

## Management of Stroke and Transient Ischemic Attack

STANLEY TUHRIM, M.D.

### Abstract

Stroke is a major cause of death and disability. The resulting burden on society continues to grow, despite recent advances in acute stroke therapy. Thrombolysis reduces stroke morbidity but is only applicable to a small percentage of stroke patients. Acute stroke units, which allow for the greatest overall improvement in outcome, provide the best facilities for acute intervention. Despite recent advances in acute management, such as endarterectomy and anticoagulation, primary and secondary preventive measures to control stroke risk factors, along with appropriate specific interventions, are the key to reducing the overall burden of stroke.

**Key Words:** Stroke, treatment, prevention, transient ischemic attack.

---

STROKE IS A MAJOR PUBLIC HEALTH PROBLEM, primarily afflicting older adults. It is the third leading cause of death in the United States. Worldwide, the mortality rate from stroke is surpassed only by that of heart disease (1, 2). In the U.S., more than 700,000 new strokes occur annually (3). Stroke is also the leading cause of disability in the U.S., with an estimated 4 million stroke survivors in this country living with stroke-related deficits (1). More than 70% of stroke survivors remain vocationally impaired, more than 30% require help with activities of daily living, and more than 20% walk only with assistance (4). Approximately half of all stroke survivors return to some form of employment, but this figure declines with age (5). Moreover, the incidence of stroke doubles in each successive decade after age 55. Until age 75 it is more common in men than in

women, but after 75 it is equally common in both groups. Half of all strokes occur in people older than 75 years, and age is the most important risk factor for stroke (3, 6, 7). Therefore, as the population in this country ages, the burden of dealing with stroke will grow, in terms of caring for an ever-increasing number of new stroke patients and stroke survivors. The discussion that follows focuses on four strategies for reducing that burden.

### Ischemic Stroke Subtypes

There are three main subcategories of cerebral infarction: (a) cardioembolic, (b) large vessel atherothrombotic, and (c) small vessel or lacunar stroke. Although the treatment of the acute form of each subtype may not differ markedly, there is some suggestion that the efficacy of therapy may differ by subtype. More significantly, preventive measures are determined by the presence of risk factors or co-morbid conditions that are associated with the particular stroke subtype.

### Cardioembolic Infarction

Embolism from thrombi that form in the heart and those that occur in large veins and

---

Address correspondence to Stanley Tuhim, M.D., Associate Professor, Department of Neurology, Box 1137, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029.

This work was supported in part by NIH (NINDS) grant #NS29762.

Adapted from a presentation at Grand Rounds to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on December 7, 1999 and updated as of November 2001.

pass through the heart via a right-to-left shunt account for approximately 30% of ischemic strokes. A variety of cardiac sources of embolism have been identified, including valvular lesions, hemostasis secondary to rhythm disturbances, and hypokinesia of the left ventricle, either globally as in a cardiomyopathy or focally, secondary to infarction. Atrial fibrillation is the most widely recognized cardiac abnormality associated with ischemic stroke. It is a condition of the elderly, occurring in 0.1% of those 50–59 years of age, but increasing gradually to 4% of those over age 80. The proportion of strokes attributed to atrial fibrillation also increases with age, rising from 7% of strokes for patients in their sixth decade, to 36% for those in their ninth decade (8). The development of transesophageal echocardiography (TEE) has made it possible to detect thrombi in the left atrial appendage, the site that generally harbors a clot in a fibrillating atrium. These thrombi are not visible on transthoracic echocardiogram. A patent foramen ovale (PFO), the most common conduit for paradoxical emboli, is also readily diagnosed by TEE, as is atherosclerotic plaque in the ascending aorta and aortic arch of elderly patients. These plaques can be ulcerated and serve as a nidus for clot formation, or protrude into the lumen as a highly mobile peduncle, likely to embolize to more distal arteries. The thickness of this plaque has been correlated with the risk of stroke (8–10).

### Lacunar Infarction

Lacunae are small, deep infarcts caused by degenerative changes within small penetrating arteries that bring blood to the internal capsule, basal ganglia, cerebral white matter, thalamus, and pons. In various series and registries, they account for at least 25% of ischemic strokes and are the most common vascular lesions found within the brain at autopsy. Hypertension is the most important risk factor for lacunar infarcts. The neurologic symptoms depend on the region of ischemia. The most common clinical presentations are: (a) pure motor stroke due to ischemia in the pons or internal capsule which is characterized by weakness of the face, arm, and leg on one side of the body; (b) pure sensory stroke due to infarction in the lateral part of the thalamus and/or posterior limb of the internal capsule which is characterized by numbness or paresthesia of the face, arm, leg, and trunk on one side of the body, without weakness; (c) ataxic hemiparesis due to infarction in the sub-

cortical white matter or pons which is characterized by a combination of incoordination and weakness on one side of the body; and (d) clumsy hand-dysarthria due to pontine infarction which is characterized by markedly slurred speech and difficulty with fine motor control of one hand (11). The diagnosis of lacunar infarction is based on the presence of risk factors, the nature of the clinical signs and symptoms, and the results of neuroimaging tests.

