

Continuing Education for Pharmacists



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Ischemic Stroke: Prevention and Treatment

Goals. The goal of this lesson is to discuss ischemic stroke (cerebrovascular accident) with focus on its clinical characteristics and treatment.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. recognize epidemiologic information and clinical characteristics relevant to ischemic stroke;
2. identify symptomatology that characterizes ischemic stroke and the principles that govern clinical confirmation and management; and
3. select from a list specific therapeutic measures that are reported to modify signs and symptoms of ischemic stroke.

Background

Worldwide, 5.5 million people die each year as a result of stroke. Another 15 million survive, but are disabled. In the United States, the incidence is at pandemic proportions; 700,000 individuals will be stricken annually, with 200,000 of these events being a recurrent event. Each year, about 46,000 more women than men in the United States experience a stroke. When considered separately from other cardiovascular disease, stroke ranks

third among all causes of death in this country, behind heart disease and cancer. The mean lifetime direct cost of ischemic stroke per individual in the United States is estimated to be \$140,048.

Pathogenesis of Stroke

Stroke can be caused by localized obstruction of the blood supply into an area of the brain due to its mechanical blockage in an artery (ischemic stroke), or by blood escaping from an artery within the brain (hemorrhagic stroke). It encompasses pathology in both the cerebrovascular and the cardiovascular circulations.

Cerebral ischemia resulting from large-vessel atherosclerosis (the most common cause of ischemic stroke) and coronary ischemia share common mechanisms including plaque accumulation within vessel walls, erosion and rupture, inflammation, apoptosis (natural or programmed cell death) and thrombus (clot) formation. Advancing age is a risk factor. Stroke prevalence varies by gender and race (Table 1). Studies have noted relationships between initial stroke, vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia), and lifestyle risk

(e.g., smoking, alcohol use, obesity, lack of physical activity). Factors correlating with recurrent stroke include large artery atherosclerosis, previous multiple strokes, disability after stroke and diabetes mellitus. Ischemic strokes are reported in American Heart Association statistics to account for 87 percent of all strokes.

Following ischemia-induced oxygen deprivation, some neurons die within minutes to cause irreversible brain injury. Surrounding the area of necrosis (the infarct) is tissue called the penumbra in which the blood supply is marginally sufficient to maintain minimal cellular activity. In the absence of sufficient blood supplied from adjacent arterioles (reperfusion) or with additional injury, a time-related death occurs to the penumbra and it will be incorporated into the infarct.

Hypertension. In humans, changes in blood pressure follow a reproducible pattern over 24 hours that includes a rapid early-morning surge associated with awakening. This response coincides with increased risk for stroke. In a meta-analysis of 31 published reports describing the circadian timing of 11,816 strokes, most events occurred

Table 1
Prevalence and annual incidence of stroke by gender and race in the United States

Population	Prevalence (%)	Incidence*
Total	2.6	700,000
Total men	2.5	327,000
Total women	2.6	373,000
White men	2.3	277,000
White women	2.6	312,000
African-American men	4.0	50,000
African-American women	3.9	61,000
Mexican-American men	2.6	----
Mexican-American women	1.8	----
Hispanic or Latino	2.2	----
Asian	1.8	----
American Indian/ Alaskan Native	3.1	----

*Includes new and recurrent strokes

Adapted from Dickerson LM, Carek PJ, Quattlebaum RG. *Am Fam Physician*. 2007;76:282.

between 6:00 a.m. and 12:00 noon. A similar variation was noted for different subtypes of stroke: ischemic (n=8,250), hemorrhagic (n=1,801) and transient ischemic attack (TIA) (n=405). It is logical to reason that antihypertensive agents and their dosing schedules should be selected that provide adequate blood pressure control during the early morning hours.

