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Prevention of stroke

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In 1999, there were nearly 700,000 acute strokes in the United States.[1] Of great concern, death rates from stroke, which had a remarkable decline of 62% between 1972 and 1990, had reached a plateau. This end in the decline in the number of stroke deaths, in addition to the aging of the US population, underscores the increasing importance of cerebrovascular disease for death and disability in the coming years. Although intravenous tPA (tissue plasminogen activator) has been approved as the first treatment for acute stroke, and other treatments such as intra-arterial urokinase show promise, at the current time these treatments are applicable only to a small minority of stroke patients.[2] The major strategy for reducing the personal, public health, and economic burden of stroke to society will continue to be prevention.

Identification of the major precursors of stroke has been the key to prevention. Some of the risk factors for ischemic stroke are non-modifiable, but they serve to identify persons at increased stroke risk in whom vigorous control of the modifiable risk factors is imperative. Non-modifiable risk factors are: age, male gender, African American race, diabetes, family history of stroke, increased fibrinogen level, and migraines. Other indicators of high stroke risk, amenable to modification, include: increased blood pressure levels and hypertension, cigarette smoking, low levels of physical activity, elevated homocysteine levels, and symptomatic, significant, extracranial, carotid stenosis. Persons with prior stroke or transient ischemic attack (TIA) are at particularly high risk. Common cardiac diseases also predispose to stroke including: coronary heart disease (CHD) or acute MI, congestive heart failure, and atrial fibrillation (AF). Other cardiac abnormalities, including left ventricular enlargement (LVH by ECG or increased left ventricular mass on echocardiogram), increased left atrial size, ulceration and thrombi in the ascending aorta, patent foramen ovale, mitral annular calcification, and others, also predispose to stroke. Unlike CHD, increased serum total cholesterol or low HDL-cholesterol have not been consistently related to increased incidence of ischemic stroke.

Observational data support cessation of cigarette smoking, increased consumption of whole grains, fruits, vegetables, fish high in omega-3 fatty acids, and moderate physical activity as strategies for stroke prevention. Clinical trial data show that controlling increased blood pressure reduces stroke incidence, particularly in Type 2 diabetics. Warfarin anticoagulation safely prevents stroke in persons with atrial fibrillation, while carotid endarterectomy clearly reduces ipsilateral stroke, if done by skilled surgeons in appropriate patients with significant extracranial carotid stenosis. Aspirin and other antiplatelet agents reduce stroke recurrence, but not initial stroke. Recently, HMG-CoA reductase inhibitor trials for cholesterol reduction have shown as much benefit for stroke as for MI. Elevated plasma homocysteine levels, have also been implicated in stroke. Identification of those at increased risk of stroke will facilitate prevention. Probability of stroke can be estimated by a stroke risk profile which accounts for the impact of each risk factor and for the cumulative increased risk of borderline levels with multiple risk factors.

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Control of hypertension and stroke prevention

A combined analysis of 9 major prospective (observational) studies of 420,000 individuals, showed a graded relationship between diastolic pressure, stroke, and CHD incidence. Risk rose as diastolic pressure level increased. In a meta-analysis of drug treatment for hypertension, incidence of stroke increased 46% and CHD 29% for every 7.5 mm Hg increase in diastolic pressure.[3] An overview of 14 randomized trials of blood pressure reduction treatment in 37,000 hypertensive subjects showed that an average blood pressure reduction of 5.8 mm Hg yielded a 42% reduction in stroke incidence, and paralleled the decline expected based on observational data.[4] The reduction of elevated blood pressure clearly prevented stroke and should finally put to rest the long-standing myth that reduction of elevated pressure in hypertensives would precipitate stroke. Although treatment in these trials was based on diastolic hypertension, stroke risk can just as clearly be related to systolic pressure levels.

