Prevention and Health Services Delivery

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The burden of stroke to the health care system in the United States continues to increase. Stroke-related hospital admissions grew from 580,000 in 1988 to 820,000 in 1997, an 18.6% increase after age adjustment. More effective stroke prevention provides the primary means of reducing these alarming statistics. This can be accomplished through better implementation of known preventive strategies and through research into new approaches to stroke prevention.

Diet can affect stroke risk, with epidemiological studies indicating an inverse relationship between fruit and vegetable consumption and cardiovascular events. For example, one study including individuals free of cardiovascular disease at baseline found that the relative risk (RR) of stroke was reduced by 31% (RR, 0.69; 95% CI, 0.52 to 0.92) for persons in the highest quintile of fruit and vegetable intake. Analysis of data from the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study supports these results. The study included 9608 adults aged 25 to 74 years who were free of cardiovascular disease at a baseline evaluation between 1971 and 1975. Consumption of fruits and vegetables ≥3 times per day compared with <1 time per day was associated with a 27% lower stroke incidence (RR, 0.73; 95% CI, 0.57 to 0.95) after adjustment for potential confounders, suggesting the benefit is not attributable to a healthy-user effect. The results reinforce present recommendations for an intake of 5 servings of fruits and vegetables daily.

Because fruits and vegetables contain antioxidants, antioxidant food supplements might be expected to have similar benefits. However, a 3-year study of patients with coronary heart disease, low levels of high-density lipoprotein cholesterol, and normal levels of low-density lipoprotein cholesterol found no reduction in cardiovascular end points (death, myocardial infarction, stroke, and revascularization procedures) with the use of antioxidant supplements (800 IU vitamin E, 1000 mg vitamin C, 25 mg β-carotene, and 100 µg selenium daily). Concomitant use of the antioxidants actually attenuated the benefit of a statin-niacin combination. The MRC/BHF Heart Protection Study used a 2×2 factorial design to test the benefits of antioxidant supplementation (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene daily) on fatal and nonfatal cardiovascular events in >20,000 patients with coronary or other occlusive arterial disease or diabetes over 5 years. The regimen raised the plasma concentrations of α-tocopherol, vitamin C, and β-carotene, but there was no significant reduction in major vascular events (RR, 1.0; 95% CI, 0.94 to 1.06), including no reduction in nonfatal or fatal stroke (5% with or without antioxidants). These studies do not provide evidence of benefit of antioxidants in the combinations and doses studied among high-risk persons.

Several epidemiological studies have suggested that low potassium consumption and low potassium serum levels are associated with elevated stroke-related mortality. The NHANES-I Epidemiologic Follow-up Study found that low dietary potassium intake was associated with an increased stroke risk. Those consuming a low potassium diet at baseline (<34.6 mmol potassium per day) had a 28% higher hazard of stroke (hazard ratio, 1.28; 95% CI, 1.11 to 1.47) after adjustment for other cardiovascular risk factors. Although unrecognized confounding could not be completely excluded, data from the Cardiovascular Health Study are consistent with this observation. The Cardiovascular Health Study includes 5888 persons age 65 years or older who were free of stroke at baseline and followed for 4 to 8 years. There was a 2.5-fold increase in the relative risk of stroke (95% CI, 1.7 to 3.5) among diuretic users with a low serum potassium level (<4.0 mEq/L) and a 1.5-fold increase (95% CI, 1.1 to 2.0) among nondiuretic users consuming ≥2.34 g/d of potassium in their diet. A prospective study is required to determine whether increasing dietary potassium would translate into a reduction in stroke incidence. However, it seems prudent to include potassium-rich fruits and vegetables as part of a healthy diet and to provide adequate potassium supplementation to diuretic users.

From the therapeutic standpoint, the MRC/BHF Heart Protection Study found that the addition of a statin (simvastatin) to existing treatments in high-risk patients resulted in a 24% reduction (95% CI, 19 to 28) in the rate of major vascular events. This included a 13% reduction in mortality (RR, 0.87; 95% CI, 0.81 to 0.94) and a 25% reduction in stroke (RR, 0.75; 95% CI, 0.66 to 0.85). These results are consistent with other studies demonstrating a reduction in stroke with statin treatment among patients with coronary heart disease. However, the Heart Protection Study also included 1820 patients with a history of stroke but no known coronary heart disease. There was a 27% reduction (RR, 0.72; 95% CI, 0.21 to 0.39) in major vascular events in this subgroup. Although encouraging, stroke patients were not prospectively randomized, and baseline imbalances in stroke risk factors may have existed. In addition, 30% of end point...
strokes were not classified as being either hemorrhagic or ischemic, and the risk of recurrent stroke among patients with stroke was not addressed. A study is ongoing (Stroke Prevention by Aggressive Reduction in Cholesterol Levels [SPARCL]) that will directly answer these critical questions. If positive, it will provide clear evidence of the benefit of statins in patients with stroke but no known coronary heart disease.