The Role of Cholesterol. The linear relationship between serum cholesterol concentration and cardiovascular disease is more clear than that between serum cholesterol concentration and stroke. Most large epidemiologic studies have not separated the various types of stroke in terms of etiology, but have grouped heterogeneous mechanisms into the single category of ischemic stroke, weakening the likelihood of finding a clear association. One investigation reported that serum cholesterol levels higher than 280 mg/dL were associated with increased risk for death from ischemic stroke while

concentrations less than 160 mg/dL were associated with increased risk for hemorrhagic stroke. Other studies demonstrated that cholesterol levels greater than 300 mg/dL were associated with increased risk for non-hemorrhagic stroke. The correlation between cholesterol level and stroke, while hazy, nevertheless associates lipid disorders to the pathogenesis of atherosclerosis in both cardiovascular and cerebrovascular disease and, as mentioned earlier, is noted as the primary cause of ischemic stroke.

Transient Ischemic Attack

Transient ischemic attack (TIA) is common with 300,000 events occurring annually in the United States. A TIA (“mini-stroke,” “small-stroke”) is experienced as a temporary focal (localized) neurologic deficit. The most common symptom is sudden onset of muscular weakness affecting one side of the body (hemiparesis). A sensation of numbness on one side of the body (hemiparesthesia), inability to speak

clearly and/or imbalance, along with blurred vision or blindness in one eye and double vision (diplopia) are others. The focal and temporary nature of symptoms differentiates TIA from ischemic stroke. Lack of clear distinction between these afflictions with regard to other symptoms has led to the emphasis of a single criterion: TIA symptoms last less than 24 hours, typically only a few minutes. This short duration, followed by complete recovery and absence of neurologic deficit on examination, makes TIA particularly challenging.

Numerous prospective, observational studies have shown that following TIA, patients are at extremely high risk for a full-blown stroke. In one study of more than 1,700 patients who appeared in an emergency department with TIA, the 90-day risk of stroke was 10.5 percent. This was a 50-fold greater risk than expected for an age-matched cohort of persons without TIA. The risk of stroke was front-ended with over half of the secondary events appearing within the first two days. Twenty-one percent of the stroke victims died and another 64 percent were disabled. From these data it was concluded that for every 100 patients with TIA, 2.2 would die and 6.7 would be disabled within three months as a result of stroke.

The most urgent need for a patient with symptoms suggesting TIA or stroke is to identify the nature of the event, whether ischemic or hemorrhagic. Even though symptoms of TIA may have abated before initial consultation, a thorough history and examination can illuminate whether the patient has experienced similar events previously. It can also yield a preliminary assessment of risk factors and possible etiology.

Since symptoms are transient and may have nonischemic causes such as seizure and syncope, and since physicians rarely actually observe a patient during a TIA, it is often difficult if not impossible to confirm a

diagnosis on the spot. Agreement between independent observers on TIA diagnosis is reported to be poor even among neurologists.

Atrial Fibrillation

Atrial fibrillation is a signature disorder of aging, with a prevalence of about 5 percent in persons aged 65 years and older and approximately 10 percent of those over the age of 80. With prevalence increasing, partly because of an aging population, it is projected that by year 2050 there will be an estimated 5.6 million people in the United States with atrial fibrillation, about half of them being over 80 years of age. Atrial fibrillation increases the risk of ischemic stroke by approximately five-fold and is the cause of an estimated 15 percent of all ischemic strokes in the United States. This proportion is even higher, approximately 24 percent, in persons aged 80 to 89 years. The prevention of atrial fibrillation-related stroke is an important public health concern since strokes occurring from atrial fibrillation result in higher mortality and disability.

Warfarin is highly effective in preventing atrial fibrillation-related stroke, reducing stroke risk by about 68 percent and mortality by 33 percent, and it also appears to prevent the most severe type of ischemic stroke. However, because elderly patients have both the highest risk for stroke without warfarin and the highest risk for hemorrhage with it, maximizing anticoagulation therapy while minimizing toxicity is a central challenge for its use in these persons. The drug's narrow therapeutic window and associated hemorrhagic toxicity can make anticoagulation management difficult. Optimal anticoagulation intensity, measured by the International Normalized Ratio (INR), is between 2.0 and 3.0. Low fixed-dose warfarin is ineffective in preventing strokes, although clinicians may settle for lower INRs in older patients. INR values under 2.0 significantly increase the risk for stroke. Older patients are less likely than younger ones to receive

anticoagulation therapy and more likely to receive insufficient doses.

