

# Virtual Mentor

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## CLINICAL PEARL

### Secondary Management of Ischemic Stroke

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Complex interactions among the 100 billion neurons that form the nervous system not only regulate and maintain basic life-preserving functions, they render us who we are as individuals.

In an instant, any or all of the characteristics that define us can be permanently taken away by an all-too-common disease—*stroke*. Stroke is the sudden death of neurons due to impaired blood flow and oxygenation resulting in neurological deficits. There are two categories of stroke: ischemic stroke, which results from the occlusion of a blood vessel and is responsible for roughly 87 percent of strokes, and hemorrhagic stroke, which results from the rupture of a blood vessel [1]. Stroke is the leading cause of disability and the third leading cause of death (after heart disease and all forms of cancer). The financial burden of stroke to individuals and the U.S. health care system is enormous and growing—with an estimated cost for medical treatment of stroke of \$68.9 billion in 2009 [1]. Approximately 795,000 strokes occur every year; of these, about 185,000 (*more than 20 percent*) are recurrent strokes [1]. This latter statistic underscores the importance of secondary stroke prevention.

In this article, we will focus on prevention of recurrent ischemic stroke, which depends on the specific etiology and associated contributing factors. In general, ischemic strokes can be classified into large-vessel territory strokes and small-vessel territory strokes.

#### Large-Vessel Territory Ischemic Strokes

Large-vessel territory ischemic strokes are caused by occlusion of a main artery supplying the brain (e.g., internal carotid, middle cerebral, vertebral, basilar, or *posterior communicating artery*) or a prominent branch of a main artery and typically result from thromboembolic events, although focal thrombotic events can also cause main artery occlusion. Blood-vessel injury, stasis/turbulent blood flow, and hypercoagulable state—known as Virchow's Triad—are often sources of thromboembolic strokes. Etiologies include artery-to-artery thromboembolic stroke, cardioembolic stroke, and stroke associated with right-to-left shunts and hypercoagulable states.

*Artery-to-artery thromboembolic stroke.* Thrombus formation at the site of arterial disease may embolize to intracranial arteries. The most common cause is carotid atherosclerosis. Prevention of recurrent carotid atherosclerosis strokes is guided by degree of stenosis.

- For symptomatic stenosis between 50 and 99 percent, surgical management via carotid endarterectomy is effective for reducing stroke risk, although the benefit is greatest among patients with severe stenosis (70 to 99 percent) [2]. Medical management (e.g., blood pressure reduction, smoking cessation, lipid-lowering treatment, antiplatelet therapy) is also recommended for these patients [3].
- If the patient is not a good candidate for surgery, endovascular interventions (carotid artery angioplasty and/or stenting) may be an option, although clinical trials comparing carotid endarterectomy to endovascular therapy have produced mixed results [4-6].
- For carotid stenosis less than 50 percent, medical management is recommended [2].

*Cardioembolic stroke.* The most common cause is atrial fibrillation. Other cardiogenic sources include acute myocardial infarction with wall-motion abnormalities, severely depressed ejection fraction, atrial myxomas, and valvular diseases. Secondary prevention usually involves anticoagulation with warfarin, particularly for atrial fibrillation (INR goal, 2 to 3) [7].

*Stroke in the setting of right-to-left shunt.* In the event of a suspected thromboembolic stroke without identifiable artery-to-artery or cardioembolic etiology, a right-to-left shunt should be considered. The most common right-to-left shunt is a patent foramen ovale (PFO), which allows thromboemboli originating in the venous circulation (e.g., deep venous thrombosis) to gain access to the arterial circulation. The concomitant presence of an interatrial septal aneurysm appears to increase stroke risk, although secondary management in these settings is unclear (e.g., PFO closure versus medical management, antiplatelet versus anticoagulation) [8-11]. Clinical studies to help establish treatment guidelines are currently ongoing.

*Stroke in the setting of a hypercoagulable state.* This is less common but should be considered if vascular imaging and cardiac evaluation are unrevealing or if the patient has a history of previous thrombotic events. Examples of hypercoagulable states include pregnancy and the early postpartum period, malignancy, and inherited or acquired hypercoagulable disease. Efforts at prevention depend on the likelihood of recurrence and usually entail anticoagulation.