### Large Artery Occlusive Disease

The large vessels that bring blood into the brain are prone to atherosclerotic narrowing, most commonly at sites of origin or bifurcation, especially the bifurcation of the common carotid into the internal and external carotid arteries in the neck. Atherosclerotic stenosis leads to infarction by reducing blood flow distal to the point of stenosis and by acting as a nidus for adhesion and aggregation of platelets, producing either thrombosis at that location or embolization to and occlusion of more distal, narrower arteries. The neurologic symptoms will depend upon the artery affected. In general terms, these symptoms can be divided into those that arise from the anterior (carotid) circulation, supplying the anterior three-fourths of each hemisphere, and those that arise from the posterior (vertebrobasilar) circulation, supplying the occipital lobes, posterior thalamus, cerebellum and brainstem.

Symptoms and signs referable to the anterior circulation include contralateral weakness, numbness and visual deficits. If the left hemisphere is affected, aphasia is common, while right hemisphere lesions produce behavioral disturbances. Symptoms and signs of posterior circulation ischemia are highly variable and overlap with those of the anterior circulation. Vertigo, diplopia, nausea and vomiting are common complaints in brainstem or cerebellar disease. Nystagmus, disconjugate eye movement abnormalities, gait or limb ataxia, crossed (i.e., ipsilateral face and contralateral limb or body) sensory or motor deficits and hemianopic visual field loss are indicative of posterior circulation ischemia.

### Treatment of Acute Infarction

The purpose of acute stroke treatment is to reduce death and disability from that event. Until recently there was no proven effective therapy. In June 1996, the Food and Drug Ad-

ministration (FDA) approved the intravenous administration of tissue plasminogen activator (t-PA) in acute ischemic stroke, given within three hours of symptom onset. This signaled a virtual revolution in the diagnosis and management of acute stroke. For the first time a proven, safe and effective treatment is available, but the time frame for its effective use requires a much more expeditious response than was customary for patients, emergency medical services, doctors and hospitals. Thus, it is now necessary for the public to be educated in order to recognize a stroke and react appropriately, particularly since only one-third of patients experiencing a stroke recognize it as such. Health care providers must also be educated to respond to stroke as an emergency. Once the patient is at the hospital, prompt triage is necessary. It is crucial to determine the time of symptom onset and the presence of signs of trauma or medical conditions that would predispose to a particular stroke type, or that would preclude the use of t-PA. A computed tomography (CT) scan must be performed as quickly as possible, to exclude intracranial hemorrhage or a non-ischemic cause of the patient's symptoms, such as a brain tumor or subdural hematoma.

The evidence that intravenous administration of t-PA is an effective treatment for acute ischemic stroke comes from the National Institute of Neurological Disorders and Stroke (NINDS)-NIH t-PA Stroke Study, in which 624 patients were treated with 0.9 mg/kg of t-PA within 3 hours of onset; half were treated within 90 minutes. Patients treated with t-PA were 30% more likely to have minimal or no disability three months later. The major risk of treatment was intracerebral hemorrhage, which occurred in 6.4% of patients treated with t-PA but in only 0.6% of those who received placebo. Mortality was similar in both groups (17% t-PA, 20% placebo). Patients with the three major stroke subtypes benefited similarly (12). Unfortunately, only 2–5% of ischemic stroke patients are currently treated with intravenous t-PA, since most arrive at a hospital later than three hours after onset.

In two other large, randomized trials with longer treatment windows, t-PA was not more effective than placebo, although post-hoc analyses suggest there may be a benefit beyond three hours if patients are appropriately selected (Table).

Intra-arterial thrombolysis, in which a microcatheter is advanced to and sometimes through the obstructing clot has gained in-

**TABLE**  
*Characteristics of Patients with Stroke Who May Be Eligible for Intravenous Tissue Plasminogen Activator Therapy*

|   |  |
|---|--|
| Age   | 18 yr  |
| Diagnosis of ischemic stroke causing clinically apparent neurologic deficit                             |  |
| Onset of symptoms less than 3 hours earlier   |  |
| No stroke or head trauma during the preceding 3 months  |  |
| No major surgery during the preceding 144 days  |  |
| No history of intracranial hemorrhage   |  |
| Systolic blood pressure   | 185 mm Hg  |
| Diastolic blood pressure  | 110 mm Hg  |
| No rapidly resolving symptoms or only minor symptoms of stroke  |  |
| No symptoms suggestive of subarachnoid hemorrhage   |  |
| No gastrointestinal or urinary tract hemorrhage within the preceding 21 days                            |  |
| No arterial puncture at a noncompressible site within the preceding 7 days                              |  |
| No seizure at the onset of stroke   |  |
| Prothrombin time  | 15 sec or international normalized ratio 1.7, without the use of an anticoagulant drug |
| Partial-thromboplastin time within the normal range, if heparin was given during the preceding 48 hours |  |
| Platelet count  | 100,000/mm <sup>3</sup>  |
| Blood glucose concentration   | > 50 mg/dL (2.7 mmol/liter)  |