In the elderly, where isolated systolic elevation is common, treatment significantly reduced stroke incidence without appreciable side effects. In the Systolic Hypertension in the Elderly Program (SHEP Trial), 4,736 persons above age 60, with systolic blood pressure levels ≥160 mm Hg and diastolic pressures <90 mm Hg, treatment reduced stroke incidence by 36% (MI and coronary death was reduced by 27%).[5] These results were confirmed in the Syst-Eur Trial of 4,695 elderly men and women with isolated systolic hypertension.[6] Since two-thirds of elderly hypertensives, aged 65-89 years, have isolated systolic hypertension and most strokes occur in this age group, these two trials have considerable importance. In post-hoc analyses of these data, the benefit was greatest in the 492 diabetics; stroke was reduced by 73%, total cardiovascular events decreased by 76%, and overall mortality by 55%.[7] Comparable dramatic reductions in stroke incidence occurred in hypertensive type 2 diabetics randomized to tighter diastolic blood pressure control (80-84 mm Hg) compared to a less tight control with target diastolic pressures of 85-89 mm Hg.[8] No corresponding reduction in stroke followed the tight blood glucose control attempted in the other arm of the study.[9]

Despite these remarkable reductions, only a fraction of the potential benefit of blood pressure reduction for stroke prevention has been achieved. Approximately 1 in 5 of the estimated 50 million Americans with elevated blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, or taking antihypertensive medication) have achieved optimal blood pressure control.[10] It has been estimated that 1 in 3 hypertensives were unaware their blood pressure was elevated, and only half were on treatment. Thus, four-fifths of American hypertensives are unaware, untreated, or uncontrolled.

As noted, although more than a dozen trials have demonstrated the efficacy of blood pressure reduction for primary stroke prevention, until recently there had been no convincing, clinical trials demonstrating this benefit in the secondary prevention of stroke. Two recent clinical trials, Post-stroke Antihypertensive Treatment Study (PATS) and Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS), reduced stroke recurrence by 29%, using indapamide (2.5 mg/day) alone for blood pressure reduction (PATS), and by 28% with a combination of a thiazide diuretic indapamide (2.0-2.5 mg/day) and perindopril (4.0 mg/day) (PROGRESS).[11] In the latter trial, some suggested that the use of the angiotensin-converting enzyme (ACE) inhibitor, perindopril, was key to preventing stroke recurrence,[11] but others have attributed the effect to blood pressure reduction alone.[12] Potentially important for the secondary prevention of stroke, perindopril did not reduce cerebral blood flow in patients with recent ischemic stroke, even when administered acutely, ie, 2-7 days following a stroke.[13] The beneficial effect of blood pressure reduction seems key and there is no convincing evidence of the superiority of one class of antihypertensives.[14]

Cessation of cigarette smoking

In a meta-analysis of 32 separate studies, cigarette smoking was a significant independent contributor to stroke incidence, increasing risk by 50%.[15] There was a dose-response; risk rose with increasing numbers of cigarettes smoked daily. This risk is reversible, and smoking cessation is followed by a rapid decline in stroke incidence. In Framingham, within 5 years of cigarette smoking cessation, risk of stroke, like the risk of MI, returned to that of persons who had never smoked.[16] There was no interaction with age or duration of smoking, reinforcing the notion that a key mechanism by which cigarette smoking acted was by *precipitating* stroke.

Increased physical activity

Increased levels of physical activity have been linked to lower stroke (and CHD) incidence. Exercise exerts a beneficial influence on stroke risk factors by: reducing elevated blood pressure; promoting weight loss; raising the HDL- and lowering the LDL-cholesterol; improving glucose tolerance; and promoting a lifestyle conducive to favorably changing detrimental health habits, such as cigarette smoking. In Framingham men, moderate physical activity was associated with significantly reduced relative risk of stroke (RR 0.41, $P = 0.0007$), but no protective effect was seen in women. In this study, moderate activity conferred as much benefit as heavy physical activity, but in the NHANES 1 epidemiological follow-up study, there was a graded inverse relationship between level of physical activity and incidence of stroke in women, as well as men, and in both blacks and whites.[17] In the Nurses Health Study, the level of physical activity had a graded protective effect on stroke incidence after 8 years of follow-up.[18] Prevention of stroke can be added as still another benefit of physical activity in both men and women.

