Randomized Clinical Stroke Trials in 2003

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Introduction
Previous studies have established the value of reducing risk factors for stroke in preventing future vascular compromise of the brain. Ongoing studies are trying to provide more specific guidelines for such treatment, to help to individualize therapy, and to test newer treatments with fewer side effects. During 2003, further studies were done on the treatment of high blood pressure and high blood lipids, and a treatment for atrial fibrillation was introduced that appears to cause fewer bleeds than the current standard, which is coumadin. In addition, a standard treatment for Alzheimer’s disease was reported to benefit cognition in people with stroke and dementia.

Treatment of Hypertension and Stroke
Two large studies confirmed that active treatment of high blood pressure is useful in preventing strokes. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [1] was an international multicenter outpatient study that enrolled 6105 patients with a past history of stroke or transient ischemic attack in the past 5 years. Subjects were randomly assigned to either the active treatment (the angiotensin-converting enzyme inhibitor perindopril [4 mg/d] for all patients, with the diuretic indapamide added at the discretion of treating physicians) or matching placebo(s). The primary outcome measures were disability (defined as a Barthel Index score of 99 out of 100) and dependency (a positive response to the following question: “In the last 2 weeks has the patient required regular help with everyday activities?”). After 4 years of follow-up, 19% of the active-treatment group and 22% of the placebo group were disabled (adjusted odds ratio of 0.76; 95% CI, 0.65 to 0.89; \( P < 0.001 \)), whereas 12% of the active-treatment group and 14% of the placebo group were dependent (adjusted odds ratio of 0.84; 95% CI, 0.71 to 0.99; \( P = 0.04 \)). According to the authors of this study, the reduction in disability and dependency was due to reduction in recurrent strokes as a result of perindopril-based blood pressure reduction. The reductions in disability (3%) and dependence (2%) in the overall population were small but certainly meaningful to the people who were spared, as well as being statistically significant.

The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) [2] study was a multicenter phase II study evaluating the safety of modest blood pressure reduction by candesartan cilexetil in the early treatment of stroke. There were 342 patients (339 valid) with cerebral ischemia and hypertension. The study had a complicated design. Of the overall group, 175 patients were randomly assigned to active treatment (the angiotensin receptor blocker candesartan) and 167 to a matching placebo on day 1. Patients who were hypertensive in the placebo group on day 7 were given candesartan, whereas those who were normotensive were administered no antihypertensive. The primary outcome measures were case fatality and score on the Barthel Index of disability at 3 months after initiation of treatment. This safety trial was stopped prematurely on the recommendations of the Safety Committee when 342 patients (339 valid) had been randomized because of an imbalance in endpoints between the two groups. The cumulative 12-month mortality and the number of cardio- and cerebrovascular events differed significantly in favor of the candesartan group (odds ratio of 0.475; 95% CI, 0.252 to 0.895). There were no significant differences in the number or type of side effects between the two groups.

Treatment of Hyperlipidemia and Stroke
Two large studies examined the relationships between active treatment of hyperlipidemia and specifically hypercholesterolemia in the prevention of stroke. Both provided data that such treatment is useful.
The MRC/BHF Heart Protection Study [3] looked at the impact of the cholesterol-lowering drug simvastatin in 5963 diabetic patients. This study examined two important stroke risk factors: diabetes and hyperlipidemia. In this study, 5963 adults with diabetes (both type 1 and 2) and 14,573 adults with no diabetes but arterial occlusive disease were randomized to either 40 mg of simvastatin or placebo daily. The primary endpoint was major coronary or vascular event (ie, stroke or revascularization). The study was conducted on an outpatient basis, with a mean follow-up of 4.8 years. The data were analyzed with an intention to treat basis. There was a 25% reduction in the incidence of first nonfatal or fatal stroke in patients allocated to the simvastatin group (95% CI, 15% to 34%; P < 0.0001). Among diabetic patients, there was a 28% reduction in strokes attributed to ischemia (102 [3.4%] for simvastatin vs 140 [4.7%] for placebo; P = 0.01), with no apparent difference in the small numbers of hemorrhagic strokes (10 [0.3%] vs 15 [0.5%]; P = 0.3).