(Adapted from: TPA Stroke Study Group Protocol Guidelines)

creased acceptance because of a recent randomized trial. This procedure is available only at selected centers. A 2<sup>1/2</sup>-year multicenter trial (PROACT II) demonstrated that patients with arteriographically confirmed occlusion of the middle cerebral artery (MCA) or its two main branches, who received intra-arterial thrombolysis with prourokinase within six hours of onset, had better outcomes three months after the stroke than did those who received only low-dose intravenous heparin (13). Because prourokinase is not commercially available, most centers that perform intra-arterial thrombolysis use t-PA. No randomized trials of intra-arterial thrombolytic therapy for vertebrobasilar disease have been completed, but several reports of improved outcome relative to the usual poor prognosis in this condition have led many authorities to recommend its use, particularly in patients who cannot be treated with intravenous t-PA within three hours of onset.

### Antithrombotic Therapy

Over the past thirty years, anticoagulation with continuous intravenous infusion of unfractionated heparin has probably been the most

widely used treatment for acute stroke, yet to date, no clinical trial has adequately tested its efficacy. Recently several trials of anticoagulation by varying methods have reported conflicting results. The International Stroke Trial (IST) enrolled nearly 20,000 patients within 48 hours of symptom onset in a 3 x 2 factorial design. These patients received subcutaneous heparin at a dose of 5,000 or 12,500 IU twice daily, or no heparin, with or without 300 mg of aspirin daily (14). There were no differences in the primary outcome measures (death at 14 days; death or dependency at 6 months) among any of the treatment groups. There was, however, an increased risk of hemorrhage in the high-dose heparin group. This study has been criticized because of the unconventional (by American standards) method of heparin administration, lack of monitoring of anticoagulant effect, lack of blinding and failure to obtain neuroimaging before randomization and initiation of treatment.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) evaluated the low-molecular-weight heparinoid, danaproid, versus placebo; 1,281 ischemic stroke patients were treated with continuous intravenous infusion for seven days, beginning within 24 hours of symptom onset. There was no significant reduction in stroke progression, 7-day mortality, or risk of stroke recurrence. In a subgroup analysis, there appeared to be a better 3-month outcome in the large vessel atherosclerotic subgroup (68% vs. 55% favorable outcome) (15). Another double-blind, placebo-controlled trial randomized 2,750 patients to a high or low dose of a different low-molecular-weight heparin (LMWH), nadroparin, or placebo subcutaneously, begun within 48 hours of symptom onset (16). There was a significant dose-dependent effect among the three study groups in favor of the LMWH. The main outcome measure was death or dependency, defined as requiring the help of others to perform activities of daily living after six months (16).

The Heparin in Acute Embolic Stroke Trial (HAEST) compared the LMWH dalteparin 100 IU/hg twice daily to aspirin 160 mg once daily, begun within 30 hours of symptom onset, for 449 patients with acute ischemic stroke and atrial fibrillation. There was no difference in the frequency of stroke recurrence in the first 2 weeks following stroke, and no difference in functional outcome at 2 weeks or 3 months (17).

Despite the lack of evidence supporting its use, intravenous unfractionated heparin remains

in widespread use for patients not eligible for thrombolysis, especially those with presumed cardioembolic infarction, antiphospholipid-antibody syndrome, extracranial carotid or vertebral artery dissection, cerebral vein thrombosis and impending large vessel thrombosis. It is usually given as a continuous intravenous infusion with a goal of maintaining the partial thromboplastin time at 1.5–2.0 times normal.

### **Antiplatelet Therapy**

Early treatment with aspirin is commonplace for patients not treated with thrombolysis or anticoagulation. This practice arose because aspirin was of proven benefit in secondary stroke prevention and in the acute management of myocardial ischemia. Recently, two trials evaluated its benefit in a total of more than 40,000 patients treated within 48 hours of stroke onset. In the IST, although there was no difference in the primary outcome measures among treatment groups, secondary analyses demonstrated a small decrease (2.8% vs. 3.9%) in the rate of recurrent ischemic stroke in patients treated with aspirin. The Chinese Acute Stroke Trial randomized 21,106 patients to aspirin 160 mg once daily, or placebo, for four weeks. A slightly lower mortality rate (3.3% vs. 3.9%) and recurrent stroke rate (1.6% vs. 2.1%) were demonstrated in the aspirin group (18).