Control and prevention of the complications of diabetes

Stroke incidence is doubled in diabetics.[19-21] Attempts to tightly control blood sugar in type 2 diabetics were unsuccessful in reducing stroke incidence in the UK Prospective Diabetes Study Group.[9] It is apparent that the combination of hypertension and diabetes increases stroke risk dramatically. In diabetics with isolated systolic hypertension, either a thiazide diuretic[22] or an intermediate-acting calcium channel blocker[7] reduced stroke incidence dramatically. In the Heart Outcomes Prevention Evaluation (HOPE) trial, the ACE inhibitor, ramipril 10 mg/day (added to the usual medications aspirin, diuretics, beta-blockers, lipid-lowering and antihypertensive agents) reduced stroke incidence by 32% overall and in diabetics.[23,24] Although there was a minimal decrease in blood pressure (1.92 mm Hg systolic and 3.30 mm Hg diastolic in the ramipril group), the benefits exceeded that expected from blood pressure reduction alone.[24]

Another strategy to reduce stroke in diabetics is to prevent the development of diabetes. In persons with glucose intolerance it may be possible by means of weight reduction (restricting total fat and saturated fat intake, increasing the intake of dietary fiber), and increasing physical activity to reduce the development of diabetes by 58% ($P<0.001$).[25]

Weight loss in the obese

Obesity has long been associated with an increased risk of stroke and MI, but its role as an independent risk factor was unclear. Recent evidence suggests that obesity, particularly central or abdominal obesity, independently contributes to risk of MI and stroke. Obesity is associated with increased blood pressure, an unfavorable blood lipid profile, and increased blood sugar levels. In the Nurses Health Study, stroke risk increased with increased body mass index (BMI) in women aged 30-55 even after adjustment for other predisposing stroke risk factors.[26] However, in men, no significant relationship was seen.[27] Using another index of overweight, abdominal obesity, risk of stroke increased significantly in men in the highest quintile of waist-hip ratio (relative risk 2.33, 95% CI, 1.25-4.37) which persisted after adjustment for body mass index, height, and other stroke risk factors.[27] Dietary interventions to achieve a favorable body mass index and to decrease abdominal obesity are recommended.

Warfarin anticoagulation in AF

Atrial fibrillation (AF) is one of the most powerful independent risk factors for stroke.[28;29] AF increases stroke incidence fivefold with rates of approximately 5% per year for initial stroke, and 12% per year for recurrent stroke events. In more than 6 clinical trials, the efficacy of warfarin anticoagulation (68%-81% risk reduction) was consistently demonstrated in primary and recurrent stroke prevention.[30] The warfarin anticoagulation was at an INR intensity of 2.0-3.0; some suggest a target of INR 3.0 as an optimal and safe level. Unless contraindicated, warfarin is the treatment of choice in all persons with AF, with the possible exception of low-risk individuals <65 years of age, who have no history of hypertension, diabetes, TIA, or stroke, and are free of structural heart disease. Low-risk individuals and those for whom anticoagulants are contraindicated may be placed on aspirin 325 mg/day, though the evidence of a protective effect is unconvincing.[31]

Antiplatelet agents

In patients with prior stroke or TIA, aspirin reduces the relative odds of a composite outcome of ischemic stroke, MI, or vascular death by 27%.[32] Ticlopidine, and more recently, clopidogrel have shown a level of protection 8%-10% above that of aspirin in large clinical trials.[33,34] Some have argued that the proper comparison group for a new antiplatelet agent in secondary stroke prevention should be limited to stroke survivors treated with aspirin where a risk reduction of 13% was seen.[35] The European Stroke Prevention Study 2 demonstrated that the combination of aspirin 25 mg and dipyridamole 200 mg twice a day in a sustained release formulation, reduced stroke recurrence by 37%.[36]

Aspirin, 325 mg, every other day reduced the incidence of MI in healthy physicians, but no benefit was seen for stroke.[37] Recently, aspirin 75 mg/day did not prevent stroke, but exerted a major influence on preventing new cardiovascular events, particularly MI, in a trial of 18,790 hypertensives.[38] Why aspirin prevents first MI, but not initial stroke, yet effectively reduces stroke recurrence, is unclear.

