondary stroke prevention. Aspirin/extended-release dipyridamole given twice daily was compared with clopidogrel alone given once daily. More than 20,000 patients were randomized and followed for an average of 2.5 years. Time to treatment initiation was comparable between the two groups (median 15 days from stroke onset). Comorbidities and baseline stroke severity were similar between groups. There was no significant difference between the rate of recurrent stroke in the aspirin/extended-release dipyridamole group and the clopidogrel group. No difference was noted in hemorrhagic complications between treatment groups; however, aspirin/extended-release dipyridamole was discontinued in more patients than clopidogrel because of adverse effects (e.g., headache, nausea, vomiting). The study showed that aspirin/extended-release dipyridamole and clopidogrel have similar efficacy for recurrent stroke prevention.

9. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–59.

This study evaluated the efficacy of ramipril 10 mg/day, telmisartan 80 mg/day, or the combination in preventing cardiovascular- or cerebral-related death in high-risk patients. The study population was composed of patients with coronary artery disease, history of myocardial infarction, angina, hypertension, and/or diabetes with end-organ damage; about 20% of the study population had a previous stroke or TIA. There was no statistical difference in primary outcome (composite mortality) among the three treatment groups. The authors concluded that telmisartan was as effective as ramipril in preventing vascular events. In addition, they concluded that the combination of ramipril and telmisartan had no added advantage over monotherapy with either drug. The concomitant administration of therapies that included statins, antiplatelet drugs, and other blood pressure drugs that are beneficial in preventing vascular events was commonly observed, which may have complicated the interpretation of these results.

10. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al; Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174–83.

In addition to the PRoFESS and ONTARGET trials, this large randomized trial compared the benefit of telmisartan with placebo in preventing cardiovascular events including stroke. Similar to the other two trials, study patients in the TRANSCEND trial were at high risk of cardiovascular events, and other interventions were allowed. The only difference in this study is that the patients enrolled were intolerant of angiotensin-converting enzyme inhibitors. The average follow-up was 4.6 years. No significant differences between the two groups in the presence of cardiovascular death, stroke, myocardial infarction, and hospitalization for heart failure were observed. However, the composite outcome of cardiovascular death, myocardial infarction, and stroke was significantly lower in telmisartan-treated patients than in the placebo group. Findings from this study, together with the PRoFESS and ONTARGET trials, suggest that telmisartan is a viable alternative to angiotensin-converting enzyme inhibitors to prevent cardiovascular events. However, its role in secondary stroke prevention is yet to be determined.

11. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, et al; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. Lancet 2011;377:741–50.

The SCAST trial was a multicenter study that evaluated the effect of acute reduction of blood pressure after an ischemic stroke. A total of 2029 patients were recruited from nine European countries. The patients were randomized within 30 hours of stroke onset to either the candesartan treatment or placebo. The treatment threshold was defined as systolic blood pressure greater than 140 mm Hg; treatment lasted for 7 days. The two coprimary outcomes of interest were all vascular events and functional outcomes at 6 months. The study did not find any significant outcome differences in the composite end point of vascular events or mortality or in the functional outcomes as measured by mRS. The study failed to show any benefit with this angiotensin receptor blocker during the acute phase of stroke. This finding is inconsistent with the outcomes previously reported in the ACCESS trial. A primary difference between the two studies is the patient population studied: the SCAST trial included a mixed population with either ischemic or hemorrhagic stroke, whereas the ACCESS trial included only patients with AIS.

12. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing, Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:517–84.

This guideline provides updates since the 2006 publication on the primary prevention of stroke. This version includes information (risk factors and prevention strategies) on both ischemic and hemorrhagic strokes. A table at the end of the chapter is new and provides an at-a-glance summary of all stroke risk factors including nonmodifiable, well-documented modifiable, and less well-documented modifiable factors and their respective recommended interventions. The AHA/ASA revisited recommendations on the use of aspirin for primary stroke prevention. Aspirin is recommended for cardiovascular disease prevention in high-risk patients and for primary stroke prevention only in high-risk women older than 55 years. Aspirin is not recommended for primary stroke prevention in the general population. The AHA/ASA also provided guidelines on preventive measures that can occur in the emergency department such as screening for hypertension and atrial fibrillation, and providing referral to a smoking cessation program.

13. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:227–76.

This guideline provides an update on the literature and evidence for secondary stroke prevention since the last publication in 2006. It addresses blood pressure

management, statin therapy, diabetes and glucose control, and behavior modifications for recurrent stroke/ TIA prevention. Discussed are management of extracranial diseases (carotid disease or vertebrobasilar disease), antithrombotic therapy for cardioembolic and noncardioembolic stroke prevention, and other high-risk populations including dissection, pregnancy, hyperhomocysteinemia, and inherited coagulopathy. The authoring panel also formulated recommendations on the use of anticoagulation, reversal of anticoagulant effect, and reinitiating therapy after spontaneous intracranial hemorrhage (a recommendation new to the guidelines). In patients who require an oral anticoagulant, it is reasonable to reinitiate the therapy in 7–10 days after the initial intracranial hemorrhage. This document is a great resource for clinicians to identify original studies supporting the recommendations.