Other oral antiplatelet drugs (e.g., clopidogrel, dipyridamole, ticlopidine), effective in secondary prevention, have not been studied in acute stroke. A phase II study of abciximab, a GPIIb/IIIa-receptor antagonist effective in acute myocardial infarction (MI) and in coronary artery stenting procedures, demonstrated safety and showed a trend toward better outcomes in the treated group. A phase III study is underway (19).

### **Neuroprotection**

Ischemic neuronal death results from a cascade of events set in motion by an inadequate supply of oxygen and nutrients. As the understanding of the process grows, so does interest in drugs that may interfere with one or more steps in the process. However, several approaches that showed promise in laboratory models have foundered in clinical trials. Potential neuroprotective agents, such as dihydropyridine-calcium channel blockers (nimodipine), N-methyl-D-aspartate-receptor antagonists

(aptiganel), antibodies to intercellular adhesion molecules (elinomab), free radical scavengers (lubeluzole) and other agents with multiple putative mechanisms of action (citicholine, clomethiazole), have failed to show efficacy in phase III trials. Various explanations, including adverse effects limiting tolerable doses, inadequate delivery of drug to ischemic tissue and delay in administration, have been given for the failure to replicate in clinical stroke the favorable responses found in laboratory models. Although research continues and enthusiasm is high for the discovery of a potentially effective agent or combination of agents, no effective neuroprotective agent has yet been demonstrated (20).

### Acute Stroke Units

Thrombolysis is currently the most dramatic and effective form of acute stroke therapy, but is applied to only about 2% of all strokes in the United States. Aspirin therapy is more widely applicable, and while statistically it was significantly better than placebo in two large trials, its use resulted in an absolute risk reduction of only about 1% in the outcome events measured. Since aspirin can be administered to most patients, its use would result in preventing three times as many deaths or dependent outcomes than can be avoided with thrombolytic therapy. However, this still translates into treating 100 patients in order to prevent one poor outcome. Anticoagulation is still widely used, but is of no proven benefit. By far the most widely applicable and effective acute stroke intervention is the use of dedicated acute stroke units. In randomized trials, this approach was shown to reduce death or dependency from stroke to the same degree as does thrombolysis, and it is applicable to all stroke patients (21).

The facilities offered by acute stroke units vary from site to site and from country to country. Some focus on the initial 48 hours, while others include rehabilitation programs. Numerous studies have demonstrated their effectiveness in providing general medical or neurologic services. While the characteristics of these units may vary, they all share an integrated approach to patient care, in which physician, nurse and therapist (e.g., speech, physical, or occupational) are involved primarily in the care of stroke patients, work together as a team, and provide close monitoring and rapid assessment and treatment of the patient. As a result, short-

term and long-term mortality rates are lower and hospitalizations are shorter. And the overall cost of the illness is reduced (22).

### Secondary Prevention

Individuals who have experienced a stroke or transient ischemic attack (TIA) are at markedly increased risk of stroke. In the first year after a TIA or stroke, the risk of stroke is approximately 10%. The cumulative three-year risk is approximately 25%. Preventive therapy should be targeted at the appropriate pathophysiologic mechanism which corresponds to the stroke subtype. There are three specific therapies of proven benefit in preventing a secondary stroke: carotid endarterectomy; anticoagulation of patients with atrial fibrillation; and platelet anti-aggregant therapy, if anticoagulation is not employed. Antiplatelet therapy has not been shown to be effective in primary prevention, but the other two treatments are effective in primary prevention in selected populations, as discussed below.

Cardioembolic stroke occurs most commonly in the setting of atrial fibrillation. Multiple trials comparing anticoagulation with warfarin to placebo, or to treatment with aspirin, have demonstrated the clear superiority of warfarin; however, these trials have excluded patients with prior stroke. The European Atrial Fibrillation Trial, however, randomized 669 patients with recent TIA or minor stroke to receive either warfarin or 300 mg of aspirin, and demonstrated an annual stroke risk reduction of from 12% for those treated with aspirin to 4% in the anticoagulated patients (23). Similarly, in the subgroup of patients with previous thromboembolism in Stroke Prevention in Atrial Fibrillation III (SPAF III), the rates of primary events (ischemic stroke or systemic embolism) were 11.9% per year with combination therapy (aspirin 325 mg plus fixed-dose warfarin set after achieving an international normalized ratio [INR] of 1.2–1.5 on two successive measurements) and 3.4% per year with adjusted-dose warfarin (target range INR = 2.0–3.0) (24).