Treatment of elevated blood pressure significantly reduces stroke risk. Extending these data, the Heart Outcomes Prevention Evaluation (HOPE) Study compared the effects of an angiotensin-converting enzyme (ACE) inhibitor (ramipril) with placebo in 9297 normotensive (mean blood pressure, 139/79 mm Hg) high-risk persons. There was a 32% (95% CI, 16 to 44) reduction in stroke over 4 years in the entire study population, with a 24% risk reduction (95% CI, 5 to 40) for stroke, MI, or vascular death among the 1013 patients with a history of stroke or transient ischemic attack (TIA). There was a 25% (95% CI, 12 to 36) reduction in these outcomes and a 33% (95% CI, 10 to 50) reduction in stroke among patients with diabetes with a previous cardiovascular event or an additional cardiovascular risk factor. Whether these benefits were a specific effect of the ACE inhibitor or attributable to a blood pressure–lowering effect remains uncertain. Although the blood pressure–lowering effect as measured during the study was minimal, a subsequently published substudy found a substantial effect on blood pressure with 24 hours of monitoring. With this background, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was specifically designed to test the effects of a blood pressure–lowering regimen including an ACE inhibitor in 6105 patients with stroke or TIA within the prior 5 years. Randomization was stratified by intention to use single (ACE inhibitor) or combination (ACE inhibitor plus the diuretic indapamide) therapy in both hypertensive (>160 mm Hg systolic or >90 mm Hg diastolic) and nonhypertensive patients. The combination resulted in a 43% (95% CI, 30 to 54) reduction in the risk of recurrent stroke and a 40% (95% CI, 29 to 49) reduction in the risk of major vascular events, with the effect present in both hypertensive and normotensive groups. However, there was no significant benefit of either antihypertensive given alone. Those given combination therapy were younger, were more likely to be men, were more likely to be hypertensive, had a higher mean blood pressure at entry, were more likely to have coronary heart disease, and were recruited sooner after the event. The overall benefit was consistent with the combination’s blood pressure–lowering effect. Although not showing a specific benefit of the ACE inhibitor, the study clearly demonstrated the importance of blood pressure lowering for secondary stroke prevention, even in those without hypertension, and provides evidence for one regimen by which this can be achieved.

These recent studies of ACE inhibitors leave an uncertainty as to whether the observed benefits in stroke reduction are specifically related to this class of drug. The Losartan Intervention for Endpoint (LIFE) Reduction in Hypertension study compared the effects of an angiotensin II type 1 receptor blocker with the β-adrenergic receptor blocker atenolol in 26365 patients with hypertension (160 to 179 mm Hg) and electrocardiographically determined left ventricular hypertrophy over 4 years. Blood pressure reductions were similar for each group, with a 13% (RR, 0.87; 95% CI, 0.77 to 0.98) reduction in MI, stroke, or death among the losartan-treated patients. This included a 25% (RR, 0.75; 95% CI, 0.63 to 0.89) reduction in fatal or nonfatal stroke. The two regimens were compared among the subgroup of 1195 persons who also had diabetes in a prespecified analysis. There was a 24% (RR, 0.76; 95% CI, 0.58 to 0.98) reduction in major vascular events and a nonsignificant 21% (RR, 0.79; 95% CI, 0.55 to 1.14) reduction in stroke among those treated with the angiotensin receptor blocker. The LIFE study shows that patients with essential hypertension and left ventricular hypertrophy with and without diabetes benefit more with treatment with an angiotensin II type 1 receptor blocker than with a β-adrenergic receptor blocker.

The use of hormone replacement therapy by postmenopausal women has been the source of considerable controversy. In the Heart & Estrogen-progestin Replacement Study (HERS), 2763 postmenopausal women with coronary heart disease were randomly assigned to take conjugated estrogen plus progestin or placebo, with a mean follow-up of 4.1 years. HRT use was not associated with the risk of nonfatal stroke (relative hazard [RH], 1.18; 95% CI, 0.83 to 1.66), fatal stroke (RH, 1.61; 95% CI, 0.73 to 3.55), or TIA (RH, 0.90; 95% CI, 0.57 to 1.42). Extending these results to a cerebrovascular population, the Women’s Estrogen for Stroke Trial (WEST) was a randomized, double-blind, placebo-controlled trial of estrogen replacement in 664 postmenopausal women with stroke or TIA. Estrogen therapy did not reduce the risk of either death (RR, 1.2; 95% CI, 0.8 to 1.8) or nonfatal stroke (RR, 1.0; 95% CI, 0.7 to 1.4), with a nonsignificant higher risk of fatal stroke (RR, 2.9; 95% CI, 0.9 to 9.0). Finally, the Women’s Health Initiative, a randomized controlled primary prevention trial, reported on the effects of estrogen plus progestin in 16 608 postmenopausal women with an intact uterus at baseline followed for a mean of 5.2 years. This part of the study was stopped prematurely because of an increased risk of invasive breast cancer among those given HRT. There was a non–statistically significant (after correction for multiple comparisons) increased risk of stroke (HR, 1.41; 95% CI, 0.86 to 2.31), including an increased risk of fatal stroke (HR, 1.20; 95% CI, 0.32 to 4.49) and nonfatal (HR, 1.50; 95% CI, 0.83 to 2.70) stroke. These studies reinforce the view that HRT should not be used in postmenopausal women for cardiovascular disease or stroke prevention.

Several studies show stroke prevention strategies are not being effectively used. The reasons for these missed opportunities are complex, and a variety of strategies are being studied to address the problem. For secondary prevention of cardiovascular disease, the CHAMP study suggests that starting these therapies in the hospital can be associated with both improved long-term use and improved clinical outcomes. The use of a computerized reminder system was found to increase use of preventive care in hospitalized patients, providing a tool for incorporating prevention into hospital-based practice.
program uses a similar strategy. The development of a better understanding of stroke risk factors, the optimal methods of risk reduction, and better ways of incorporating both primary and secondary prevention into clinical practice will hopefully result in a reduction in the burden of stroke facing our patients and the health care system.

References


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