14. Michaels AD, Spinler SA, Leeper B, Ohman EM, Alexander KP, Newby LK, et al. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. Circulation 2010;121:1664–82.

This is a joint statement issued by the stroke council from AHA. The article addresses the common and serious drug errors (dosing, dispensing, timing, and omission errors) identified in the management of cardiovascular disease and methods to reduce drug errors. The statement also examines drug errors specific to each disease state including acute coronary syndrome, acute heart failure, and acute stroke. Effective ways to reduce drug errors require an integrated system including computerized systems; smart pumps; effective drug reconciliation; good communication between health care providers, patients, and family; and involvement of a multidisciplinary team including physicians, pharmacists, and nurses. Pharmacist involvement was associated with reduction in medication errors, improvement in patient safety, improvement in prescribing appropriate medication for cardiovascular protection, and reduction in hospital mortality rate. This is an important document to show the value of clinical pharmacists.

Self-Assessment Questions

1. A 52-year-old man states that his wife just watched a documentary on stroke and now she thinks he needs to take aspirin daily to prevent a stroke. When you inquire about his risk factors, he states his physician has given him a clean bill of health. He sees his primary care physician annually and also exercises and runs in marathons at least twice a year. Both of his parents were smokers; his father died of a stroke at age 56, and his mother died of a myocardial infarction at age 70. **Which one of the following best represents this patient's risk of stroke and his optimal stroke prevention strategy?**

   A. High risk of stroke; aspirin 81 mg daily because of male sex, age older than 45 years, and family history of stroke.
   B. Low risk of stroke; no indications for aspirin at this time because of a healthy lifestyle and strenuous cardiovascular workouts.
   C. Low risk of stroke; aspirin 81 mg daily for prevention of myocardial infarction because of age, and family history of cardiovascular disease.
   D. High risk of stroke; aspirin 325 mg daily because of family history of cardiovascular disease.

Questions 2 and 3 pertain to the following case.
S.B. is a 28-year-old white woman who presents to the emergency department with a chief concern of headache. When showering this morning, she became disoriented and went to the kitchen for a glass of water without dressing. Her husband considered this behavior odd and questioned his wife. S.B. answered inappropriately, stating the flowers should be blooming soon and everything would be all right. Her husband called 9-1-1. S.B. presents to the emergency department within 1 hour of symptom onset and is now alert and oriented x 3 but has no memory of the event that landed her in the hospital. She denies taking any drugs except for her oral contraceptive, a triphasic estradiol and levonorgestrel, which she began a year ago. She drinks 1 glass of wine every few weeks and has smoked 1 pack/day of cigarettes for the past 6 years. Her mother and sister have a history of blood clots. Her husband states that S.B. is sedentary and likes to read.

2. **Which one of the following risk factors places S.B. at highest risk of stroke?**

   A. Estrogen use and smoking.
   B. Wine consumption and smoking.
   C. Family history of blood clots.
   D. Sedentary lifestyle.

3. S.B. is suspected of having a venous stroke. **Which one of the following is the best management for S.B.?**

   A. Intravenous alteplase.
   B. Heparin drip with oral anticoagulation.
   C. Enoxaparin 30 mg subcutaneously every 12 hours.
   D. Aspirin 325 mg orally now then daily.

Questions 4–6 pertain to the following case.
L.S. is a 62-year-old Hispanic man who presents to the emergency department with a chief concern of left-sided upper extremity weakness that resolved 20 minutes after symptom onset. A transient ischemic attack (TIA) is suspected. L.S. states he began having symptoms yesterday morning. His current blood pressure is 162/102 mm Hg. L.S. takes no drugs and has not been to a physician in 3 years because he lost his job and insurance. During his emergency department visit, L.S. has a similar episode that lasts about 15 minutes; the episode resolves with no residual deficits.

4. **Which one of the following best describes L.S.'s risk of subsequent stroke within 48 hours?**
   A. 5.0%.
   B. 8.1%.
   C. 4.1%.
   D. 1.3%.

5. L.S. went for a neuroimaging test about 25 hours after initial symptom onset, and an acute infarct was noted on the scan. His blood pressure is now 200/105 mm Hg. **Which one of the following treatments is best to accomplish the immediate blood pressure goal for L.S.?**

   A. Start intravenous labetolol and target blood pressure to less than 180/105 mm Hg.
   B. Start ramipril and target blood pressure to less than 140/90 mm Hg.
   C. Start intravenous labetolol and target blood pressure to a 25% reduction from baseline.
   D. No acute antihypertensive drug is indicated at this time to allow for permissive hypertension.