Cardioembolic strokes can also occur in association with acute myocardial infarction, particularly when they involving the anterior wall, mitral valve prolapse, patent foramen ovale, and prosthetic mechanical heart valves. Patients with atrial fibrillation and mitral stenosis, and patients with mechanical heart valves are generally treated with warfarin with a target INR range of 3.0–3.5 (25). Anticoagulation may be

used to prevent stroke recurrence in the setting of presumed paradoxical embolus from PFO, for stroke thought to be secondary to an underlying hypercoagulable state, or for stroke secondary to intracranial arterial stenosis, although there is no clear evidence yet available regarding optimum treatment for these conditions.

### **Carotid Stenosis**

Narrowing of the lumen of the internal carotid artery is associated with an increased risk of stroke. A residual lumen that is less than 20% of normal diameter correlates highly with the development of total occlusion of the internal artery or the development of symptoms related to that artery (26). Endarterectomy is the specific treatment most widely used for this condition. In the past decade, several large-scale randomized trials involving symptomatic and asymptomatic individuals have provided data that allow a rational selection of appropriate patients for this procedure. In both the European Carotid Stenosis Trial (ECST) (27) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (28), individuals with symptoms referable to a highly stenotic carotid artery clearly benefited from surgery. The ipsilateral stroke rate in the nonsurgical arm was 22% in ECST and 26% in NASCET, but in the surgical arm in these patients it was only 10% and 9% respectively. Individuals with moderate symptomatic stenosis had stroke rates approximately one-half those of the highly stenotic groups. While the benefit of surgery in reducing subsequent stroke risk in the symptomatic highly stenotic groups was clearcut, this benefit disappeared once the degree of stenosis was less than 50% by NASCET criteria (comparable to approximately 75% by ECST criteria) (29). In the Asymptomatic Carotid Atherosclerosis Study, the overall benefit of carotid endarterectomy to asymptomatic individuals with at least 60% stenosis was statistically significant but less dramatic. Women with asymptomatic carotid stenosis may not benefit from endarterectomy at all (30).

### **Antiplatelet Therapy**

A majority of cerebral ischemic events, whether transient or persistent, are due to thrombosis or thromboembolism. Several trials have demonstrated the efficacy of a variety of antiplatelet and antithrombotic agents in the secondary prevention of stroke among persons

at high risk as a result of previous TIA or ischemic stroke. These agents have been shown to reduce the risk of subsequent stroke. After a TIA or stroke, the risk of stroke is high, particularly in the first 30 days, and it remains elevated over time. There is a 40% rate of subsequent stroke within 5 years (31).

The Antiplatelet Trialists' Collaboration was a meta-analysis of 17 trials intended to determine the efficacy of antiplatelet treatment (with any agent) in various populations at risk for vascular events. This analysis showed that antiplatelet agents reduced the odds of nonfatal stroke, MI or vascular death by 22% for persons with a history of TIA or stroke. The benefit was seen in men and women of all ages, with or without hypertension or diabetes mellitus. Long-term antiplatelet therapy was seen to prevent about 36 serious vascular events per 100 patients treated for 3 years (32).

In the past decade, several other antiplatelet agents have been widely used for secondary prevention of stroke (33). Clopidogrel was studied in the "Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events" (CAPRIE) trial, a single trial including patients with atherosclerotic vascular disease, defined as prior MI, stroke or peripheral vascular disease. The annual incidence of stroke, MI or vascular death was 5.83% in the aspirin group and 5.32% in the clopidogrel group, an 8.7% ( $p=0.05$ ) relative risk reduction. Among patients with prior stroke, there was a nonsignificant reduction in the incidence of these vascular outcomes (7.71% with aspirin vs. 7.15% with clopidogrel). In two large randomized trials, compared with placebo, ticlopidine significantly reduced the risk of stroke, MI or vascular death. In the Ticlopidine Aspirin Stroke Study (TASS), compared with high-dose aspirin in patients with TIA or minor stroke, ticlopidine provided a 12% reduction ( $p=0.05$ ) in the risk of stroke or death, and a 21% reduction ( $p=0.02$ ) in the risk of fatal or nonfatal stroke at 3 years for patients with TIA or minor stroke (34). For fatal or nonfatal stroke, the cumulative event rate at one year was 4.8% for patients receiving ticlopidine and 7.5% for those receiving aspirin. Minor stroke was the qualifying event in 927 patients (463 on ticlopidine, 464 on aspirin) entered in TASS. Among these patients, the cumulative event rate at one year for nonfatal stroke or death was 6.3% for those receiving ticlopidine and 10.8% for those receiving aspirin (42% risk reduction). The Canadian American Ticlopidine Study (CATS) randomized patients with