Aspirin provides some protection from stroke in persons for whom warfarin is contraindicated. Although aspirin reduces stroke risk by about 21 percent and has fewer hemorrhagic complications than warfarin, a randomized trial comparing the two treatments in persons between the ages of 80 and 90 years showed that more patients discontinued aspirin therapy compared with warfarin, mostly due to gastrointestinal side effects.

The warfarin arm of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study showed warfarin to be superior to combined clopidogrel (Plavix) plus aspirin with similar rates of hemorrhagic complications. Investigations into other antithrombotic agents continue; for now however, warfarin remains the most effective drug to prevent stroke in patients with atrial fibrillation.

Symptoms and Confirmation of Acute Ischemic Stroke

Acute stroke is characterized by the sudden onset of a focal neurologic deficit, although some patients experience a stepwise or gradual progression of symptoms. Common deficits include impaired speech (dysphasia), defective vision or blindness in half of the visual field (hemianopia), weakness, ataxia and sensory loss. Signs and symptoms are typically unilateral, and consciousness is generally normal or only slightly impaired. Persistence of any neurological deficit beyond two hours, even if the patient subsequently recovers, nearly always is accompanied by some degree of tissue destruction. Ischemic stroke cannot be distinguished with certainty from intracerebral hemorrhage on the basis of signs and symptoms alone. In all patients with suspected stroke, computed

tomography (CT, CAT scan) or magnetic resonance imaging (MRI) of the brain is necessary. Both CT and MRI have a high sensitivity for acute intra-cranial hemorrhage, but MRI has a much higher sensitivity than CT for acute ischemic changes, especially in the first hours after an ischemic stroke.

Prevention and Treatment

Patients with a history of ischemic stroke and/or TIA are high risk for subsequent cerebrovascular and cardiovascular events. Current guidelines for prevention support the aggressive modification of risk factors, including smoking cessation, reduction in alcohol consumption for heavy drinkers, weight reduction, antihypertensive therapy and rigorous control of blood glucose. Four antiplatelet agents have been shown to reduce the risk for recurrent ischemic stroke: aspirin, ticlopidine, clopidogrel, and dipyridamole. These are discussed subsequently.

Treatment of Acute Ischemic

Stroke. Responses from numerous clinical trials are in agreement that patients who receive care in a primary stroke center are more likely to survive, regain independence and return home than are those who do not receive such specialized care. Once ischemic stroke has been confirmed, the next step is to determine whether the patient might be a candidate for thrombolysis therapy. Acute thrombolysis is the most promising approach to treat acute stroke.

Intravenous Thrombolysis with a Recombinant Tissue Plasminogen Activator (rt-PA).

Despite FDA approval more than a decade ago and the fact that alteplase (Activase) is currently the only approved rt-PA treatment for this condition, alteplase reportedly remains underused in the United States. In one study, 69 percent of hospitals did not use thrombolysis at all. In hospitals that did (mostly those with a high volume of stroke patients), only 1 percent of stroke patients received

thrombolysis. Other estimates are that 6 to 8 percent of ischemic stroke patients are potentially eligible for rt-PA based on published criteria, but only 3 to 4 percent receive it.

The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study was a multicenter, randomized trial that demonstrated efficacy of treatment with intravenous alteplase started within three hours after onset of symptoms. Thirty-one to 50 percent of 624 patients receiving alteplase at a dose of 0.9 mg/kg of body weight, 10 percent of the dose given as a bolus and the remainder infused over one hour at a maximum total dose of 90 mg, had a favorable neurologic or functional outcome at three months, compared with 20 to 38 percent of patients given placebo. Symptomatic intracerebral hemorrhage occurred in 6.5 percent of patients receiving intravenous 4 rt-PA and in 0.6 percent of controls.

Intracerebral hemorrhage following thrombolysis is higher in patients with increased age and those with more severe strokes. Similar concerns have been voiced about the efficacy and safety of routinely using rt-PA in patients with early ischemic changes on CT. Further analysis of data from the NINDS rt-PA Stroke Study showed that in the first three hours after onset of symptoms, the appearance of ischemic changes on CT was not an independent predictor of increased risk of symptomatic intracerebral hemorrhage or other adverse outcomes following treatment with rt-PA. Several studies have concluded that intravenous thrombolysis with rt-PA can be used in the community hospital setting with efficacy and safety similar to that found in the randomized trials. The effect of aspirin in combination with rt-PA is unknown, so it is recommended that aspirin be withheld for 24 hours in patients treated with intravenous thrombolysis. Neither dipyridamole nor clopidogrel have been tested in

randomized trials in the acute phase of ischemic stroke.