6. Assume that L.S. presented to the emergency department within 3.5 hours of his first symptom onset. His current blood pressure is 176/95 mm Hg, and his laboratory values include prothrombin time 13 seconds, INR 1.1, and platelet count 150,000/mm³. He has no exclusions to the 3-hour time window. **Which one of the following would**

most likely exclude L.S. from receiving intravenous alteplase?

A. History of diabetes.
B. History of ischemic stroke.
C. Modified Rankin Score (mRS) score of 4.
D. National Institutes of Health Stroke Scale (NIHSS) score of 28.

Questions 7 and 8 pertain to the following case.

K.C. is a 78-year-old man brought by emergency medical services to the emergency department with stroke symptoms. He presents 2.5 hours after stroke symptom onset. Door-to-computed tomography (CT) completion time was 25 minutes. Within another 20 minutes, the CT results were interpreted as a right frontal lobe infarction. K.C.'s medical history includes diabetes, myocardial infarction, stroke, and hypertension. His home medications are glyburide, sotalol, and warfarin. K.C. states he chewed an aspirin 325 mg after initial symptom onset because that worked when he had his myocardial infarction. His INR is 1.2, platelet count 174,000/mm^3, prothrombin time 13 seconds, partial thromboplastin time 32 seconds, and blood pressure 168/74 mm Hg; electrocardiography (ECG) indicates heart rate 120 beats/minute with atrial fibrillation. Other pertinent laboratory values are glucose 97 mg/dL, sodium 137 mEq/L, potassium 3.8 mEq/L, blood urea nitrogen 15 mg/dL, and creatinine 0.5 mg/dL. K.C.'s NIHSS score is 8, and his mRS score is 2. He has passed the swallowing test.

7. **Which one of the following statements best describes the role of intravenous alteplase for K.C.?**

A. Not a candidate for alteplase because he took an aspirin.
B. Not a candidate for alteplase because he is taking warfarin.
C. A candidate for alteplase because he has no contraindications.
D. A candidate for alteplase because he is younger than 80 years.

8. K.C.'s blood pressure is now 190/80 mm Hg, and oxygen saturation is 98% on 2 L by nasal cannula. Other laboratory values are glucose 125 mg/dL, triglycerides 160 mg/dL, and low-density lipoprotein cholesterol 110 mg/dL. **Which one of the following is the best additional treatment for him in the first 24 hours?**

A. Atorvastatin daily.
B. Continuous insulin infusion.
C. Continuous nicardipine infusion.
D. Intravenous phenytoin.

9. A woman with acute ischemic stroke (AIS) is admitted to the medical intensive care unit (ICU) of a primary stroke center in a small community hospital. She does not qualify for intravenous alteplase. The critical care physician approaches you about the role of induced hypothermia in this patient. **Which one of the following statements best describes the use of induced hypothermia in this patient?**

A. Appropriate based on two studies conducted in the AIS population.
B. Inappropriate because of unknown efficacy and safety in the AIS population.
C. Appropriate if performed in a primary stroke center.
D. Inappropriate because it must be done in conjunction with thrombolytic therapy.

Questions 10 and 11 pertain to the following case.

R.J., a 72-year-old man with no known medical history, is admitted to a comprehensive stroke center with AIS. He was 2 hours from symptom onset upon arrival in the emergency department. R.J.'s initial assessment reveals an NIHSS score of 27 and an mRS score of 5. Neuroimaging indicates a large malignant occlusion of his middle cerebral artery (MCA) with cerebral edema. His blood pressure is 170/82 mm Hg, heart rate 100 beats/minute in sinus rhythm, and respiratory rate 16 breaths/minute. His glucose is 178 mg/dL, INR is 1.5, platelet count 202,000/mm^3, prothrombin time 14 seconds, and partial thromboplastin time 32 seconds. R.J.'s surgical history is noncontributory. The stroke neurologist completes the stroke workup within 45 minutes.

10. **Which one of the following is R.J.'s most important risk factor for symptomatic hemorrhagic transformation with intravenous alteplase?**

A. Elevated blood pressure.
B. INR greater than 1.4.
C. Malignant MCA occlusion.
D. Elevated glucose concentration.

11. Three weeks later, R.J. is discharged to a rehabilitation center. Drugs upon discharge include candesartan, clopidogrel, simvastatin, famotidine, heparin, ciprofloxacin, and insulin sliding scale. **Which one of the following is best to recommend for R.J.'s secondary stroke prevention regimen?**

A. Change clopidogrel to aspirin/extended-release dipyridamole.
B. Change simvastatin to atorvastatin.
C. Add aspirin to clopidogrel.
D. Change candesartan to ramipril.