mild or moderate, non-cardioembolic stroke to ticlopidine or placebo. Ticlopidine was more efficacious than placebo in preventing recurrence (11.4% stroke or stroke death per year in the placebo group vs. 7.8% in the ticlopidine group) (35). In the European Stroke Prevention Study-2 (ESPS-2) (36), the combination of low-dose (25 mg) aspirin and extended-release dipyridamole (200 mg) (Aggrenox) twice daily was twice as effective for stroke prevention as was either drug alone. There was a 15% risk reduction relative to placebo with either drug alone and a 30% reduction with the combination. The 24-month stroke-free survival rate was 84.2% in the placebo group, 86.8% in the dipyridamole group, 87.1% in the aspirin group and 90% in the combination-therapy group. A comprehensive review by the Cochrane Collaboration of all published studies indicated that thienopyridine derivatives (ticlopidine, clopidogrel) are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk (specifically for TIA/ischemic stroke), but suggested there is uncertainty about the size of this additional benefit (between 3 and 28 strokes avoided per 1,000 patients treated for 2 years) (37).

There is no single definitive trial establishing the optimal aspirin dose for preventing stroke and other vascular events in persons with prior TIA/stroke. A meta-analysis of aspirin trials for patients with cerebrovascular disease revealed a 15% overall relative risk reduction for stroke, which appeared uniform across dosages ranging from 50–1500 mg daily (38).

In response to the evidence indicating the efficacy of low-dose aspirin for stroke prevention, the FDA issued new professional labeling for aspirin that indicates that the appropriate dose for stroke prevention after TIA or stroke is 50–325 mg daily. The American College of Chest Physicians has issued similar guidelines for first-line preventive treatment after noncardioembolic TIA or stroke, suggesting that there are no important differences in daily doses of aspirin between 30 mg and 1300 mg in the prevention of stroke and other vascular events (39).

Antiplatelet therapy is the most commonly prescribed stroke prevention remedy and is usually appropriate for any symptomatic individual who does not require anticoagulation. Most patients are maintained on enteric-coated aspirin, and 325 mg daily is the most commonly prescribed dose in the United States. However, as the above data suggest, there is no consensus

regarding the optimal dose, with the most recent recommendations suggesting a range of 50–325 mg (40). However, other authorities suggest that higher doses, if tolerated, are more effective (41). The newer medications may have somewhat greater efficacy than aspirin, but the cost for an individual in the U.S. is currently in excess of \$1,000/year when the drug is purchased at a retail pharmacy. Since the differences among various agents are small when compared with the effect of taking no antiplatelet agent at all and compliance has been shown to be a major problem, encouraging patients to be compliant and maintaining compliance with the prescribed regimen, is likely to be the most effective therapeutic intervention.

### Primary Prevention

Although effective treatment of acute stroke is available, prevention is far better. Effective prevention consists of addressing stroke risk factors and treating specific etiopathologic mechanisms identified in a given individual. Patients with prior TIA or stroke are at markedly increased risk of stroke and benefit most from specific interventions. However, primary prevention (treatment of individuals free of cerebrovascular disease) by treatment of stroke risk factors is also effective in reducing an individual's stroke risk.

### Hypertension

Hypertension is the most important modifiable stroke risk factor. This was first demonstrated by investigators in The Framingham Heart Study, who found that stroke risk increased in proportion to both systolic and diastolic blood pressures throughout the measured range (42). This effect has been found to be consistent in many populations (43). Subsequent studies have demonstrated that reduction of blood pressure lowers stroke risk (44). Treatment of isolated systolic hypertension is also clearly beneficial, especially in the elderly (45, 46). The choice of specific antihypertensive agent is less important than actually obtaining satisfactory control and should be determined by individual patient characteristics. However, a recent study suggested that an angiotensin-converting-enzyme (ACE) inhibitor may provide stroke protection beyond its antihypertensive effect (47). Since ACE inhibitors are generally well-tolerated in the elderly, this class of agents should be considered as the ini-

tial antihypertensive treatment in a stroke-prone individual. Recently published national guidelines suggest blood pressure of less than 140/85 mm Hg (135/80 in diabetics) as the appropriate treatment goal (48). The effect of angiotensin receptor blockers has not been studied.

