

CONTROVERSIES IN ISCHEMIC STROKE PREVENTION

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This course will provide a logical framework for promptly implementing stroke prevention strategies after recent cerebral ischemia, including selection of antithrombotic agents, lipid modifiers, antihypertensive therapies, and revascularization procedures based on the underlying presumed mechanism of disease. Recommendations are largely adapted from the AHA/ASA secondary prevention guidelines. In addition, current clinical trials testing new approaches to stroke prevention will be discussed.

General concepts of Risk Factor Control:

Hypertension:

Hypertension is present in approximately 70% of ischemic strokes and is the most prevalent stroke risk factor. Among stroke patients who have an established SBP >140 mmHg or DBP > 90 mmHg, initiation of antihypertensive therapy is indicated. The timing of initiation of BP reduction is currently recommended to be a few days after the acute stroke. The optimal drug regimen to achieve the recommended level of BP reductions is uncertain, but the available data indicate that diuretics or the combination of diuretics and an ACEI are useful.

Hyperlipidemia:

Current guidelines have moved away from treating to specific cholesterol targets and recommend that patients with stroke or TIA due to atherosclerosis should be treated with statins, regardless of LDL-C levels.

Diabetes:

Diabetes is associated with an increased risk for incident ischemic stroke. So patients with stroke or TIA should be screened for diabetes. Recommendations for secondary stroke prevention are based on studies of heterogeneous cardiovascular disease prevention and the ADA guidelines should be followed. Intensive treatment does not appear to reduce all-cause mortality or stroke risk and increases the risk for severe hypoglycemia based on current evidence. The results of the recent IRIS trial will also be discussed, along with implications on stroke prevention practices.

Obesity:

Obesity is a risk factor for stroke. The risk increases starting at a BMI of 20 kg/m², with each 1 kg/m² increase in BMI associated with a 5% increase in risk for stroke. Obese patients with recent TIA or stroke should be encouraged to lose weight.

Physical Activity:

For stroke or TIA patients who are capable of engaging in physical activity, at least 3-4 sessions per week of moderate-vigorous intensity aerobic physical exercise is reasonable to reduce stroke risk factors. Each session should last about 40 minutes.

Diet:

Based on recent clinical trial evidence, it is reasonable to counsel stroke or TIA patients to follow a Mediterranean-type diet, which emphasizes vegetables, fruits, and whole grains and includes low-fat dairy products, poultry, fish, legumes, and nuts. It limits intake of sweets and red meats. A low salt diet should also be encouraged.

Smoking cessation:

Current guidelines encourage smoking cessation. However, little is known about the impact of E-cigs on stroke recurrence.

Atherosclerotic Stroke:

Extracranial atherosclerosis:

For prevention of recurrent stroke in patients with 70-99% carotid stenosis, carotid endarterectomy (CEA) has been reported to be superior to medical therapy alone in 3 major trials (ECST, NASCET, VACS), but the

benefit is less clear in patients with 50-69% stenosis. Carotid artery stenting (CAS) can be an alternative to CEA in patients with 70-99% stenosis by noninvasive imaging or 50-99% by angiography or non-invasive imaging with corroboration if the anticipated rate of periprocedural stroke or death is less than 6%. CEA may be associated with improved outcome compared with CAS in older patients (> age 70) and CAS may be as good or better than CEA in younger patients. CAS and CEA should be performed by operators with a complication rate of < 6% and revascularization should be performed within 2 weeks of the ischemic event.

Intracranial stenosis:

Patients with recent stroke or TIA due to 50-69% stenosis of a major intracranial artery should be treated with aspirin 325 mg and intensive risk factor control. Patients with recent stroke or TIA due to 70-99% stenosis should be treated with aspirin plus clopidogrel for 90 days followed by aspirin monotherapy and intensive risk factor control. Intensive risk factor control should target an LDL-C < 70 and SBP < 140 and include lifestyle counseling to encourage healthy diet, exercise, and smoking cessation.

Cardioembolic Stroke:

Atrial fibrillation:

Approximately 10% of ischemic strokes are due to atrial fibrillation. An additional 11% of stroke patients who are monitored with continuous ECG monitoring will have atrial fibrillation detected within 30 days of discharge. Warfarin, apixaban, rivaroxiba, and dabigatran are all indicated for the prevention of first and recurrent stroke in patients with atrial fibrillation. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, such as renal function and mode of administration (e.g. oral or via peg tube). The combination of anticoagulants and antiplatelet agents is not recommended in unselected patients, but may be reasonable in patients with concomitant ischemic heart disease or stent placement. In patients who cannot take anticoagulation, there is no clear benefit of combination aspirin and clopidogrel over aspirin alone.

Anticoagulation should be initiated within 2 weeks of acute stroke, unless there may be high risk of hemorrhagic transformation. For stroke patients with atrial fibrillation and concomitant CAD, the benefit of adding antiplatelet agents to warfarin for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events has not been demonstrated.

Other cardioembolic causes:

Patients with stroke due to acute anterior ST-elevation MI without demonstrable left ventricular mural thrombus formation but with anterior apical akinesis or dyskinesis may be considered for anticoagulation with warfarin (INR 2-3) for 3 months. If such as patient has a low EF (<40) and is intolerant to warfarin, the new oral anticoagulants or LMWH may be used. In patient with ischemic stroke or TIA due to LV thrombus or mechanical LVAD, anticoagulation with warfarin (INR 2-3) is indicated. In patients with ischemic stroke or TIA with either dilated cardiomyopathy (LV ejection fraction \leq 35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus or atrial fibrillation, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized.

For patients with ischemic stroke due to rheumatic mitral valve disease, with or without atrial fibrillation, anticoagulation is recommended. However, for patients with stroke due to non-rheumatic mitral valve disease, mitral annular calcification, or mitral regurgitation, antiplatelet therapy is recommended.

Heterogeneous and Cryptogenic stroke:

In patients with noncardioembolic stroke, antiplatelet agents are preferred. The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and continuation for 90 days, but should not be continued long-term due to increased bleeding risk. Aspirin (50-325 mg), clopidogrel, and aspirin plus dipyridamole (Aggrenox) are reasonable to use for secondary stroke prevention and the selection of which agent to use should be based on factors such as cost, tolerance, etc.. For patients with stroke or TIA on aspirin, there is no data suggesting that switching to other antiplatelet agent or increasing the dose of aspirin is more likely to prevent recurrent stroke.

Recommended additional reading:

Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45:2160.

Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45:1545.

Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; 129:S1