Surgery for extracranial carotid artery stenosis

Endarterectomy by skilled surgeons for symptomatic patients with high-grade, extracranial, carotid stenosis 70%-99%, using North American Symptomatic Carotid Endarterectomy Trial (NASCET) measurement methods (or >75%-99% using European Carotid Surgery Trial [EST] criteria), clearly prevents ipsilateral stroke.[39] The benefit of surgery in asymptomatic subjects with carotid stenosis 60%-99% was demonstrated in men by the Asymptomatic Carotid Atherosclerosis Study (ACAS), but not in women.[40] However, the results were entirely dependent upon attaining an extremely low surgical complication rate of less than 3% in ACAS, which may be difficult to match in non-clinical trial surgical practice. For this reason, some critics believe the risk of complications does not warrant the 1% annual reduction in absolute risk of stroke.[41]

HMG-CoA reductase inhibitors to lower LDL-cholesterol in patients with coronary heart disease

Despite the lack of uniform and convincing evidence of a link between elevated total and LDL-cholesterol or low HDL-cholesterol and stroke incidence (including a meta-analysis of 45 prospective, observational cohorts

containing 450,00 patients), there is compelling evidence for a substantial protective impact by HMG-CoA reductase inhibitors on stroke incidence.[42] Two, large, randomized, clinical trials of the HMG-CoA reductase inhibitor, pravastatin, in patients with CHD, whose total and LDL-cholesterol levels were in the average range, resulted in a remarkable 31% reduction in stroke incidence.[43,44] In addition, the rapid benefit from pravastatin on stroke incidence suggests that in addition to reducing LDL-cholesterol, these agents serve to prevent precipitation of clinical events by stabilizing the atherosclerotic plaque, improving endothelial function, and exerting beneficial effects on clotting.[45]

Folic acid to reduce plasma homocysteine levels

Several case-control studies have related elevated plasma homocysteine (tHcy) to incidence of CHD and stroke.[46,47] The level of tHcy may be reduced by folic acid and pyridoxine, therefore, possibly reducing stroke or CVD risk. In the British Regional Heart Study cohort, stroke cases had higher non-fasting tHcy levels than controls, with a graded increase in risk from increasing levels of tHcy.[46] Utilizing Framingham Study data, there was a relative risk of 1.82 for stroke, comparing the highest quartile of non-fasting tHcy level with the lowest quartile (95% CI 1.14-2.91).[48] These prospective data support the contention of a graded increase in stroke and transient ischemic attack incidence with increasing levels of plasma homocysteine. Previous investigations have linked elevated non-fasting tHcy in Framingham to the presence of cervical carotid artery stenosis and to lower levels of plasma vitamins: folic acid, vitamin B_6, and B_{12}.[49] After adjusting for pertinent risk factors, including vitamin levels, those in the upper quartile of tHcy level (≥14.4 µmol/l) had approximately double the rate of carotid stenosis ≥25% as persons in the lowest quartile (≤9.1 µmol/l).[49] The Vitamin Intervention for Stroke Prevention (VISP) Trial underway for several years should settle the question whether lowering elevated plasma homocysteine in stroke survivors with high doses of folic acid, B_{12} and B_6 reduces recurrent stroke, myocardial infarction, and death. In the interim, given the potential benefit and the low risk of vitamin therapy, treatment with folic acid, B_{12} and B_6 might be considered in most adults, particularly in persons with elevated homocysteine levels and symptomatic vascular disease.