### Hyperlipidemia

Elevated serum cholesterol is an important risk factor for coronary artery disease, but its role in stroke is unclear. The Multiple Risk Factor Intervention Trial (MRFIT) screened 351,000 men and demonstrated a curvilinear relationship, in which serum cholesterol of more than 240 mg/dL was associated with an increased risk of ischemic stroke mortality, while a level of less than 140 mg/dL was associated with an increased rate of intracerebral hemorrhage (49). However, in a meta-analysis of 45 studies, the Prospective Studies Collaboration failed to find a relationship between total cholesterol and stroke among 450,000 individuals (50). Similarly, neither the Framingham Study (51) nor the Cardiovascular Health Study (52) demonstrated a relationship between cholesterol and stroke. Consistent with these primarily negative findings, early cholesterol reduction studies showed a beneficial effect on heart disease, but not on stroke. Surprisingly, results in more recent trials using hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors consistently demonstrated a relative risk reduction of 20–30% for stroke in patients with coronary artery disease, which is similar to the risk reduction demonstrated for the various cardiovascular events studied (53, 54). This seemingly paradoxical finding may be explained by the putative beneficial effects of statins on platelets, plaque stabilization, smooth muscle cells, endothelial cell function, and inflammation, in addition to lowering low-density lipoprotein (LDL) cholesterol (55). The effect of triglycerides on stroke risk is also unclear, but a recent study of gemfibrozil demonstrated a similar degree of stroke risk reduction with minimal effect on high-density or low-density lipoproteins, but significant lowering of triglycerides. This suggests that triglycerides may also play a more significant role in stroke than previously recognized (56).

### Other Factors

The Framingham Study was also among the first prospective cohort studies to demonstrate

an increased stroke risk for cigarette smokers. Smokers had twice the risk of stroke as non-smokers, but that risk was eliminated within about two years of cessation of smoking (57).

Most studies have shown an increased risk of stroke with heavy alcohol consumption, but recently, moderate consumption (< 2 drinks/day) has been shown to be protective against stroke (58). While urging heavy drinkers to decrease or eliminate their alcohol consumption is advisable for many reasons, the idea of encouraging nondrinkers to begin is controversial.

Elevated levels of homocysteine in the blood (hyperhomocysteinemia) has recently been associated with increased risk of stroke and myocardial infarction (59). Individuals with levels above 15  $\mu\text{mol/L}$  appear to have five times the risk of stroke as compared to those with levels below 10  $\mu\text{mol/L}$ . The efficacy of reducing stroke risk by lowering blood homocysteine levels with a combination of vitamins B<sub>6</sub>, B<sub>12</sub> and folic acid is currently being assessed (60), but at least recommending the use of a multivitamin containing these elements, especially by the elderly, appears prudent.

A substantial increase in the age of our population will, unfortunately, lead to an increased incidence of stroke, especially recurrent stroke. Advances in acute stroke treatment will reduce the degree of damage caused by strokes and also reduce case fatality rates, but prevention, both primary and secondary, will remain the most effective means of reducing the overall burden of stroke on our society.

### References

1. American Heart Association. 1999 Heart and stroke statistical update. Dallas (TX): American Heart Association. 1998.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; 349(9061):1269–1276.
3. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: Preliminary first-ever and total incidence rates of stroke among blacks. *Stroke* 1998; 29(2):415–421.
4. Gresham GE, Fitzpatrick TE, Wolf PA, et al. Residual disability in survivors of stroke — the Framingham study. *N Engl J Med* 1975; 293(19):954–956.
5. Black-Schaffer RM, Osberg JS. Return to work after stroke: Development of a predictive model. *Arch Phys Med Rehabil* 1990; 71(5):285–290.
6. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: The Northern Manhattan Stroke Study. *Am J Epidemiol* 1998; 147(3):259–268.
7. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: Results from an international collaboration. *International Stroke Incidence Collaboration. Stroke* 1997; 28(3):491–499.