Anticoagulants. A meta-analysis of six randomized trials involving 21,966 patients found no evidence that anticoagulants (unfractionated heparin, low-molecular-weight heparins, heparinoids, thrombin inhibitors, or oral anticoagulants) administered during the acute phase of stroke improve functional outcomes. While their use does not improve overall functional outcomes, subcutaneously administered low-dose unfractionated heparin or low-molecular-weight heparin has been recommended in patients at high risk for deep venous thrombosis, such as those who are immobile. The use of heparin in patients with ischemic stroke, even progressing stroke, remains controversial.

HMG-Co A Reductase Inhibitors.

These drugs (also called "statins") reduce stroke risk in persons with hyperlipidemia and are a powerful tool in stroke prevention. Non-statin lipid-lowering agents are not associated with decreased risk. The mechanism for statins is probably multifactorial. Reducing LDL-cholesterol levels is a benefit, but other actions may also be at play. These include effects on endothelial function, cell proliferation, inflammatory response, immunologic reactions, platelet function, and lipid oxidation. Statins have also been shown to prevent atrial fibrillation in patients in a number of different circumstances. One possible explanation may be that they reduce inflammation since markers such as C-reactive protein, which is increased in atrial fibrillation, are reduced by high doses of statins. Statins may also have independent neuroprotective effects since their use is associated with improved outcomes and functional capacity in patients who have experienced ischemic strokes.

Secondary Stroke Prevention

Recurrent stroke prevention is a high

public health priority due to resultant morbidity and mortality, as well as the healthcare costs associated with disability. The majority of strokes in the United States are noncardioembolic ischemic events, so antiplatelet agents are the recommended first-line therapy for secondary stroke prevention.

Aspirin. Patients with a history of ischemic stroke treated with aspirin have a lower risk of stroke and death, compared with placebo. Both low-dose (50 to 166 mg/day) and high-dose (325 mg/day) regimens are similarly effective in preventing vascular events. Higher doses are associated with more gastrointestinal side effects and bleeding episodes. Specifically, patients receiving more than 200 mg/day for at least one month have more gastrointestinal bleeding, fatal or life-threatening bleeding and total bleeding episodes compared with persons receiving less than 100 mg/day. The overall risk for major bleeding associated with aspirin (75 to 500 mg/day) is small.

Clopidogrel. Clopidogrel (Plavix) is approved for prevention of recurrent vascular events (MI, stroke, vascular death). In one randomized controlled trial, persons with recent ischemic stroke, MI or symptomatic peripheral arterial disease received clopidogrel (75 mg) or aspirin (325 mg) daily for two years. There was a statistically significant difference in effectiveness (although of borderline clinical significance) with clopidogrel compared with aspirin (5.32 vs. 5.83 percent risk of ischemic events).

Clopidogrel has been studied in combination with aspirin for prevention of recurrent stroke; however, the combination therapy is not recommended in patients with a history of stroke. In one trial, more than 7,000 patients with previous stroke received clopidogrel (75 mg) plus aspirin (325 mg) or clopidogrel alone for 18 months. Combination therapy was not superior to clopidogrel monotherapy in preventing secondary ischemic

stroke, MI, vascular death or rehospitalization for ischemic events. The combination regimen did increase the risk of life-threatening bleeding and major bleeding.

Dipyridamole and Aspirin. Extended-release dipyridamole and aspirin are available in a combination product (Aggrenox) approved for prevention of recurrent stroke. In one trial, 6,602 patients receiving dipyridamole (200 mg twice daily) plus aspirin (25 mg twice daily) experienced a lower risk of ischemic stroke and TIA over the two-year period compared with aspirin alone. Combination therapy did not increase the risk of major or minor bleeding.