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) study [4••] was a multicenter trial of the effect of lowering cholesterol in hypertensive patients. Of the 19,342 hypertensive patients (aged 40 to 79 years with at least three other cardiovascular risk factors) randomized to one of two antihypertensive regimens in the Anglo-Scandinavian Cardiac Outcomes Trial, 10,305 patients with nonfasting total cholesterol concentrations of 6.5 mmol/L or less were randomly assigned to 10 mg/d of atorvastatin or placebo, in addition to their previous clinical regimen. These patients formed the lipid-lowering arm of the study. They were followed-up for an average of 5 years. The primary endpoint was nonfatal myocardial infarction and fatal coronary heart disease. Data were analyzed by intention to treat. Treatment was stopped after a median follow-up of 3.3 years, as by this time 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group (hazard ratio of 0.64; 95% CI, 0.50 to 0.83; P = 0.0005). This benefit was noted in the first year of follow-up. There were 89 fatal and nonfatal strokes in the atorvastatin group compared with 121 in the placebo group (0.73; 95% CI, 0.56 to 0.96; P = 0.024). This trial confirmed the results of other studies that have indicated reductions in stroke rates associated with statin use [5].

**Antithrombotic Treatments in Stroke**

Two large studies suggested that the addition of other platelet antagonists to aspirin does not provide additional benefit compared with aspirin alone. A third study argued for the use of a thrombin inhibitor rather than warfarin in preventing strokes in patients with atrial fibrillation. The former medication had a more attractive side-effect profile, including a reduction in bleeds.

The Triflusal versus Aspirin in Cerebral Infarction Prevention (TACIP) study [6] was a randomized, double-blind, multicenter study to test the efficacy of triflusal (600 mg/d) versus aspirin (325 mg/d) for prevention of vascular events in patients with stroke or transient ischemic attack. Of the 2113 patients with transient ischemic attack or non-disabling stroke, 1058 received triflusal and 1055 received aspirin, with a mean follow-up period of 30.1 months. The primary endpoints were combined endpoints (incidence of nonfatal ischemic stroke, nonfatal acute myocardial infarction, or vascular death) as well as the incidence of these events separately, and the incidence of major hemorrhage. The survival analysis showed no differences between groups (hazard ratio [HR] for triflusal vs aspirin of 1.09; 95% CI, 0.85 to 1.38), whereas the incidence of combined endpoints was marginally higher for triflusal and aspirin compared with aspirin alone (13.1% vs 12.4%). The incidence of nonfatal stroke (HR of 1.09; 95% CI, 0.82 to 1.44), nonfatal acute myocardial infarction (HR of 0.95; 95% CI, 0.46 to 1.98), and vascular death (HR of 1.22; 95% CI, 0.75 to 1.96) was similar between the two groups. The overall incidence of hemorrhage was significantly lower in the triflusal group (16.7% vs 25.2%; odds ratio of 0.76; 95% CI, 0.67 to 0.86; P < 0.0001). This study did not show superior efficacy of triflusal over aspirin in the long-term prevention of vascular events among stroke patients, although triflusal was associated with a significantly lower rate of hemorrhagic complications.

The African American Antiplatelet Stroke Prevention Study (AAASPS) [7••] was a randomized, double-blind, investigator-initiated multicenter trial of 1809 black men and women with a recent noncardioembolic ischemic stroke recruited between December 1992 and October 2001 from 62 academic and community hospitals in the United States and followed-up for up to 2 years. The primary endpoints were recurrent stroke, myocardial infarction, or vascular death (according to intention to treat analysis), and the secondary outcome measures were fatal or nonfatal stroke. During the 2-year follow-up, no statistically significant difference was found between ticlopidine and aspirin in the prevention of recurrent stroke, myocardial infarction, or vascular death (133 of 902 [14.7%] ticlopidine patients vs 112 of 907 [12.3%] aspirin patients). However, there was a nonsignificant trend in the reduction of fatal or nonfatal stroke among those in the aspirin group (P = 0.08 by log-rank test). Based on these data and the risk of serious adverse events with ticlopidine, the authors suggested aspirin alone to be the better treatment option for aspirin-tolerant black patients with noncardioembolic ischemic stroke.

The Stroke Prevention using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III) study [8••] was an open-label, randomized, noninferiority trial. Warfarin has been found to reduce the risk of ischemic stroke by 62% compared with placebo in a meta-analysis [9]. This benefit is associated with a seven- to 10-fold increase in intracranial hemorrhage, particularly in elderly patients. The SPORTIF III study compared the safety and efficacy of ximelagatran (an oral direct