12. A patient presenting several new prescriptions states he was recently released from the hospital after being in the ICU for a month because of a bleeding ulcer. He also states he had a minor stroke upon admission and now has heart failure. His prescriptions include lansoprazole 30 mg daily and clopidogrel 75 mg daily. **Which one of the following is the best action regarding this patient's prescriptions?**

    A. Refuse to fill the lansoprazole and recommend ranitidine.
    B. Ask the patient if he had pharmacogenomic testing done.
    C. Fill both prescriptions because benefit outweighs risks.
    D. Call the physician and ask to replace clopidogrel with prasugrel.

13. A patient with atrial fibrillation presents to your anticoagulation clinic for follow-up after a stroke that occurred last month. His INR was 2.1 at the time of his breakthrough stroke. He has been seen in your clinic since he was given a diagnosis of non-valvular atrial fibrillation 5 years ago, and his time within therapeutic INR remains around 70%. He has had two TIAs during the past 5 years while within therapeutic INR range. **Which one of the following is the best approach to secondary stroke prevention in this patient?**

    A. Change warfarin to dabigatran.
    B. Add aspirin to warfarin.
    C. Change warfarin to aspirin.
    D. Increase INR goal from 2.2 to 3.2.

14. In the ECASS-3 trial, 52.4% of alteplase-treated patients experienced a favorable outcome compared with 45.2% in the placebo group. The symptomatic intracranial hemorrhage rate was reported to be 2.4% in the alteplase group and 0.2% in the placebo. **Which one of the following is the best estimate of the number needed to harm?**

    A. 2.2.
    B. 8.
    C. 45.
    D. 500.

15. A 22-year-old African American college student has an episode of acute-onset severe headache, numbness and tingling periorbitally, and left-sided weakness; the episode resolves within a few minutes. Her family notices that she has some slurred speech. She currently takes amoxicillin/clavulanate for a sinus infection that began 3 days ago and an oral contraceptive. She does not smoke or drink. Her mother had an AIS at age 60, and her sister has had blood clots after taking long airline flights. **Which one of the following groups of risk factors is most important for this patient's cerebral venous thrombus–related stroke?**

    A. Age and African American race.
    B. Family history and oral contraceptive.
    C. Antibiotic and family history.
    D. Sinus infection and oral contraceptive.

16. A 55-year-old man receives intravenous alteplase for a lacunar stroke in the emergency department. He is subsequently admitted to the ICU for neuromonitoring. **Which one of the following is the most appropriate management 24 hours after the thrombolytic therapy?**

    A. Subcutaneous heparin for venous thromboembolism prophylaxis.
    B. Dabigatran for stroke prevention.
    C. Phenytoin for seizure prevention.
    D. Hypothermic therapy for neurologic recovery.

Questions 17–19 pertain to the following case.
A.J., a 68-year-old man (weight, 72 kg), is admitted to the ICU for 24-hour neuromonitoring after administration of intravenous thrombolytic therapy. He passes the swallowing screen, and a regular diet is ordered. A.J.'s blood pressure is 165/85 mm Hg, heart rate 100 beats/minute and sinus rhythm, respiratory rate 18 breaths/minute, temperature 99.6°F, and glucose 179 mg/dL.

17. **Which one of the following is the best action regarding A.J.'s glucose management?**

    A. Continue to monitor glucose.
    B. Start normal saline with dextrose.
    C. Start metformin.
    D. Start insulin therapy.

18. On day 2 of hospital admission, A.J. has a temperature of 101.8°F, and a workup to rule out infection is performed. **Meanwhile, which one of the following is the best measure to manage A.J.'s fever?**

    A. Start scheduled acetaminophen.
    B. Start therapeutic hypothermia.
    C. Start appropriate antibiotics.
    D. Observe because fever is natural process.

19. Fifteen hours after the ICU admission, A.J. experiences a headache and has one episode of nausea and vomiting. His vital signs include temperature 100.8°F (38.2°C), respiratory rate 14 breaths/minute, heart rate 95 beats/minute, and blood pressure 175/100 mm Hg. His glucose is 199 mg/dL; all other laboratory values are within the normal range.

Which one of the following is now the best action to take for A.J.?

A. Nicardipine infusion.
B. Immediate head CT scan.
C. Aspirin 325 mg.
D. Insulin infusion.

20. **Based on published evidence, which neuroprotective strategy is most likely to be of benefit after an AIS?**

A. Minocycline therapy.
B. Therapeutic hypothermia.
C. Epoetin.
D. Magnesium infusion.