Guidelines for Medical Treatment for Stroke Prevention

The numbers in square brackets are cross-references to the numbered paragraphs in the review article "Medical Treatment for Stroke Prevention" (see pages 41-53).


Stroke includes various disorders that lead to the destruction of brain tissue, functional disability, and often death. The most common strokes result from atherothrombosis in the extracranial and larger intracranial arteries. Approximately 30% of ischemic strokes are of this origin. Cardiogenic strokes account for 20% to 25% of all ischemic strokes. Intracardiac thrombi secondary to myocardial infarction or atrial fibrillation are the two most common causes of such strokes. Lacunar strokes account for 15% to 20% of ischemic lesions and are most commonly caused by the small vessel changes associated with hypertension of long duration. The remaining 30% of ischemic strokes are secondary to less common conditions or of unknown origin. Approximately 15% of strokes result from cerebral hemorrhage, usually due to rupture of aneurysms or other vascular malformations, hypertensive arterial disease, and "lobar" hemorrhages in the elderly due to amyloid angiopathy.

Therapeutic interventions directed at general, modifiable risk factors for stroke should be part of any effort to reduce the risk for stroke, regardless of whether the patient receives more specific medical or surgical treatment. These potentially modifiable risk factors include hypertension (including isolated systolic hypertension), heart disease, cigarette smoking, diabetes mellitus, heavy alcohol use, and hypercholesterolemia [2.1.1]. Several conditions are associated with an especially high risk for stroke and are potentially amenable to medical treatment, including carotid artery stenosis in asymptomatic patients, atrial fibrillation, transient ischemic attacks (TIAs) or stroke, and previous myocardial infarction [2.1.2].

Treatment Strategies for Stroke Prevention

The question of medical treatment for stroke prevention must be considered in the context of surgical options, particularly carotid endarterectomy. Three recently completed studies have indicated that when surgery can be done in a low-risk setting (total perioperative stroke and death rate less than 6%), symptomatic patients who have anterior circulation TIAs or minor completed strokes and carotid stenosis greater than 70% (by strict measurement criteria) benefit from carotid endarterectomy. The evidence is less clear for patients with lower degrees of stenosis or asymptomatic patients with high degrees of stenosis. On average, patients with less than 30% stenosis have been shown to have worse outcomes with carotid endarterectomy [2.2]

Medical treatments for stroke prevention include anticoagulation (for example, warfarin) and platelet antagonists (for example, aspirin and ticlopidine). Additional interventions for stroke prevention include methods for controlling risk factors, such as management of hypertension, smoking cessation, and control of blood cholesterol.

Recommendations

Recommendations are graded A, B, or C according to the level of evidence that supports them. Grade A recommendations are supported by one or more level I studies or by a meta-analysis where the lower limit of the confidence interval for the effect of treatment exceeds the minimal clinically significant benefit. Grade B recommendations are supported by one or more level II studies or by a meta-analysis where the estimate of treatment effect exceeds the minimal clinically significant benefit but the lower limit of the confidence interval does not. Grade C recommendations are supported by published data other than randomized trials including secondary analyses of level I or II studies. Level I studies are randomized trials with low false-positive or low false-negative errors, or both. Level II studies are randomized trials with high false-positive and high false-negative errors.

Based on the evidence cited, several recommendations can be supported.

1. Nonvalvular atrial fibrillation: Warfarin is the drug of choice for patients who are candidates for anticoagulation (grade A recommendation). However, patients younger than 60 years without specific clinical or echocardiographic risk factors have a low risk for stroke and do not need treatment with warfarin (grade C recommendation). To achieve an acceptable benefit-to-risk ratio, it is crucial to carefully monitor the intensity of anticoagulation based on the international normalized ratio (INR), aiming for a ratio approximately between 2 and 3 (grade C recommendation). For patients unwilling or unable to take warfarin, aspirin is an appropriate alternative (grade A recommendation). The dose of 325 mg/d is supported by available
evidence (grade A recommendation). For patients older than 75 years, aspirin may not be effective (grade C recommendation). Data are currently unavailable on the effectiveness of aspirin in lower-risk patients, such as those younger than 60 years without specific clinical or echocardiographic risk factors [4.1.2, 4.2.1].

2. **Transient ischemic attack and stroke:** Aspirin is effective in reducing the risk for stroke in patients with TIA and minor stroke (grade A recommendation); however, the benefit-to-risk ratio is approximately 5:2. All aspirin doses studied have been found to be similarly effective, which suggests that decisions about dose should be based on patient tolerance (grade C recommendation). No evidence suggests that aspirin reduces the risk for stroke in patients who have had major stroke, but aspirin therapy is a reasonable option (grade C recommendation). Patients who do not respond to or tolerate aspirin are candidates for ticlopidine (grade A recommendation). Patients offered ticlopidine must be willing to accept the supervision and expense associated with this agent [4.1.3, 4.2.2].

3. **Previous myocardial infarction:** Warfarin has been shown to reduce the rate of stroke in patients who have had myocardial infarction (grade A recommendation). However, this recommendation is tempered by the high rate of major complications in several studies. The resulting estimate of benefit-to-risk ratio is 3:2. These high complication rates may be caused by the use of relatively high-intensity anticoagulation in the included studies (INR, 2.5 to 4.8). Lower levels of anticoagulation are safer and, if as effective as the studied doses, would make warfarin a clear recommendation (grade C recommendation). Aspirin is an alternative treatment strategy for stroke reduction in patients who have had myocardial infarction (grade B recommendation); however, the benefits of this are likely to be small. For patients who have had myocardial infarction, neither anticoagulation nor antiplatelet agents are specifically recommended for stroke reduction. However, use of these agents may be justified on the basis of reduction in all nonfatal vascular events [4.1.4, 4.2.3].

**Rationale**

These recommendations are primarily based on data from randomized controlled trials indicating that three agents significantly reduce the risk for stroke in specific high-risk patients: warfarin for patients with atrial fibrillation or myocardial infarction, aspirin for patients with TIA or minor completed stroke, and ticlopidine for patients with TIA and completed stroke. However, the clinical decision to use medical therapy for stroke prevention is complicated by the potential risk of complications, some of which may be fatal. These recommendations are based ultimately on a judgment about when benefits appear to sufficiently outweigh risks.

Requests for Reprints: Linda Johnson White, Director, Department of Scientific Policy, American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572.