8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke* 1991; 22(8):983–988.
9. Horowitz DR, Tuhrim S, Weinberger JM, et al. Transesophageal echocardiography: Diagnostic and clinical applications in the evaluation of the stroke patient. *J Stroke Cerebrovasc Dis* 1997; 6:332–336.
10. Amarenco P, Cohen A, Tzourio C, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. *N Engl J Med* 1994; 331(22):1474–1479.
11. Fisher CM. Lacunar strokes and infarcts: A review. *Neurology* 1982; 32(8):871–876.
12. Hacke W, Brodt T, Caplan L, et al. Thrombolysis in acute ischemic stroke: Controlled trials and clinical experience. *Neurology* 1999; 53(7 Suppl 4):S3–S14.
13. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II Study: A randomized controlled trial. Prollyse in Acute Cerebral Thromboembolism. *JAMA* 1999; 282(21):2003–2011.
14. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* 1997; 349(9065):1569–1581.
15. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: A randomized controlled trial. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. *JAMA* 1998; 279(16):1265–1272.
16. Kay R, Wong KS, Yu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Engl J Med* 1995; 333:1588–1593.
17. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: A double-blind randomised study. HAEST Study Group. *Heparin in Acute Embolic Stroke Trial*. *Lancet* 2000; 355(9211):1205–1210.
18. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet* 1997; 349(9066):1641–1649.
19. Abciximab in acute ischemic stroke: A randomized, double-blind, placebo-controlled, dose-escalation study. The Abciximab in Ischemic Stroke Investigators. *Stroke* 2000; 31(3):601–609.
20. Lee JM, Zipfel GJ, Choi DW. The changing landscape of ischaemic brain injury mechanisms. *Nature* 1999; 399(6738 Suppl):A7–A14.
21. Hankey GJ. Stroke: How large a public health problem, and how can the neurologist help? *Arch Neurol* 1999; 56(6):748–754.
22. How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. Stroke Unit Trialists Collaboration. *Stroke* 1997; 28(11):2139–2144.
23. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154(13):1449–1457.
24. Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; 348(9028):633–638.
25. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br Med J* 1964; 1:1209–1212.
26. Roederer GO, Langlois YE, Jager KA, et al. The natural history of carotid arterial disease in asymptomatic patients with cervical bruits. *Stroke* 1984; 15(4):605–613.
27. MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet* 1991; 337(8752):1235–1243.
28. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* 1991; 325(7):445–453.
29. Chassin MR. Appropriate use of carotid endarterectomy. *N Engl J Med* 1998; 339(20):1468–1471.
30. Barnett HJ, Meldrum HE, Eliasziw M. The dilemma of surgical treatment for patients with asymptomatic carotid disease. *Ann Intern Med* 1995; 123(9):723–725.
31. Sacco RL. Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology* 1997; 49(5 Suppl 4):S39–S44.
32. Collaborative overview of randomised trials of antiplatelet therapy — I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994; 308(6921):81–106.
33. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996; 348(9038):1329–1339.
34. Hass WK, Easton JD, Adams HP, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. *N Engl J Med* 1989; 321(8):501–507.
35. Harbison JW. Ticlopidine versus aspirin for the prevention of recurrent stroke. Analysis of patients with minor stroke from the Ticlopidine Aspirin Stroke Study. *Stroke* 1992; 23(12):1723–1727.
36. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143(1–2):1–13.
37. Hankey GJ, Sudlow CL, Dunbabin DW. Thienopyridine derivatives (ticlopidine, clopidogrel) versus aspirin for preventing stroke and other serious vascular events in high vascular risk patients. *Cochrane Database Syst Rev* 2000; 2:CD001246.
38. Johnson ES, Lanes SF, Wentworth CE, et al. A meta-regression analysis of the dose-response effect of aspirin on stroke. *Arch Intern Med* 1999; 159(11):1248–1253.
39. Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 2001; 119(1 Suppl):300S–320S.
40. Albers GW, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. *Chest* 1998; 114(5 Suppl):683S–698S.
41. Dyken ML, Barnett HJ, Easton JD, et al. Low-dose aspirin and stroke. "It ain't necessarily so." *Stroke* 1992; 23(10):1395–1399.
42. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke. The Framingham study. *JAMA* 1970; 214(2):301–310.
43. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994; 50(2):272–298.
44. Five-year findings of the hypertension detection and follow-up program. III. Reduction in stroke incidence among persons with high blood pressure. Hypertension Detection and Follow-up Program Cooperative Group. *JAMA* 1982; 247(5):633–638.

45. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *JAMA* 1991; 265(24):3255–3264.
46. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350(9080):757–764.
47. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342(3):145–153.
48. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; 157(21):2413–2446.
49. Iso H, Jacobs DR, Jr, Wentworth D, et al. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989; 320(14):904–910.
50. Qizilbash N, Lewington S, Duffy S. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts: Prospective Studies Collaboration. *Lancet* 1995; 346:1647–1653.
51. Wolf PA, D'Agostino RB, O'Neal MA, et al. Secular trends in stroke incidence and mortality. The Framingham Study. *Stroke* 1992; 23(11):1551–1555.
52. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1991; 1(3):263–276.
53. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA* 1997; 278(4):313–321.
54. Prevention of cardiovascular events and death with mavastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; 339(19):1349–1357.
55. Furberg CD. Natural statins and stroke risk. *Circulation* 1999; 99(2):185–188.
56. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999; 341(6):410–418.
57. Wolf PA, D'Agostino RB, Kannel WB, et al. Cigarette smoking as a risk factor for stroke. The Framingham Study. *JAMA* 1988; 259(7):1025–1029.
58. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *JAMA* 1999; 281(1):53–60.
59. Giles WH, Croft JB, Greenlund KJ, et al. Total homocyst(e)ine concentration and the likelihood of nonfatal stroke: Results from the Third National Health and Nutrition Examination Survey, 1988–1994. *Stroke* 1998; 29(12):2473–2477.
60. Spence JD, Howard VJ, Chambless LE, et al. Vitamin Intervention for Stroke Prevention (VISP) trial: Rationale and design. *Neuroepidemiology* 2001; 20(1):16–25.