Ticlopidine. In various studies comparing ticlopidine (Ticlid) with aspirin, the antiplatelet has shown both greater and lesser activity than aspirin in reduction of risk for secondary stroke. Ticlopidine is not typically chosen for first-line use because it carries a small risk for severe neutropenia and is associated with a risk of thrombotic thrombocytopenia purpura. This is a rapidly fatal or occasionally protracted disease due to

formation of fibrin or platelet clots in arterioles and capillaries of many organs.

Risk Factor Reduction in Persons with Cerebrovascular Disease. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends maintaining a blood pressure goal of less than 140/90 mmHg. The American Heart Association/American Stroke Association guidelines recommends slowly reducing the blood pressure to goal level. These guidelines state that hypercholesterolemia should be managed according to National Cholesterol Education Panel guidelines. Statins should be used to achieve an LDL-cholesterol level under 100 mg/dL, or less than 70 mg/dL for patients with multiple risk factors. Other lifestyle recommendations include smoking cessation with reduction or elimination of alcohol consumption. Patients who are heavy drinkers (more than five drinks/day) should eliminate or reduce their consumption; light to moderate intake (fewer than two drinks/day for men and one/day for nonpregnant women) may be

considered. For weight reduction to a goal body mass index under 25 kg/m² and waist circumference less than 35 inches for women and less than 40 inches for men, patients should be encouraged to engage in physical activity for at least 30 minutes most days of the week.

Summary and Conclusions

Atrial fibrillation is a common affliction of older adults and a major risk factor for stroke. Its management is directed at preventing thromboembolism with warfarin, as well as controlling the heart rate and rhythm. Regardless of extent or duration of acute effects, TIA is a prodrome (warning sign) for ischemic stroke and carries the risk for secondary stroke comparable to that associated with ischemic stroke. Pharmacologic and nonpharmacologic interventions aimed at reducing the risk of secondary stroke should, therefore, be initiated as soon as possible after the initial event.

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Quiz

Ischemic Stroke: Prevention and Treatment

1. The most common cause of ischemic stroke is:

- a. deep vein thrombosis.
- b. large-vessel atherosclerosis.
- c. myocardial infarction.
- d. variant angina.

2. The tissue surrounding the area of necrosis following ischemia-induced cell death due to oxygen deprivation is called the:

- a. thrombus.
- b. tamponade.
- c. penumbra.
- d. plaque.

3. A meta-analysis of 31 published reports found that most strokes occur between:

- a. 12 noon and 6 p.m.
- b. 6 p.m. and 12 midnight.
- c. 12 midnight and 6 a.m.
- d. 6 a.m. and 12 noon.

4. The linear relationship between serum cholesterol concentration and cardiovascular disease is:

- a. more clear than that between serum cholesterol concentration and stroke.
- b. less clear than that between serum cholesterol concentration and stroke.

5. The most urgent need for a patient with symptoms suggesting TIA or stroke is to identify the:

- a. nature of the event.
- b. patient's blood type.
- c. renal perfusion rate.
- d. serum cholesterol levels.

6. The most effective drug to use to prevent stroke in patients with atrial fibrillation is:

- a. aspirin.
- b. digoxin.
- c. heparin.
- d. warfarin.

7. A patient with dysphasia is experiencing impaired:

- a. body movements.
- b. breathing.
- c. speech.
- d. swallowing.

8. The effect of aspirin in combination with rt-PA is best described as:

- a. effective.
- b. unknown.
- c. ineffective.

9. All of the following are true EXCEPT:

- a. the use of heparin in patients with ischemic stroke, even progressing stroke, remains controversial.
- b. HMG-CoA reductase inhibitors reduce stroke risk in persons with hyperlipidemia.
- c. patients with a history of ischemic stroke treated with aspirin have a lower risk of stroke and death, compared with placebo.
- d. combination therapy with clopidogrel plus aspirin is superior to clopidogrel monotherapy in preventing secondary ischemic stroke.

10. In patients with multiple risk factors, the National Cholesterol Education Panel guidelines state that statins should be used to achieve an LDL-cholesterol level under:

- a. 70 mg/dL.
- b. 60 mg/dL.
- c. 50 mg/dL.
- d. 40 mg/dL.

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