### **Small-Vessel Territory Ischemic Strokes**

Small-vessel territory ischemic strokes are caused by occlusion of small, penetrating cerebral blood vessels (e.g., lenticulostriate branches of the MCA), resulting in lacunar infarcts that commonly occur in the deep subcortical regions of the brain, such as the basal ganglia, thalamus, internal capsule, centrum semiovale, and periventricular area, as well as in the pons.

The main risk factors include hypertension, diabetes mellitus, dyslipidemia, and smoking. Prevention of hypertension mandates appropriate management of the following four pervasive risk factors.

*Hypertension.* Treatment of hypertension leads to reduction in stroke risk of approximately 30 to 40 percent [12]. While lifestyle modifications (e.g., weight loss, exercise, low-salt diet) should be encouraged in all patients, most require antihypertensive medications. The optimal drug regimen for prevention of recurrence remains unclear and may depend on individual medical circumstances, but data supports the use of thiazide diuretics alone, or in combination with angiotensin-converting enzyme (ACE) inhibitors [3, 13].

*Diabetes.* Diabetes is a significant risk factor for recurrent stroke [14]. Glucose control to near-normoglycemic levels is recommended with goal hemoglobin A1C less than or equal to 7 percent [3].

*Dyslipidemia.* Treatment of dyslipidemia involves exercise, dietary guidelines, and medications with goal low-density lipoprotein less than 100 mg/dL and less than 70 mg/dL in patients with multiple vascular risk factors who are at very high risk for vascular disease [15]. Clinical trials have demonstrated that statins reduce stroke risk, and their use is recommended for prevention of recurrent stroke [3, 16, 17].

*Smoking.* Cigarette smoking increases the risk of stroke, so smoking cessation is crucial [18, 19]. Treatment strategies include counseling, nicotine products, and oral smoking cessation medications.

While these risk factors are discussed in the section on small-vessel territory ischemic stroke, their damaging effects on the vasculature are indiscriminate of vessel size. Thus, secondary management of large-vessel territory strokes would be incomplete without treating the concomitant vascular risk factors of hypertension, diabetes, dyslipidemia, and smoking.

### **Antiplatelet Therapy**

Secondary management of noncardioembolic stroke with an antiplatelet agent has been shown to reduce stroke recurrence [20]. Antiplatelet agents include aspirin, clopidogrel, and extended-release dipyridamole, the last of which is used in combination with low-dose aspirin. Aspirin monotherapy, the combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for secondary stroke prevention [3].

### **Lifestyle Modification**

Prevention of recurrent stroke must also include lifestyle modifications to address habits and conditions that directly or indirectly increase stroke risk.

*Alcohol.* Heavy drinking is a risk factor for stroke. Patients should be strongly encouraged to eliminate alcohol use or limit consumption to fewer than or equal to 2 drinks per day [21].

*Obesity.* The relationship between obesity and stroke is complex, inasmuch as many obese people have other associated risk factors for stroke (e.g., diabetes, hypertension, dyslipidemia). Losing weight significantly improves blood pressure

control, fasting glucose and lipid levels, and most likely has a global impact on reducing stroke risk [22].

*Inactivity.* Regular exercise lowers stroke risk, probably due to the effect of physical activity on blood-pressure reduction and improved glucose tolerance [23].

*Sleep apnea.* Sleep apnea is an independent risk factor for stroke, and untreated sleep apnea can worsen functional outcomes in stroke patients [24, 25]. Signs and symptoms of sleep apnea include snoring, daily fatigue, and daytime napping. Studies have shown that in patients with stroke and obstructive sleep apnea treatment with continuous positive airway pressure (CPAP) improves well-being and reduces risk of recurrent stroke and mortality [26-28].

While the discussion above encompasses many of the etiologies of stroke, further evaluation and prevention is required when less-common causes of stroke such as vasculitis, arterial dissection, and moya moyo are recognized. Overall, appropriate recognition and management of stroke risk factors can not only prevent death and disability, but save the health care system billions.

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