Diet: consumption of whole grains, fruits and vegetables, vitamins C and E

Observational data suggest increased whole grain consumption was associated with a lower stroke incidence in the Nurses Health Study.[50] The relative risk for ischemic stroke in the highest quintile of whole grain consumption was 0.69, relative to the lowest quintile, adjusted for other stroke risk factors. Consumption of fruits and vegetables was also protective in the NHS Nurses Health Study and in the Health Professionals Follow-up Study (HPFS), where the relative risk of stroke was 0.69 (95% CI, 0.52-0.92) for persons in the highest quintile of intake.[51] The NHS Nurses Health Study also investigated the relationship between omega-3 fatty acids and stroke. Consuming ≥5 servings of fish per week reduced the relative risk for stroke by 62%, compared with consuming <1 serving per month.[52] Conflicting results were seen in two studies relating vitamin C levels and the incidence of stroke.[53] In the other arm of the Heart Outcomes Prevention Trial (HOPE), 9,541 patients, ≥55 years old with coronary heart disease, stroke, peripheral vascular disease, or diabetes mellitus and one other risk factor, received (in a 2 x 2 factorial design) either vitamin E or placebo.[54] There was no benefit from vitamin E intake on the composite outcome of MI, stroke or vascular death. In summary, consumption of fruits and vegetables, whole grains, and omega-3 fatty acids in the form of fish reduces the risk of stroke. There is conflicting evidence regarding vitamin C, possibly due to differences in methods of measurement or differences in study populations. There is no evidence that vitamin E prevents stroke.

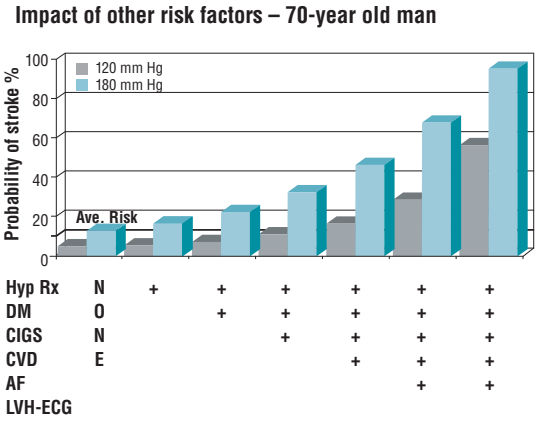
Alcohol consumption in moderation

The relationship of alcohol consumption to stroke is complex. The risk of intracerebral and subarachnoid hemorrhage rises with increasing consumption, yet there is a protective effect for ischemic stroke with moderate consumption.[55] The Physicians Health Study followed 22,071 male physicians, aged 40-84 for a mean of 12.2 years. Physicians consuming 2-4 drinks per week at entry had a RR of stroke of 0.75 (95% CI, 0.58-0.96) compared to non-drinkers, after adjustment for other stroke risk factors.[56] Those consuming 1 drink per week, 5-6 per week and >1 per day also had lower relative risks compared to non-drinkers, but the difference was not significant. Although moderate alcohol consumption may be protective against ischemic stroke and myocardial infarction, few would recommend that non-drinkers take up the habit.

Identification of high-risk candidates for stroke prevention

Each physician can identify those patients at increased risk of stroke. Persons with higher than the optimal blood pressure of ≤120/≤80 mm Hg, and particularly those with blood pressure levels indicating mild hypertension or greater (≥140 mm Hg systolic and ≥90 mm Hg diastolic) are at definite increased

Figure 1: Probability of stroke in 10 years at two systolic BP levels



risk of stroke and need attention. High-risk individuals have benefited substantially from the addition of ACE inhibitors. Cigarette smoking cessation, weight reduction in obese patients, and a program of moderate physical activity may be generally recommended. A diet rich in fish, fruits, vegetables and grains, as well as vitamin supplementation with folic acid, vitamin B_6 and B_{12} will help reduce stroke risk. Clearly, reduction of elevated total and LDL-cholesterol with statins, although most of the evidence is based on trials using pravastatin, should be considered for stroke-prone patients, even patients with average blood lipids. but particularly those with prior coronary heart disease.

Probability of stroke may be quantitatively determined using a profile such as the Framingham stroke risk profile.[57,58] Using medical history and physical examination findings (and the EKG), probability of stroke in 10 years may be computed using a point system based on: age; systolic blood pressure level; antihypertensive therapy use; presence of diabetes; cigarette smoking; history of cardiovascular disease (CHD or CHF); and EKG abnormalities (LVH or AF). Risk of stroke in ten years may then be compared to risk of an average man or woman of the same age (Figure 1). This *quantitative* assessment of risk is particularly helpful in guiding the patient, and the physician, in determining how vigorously to reduce stroke risk factors, particularly in the patient with multiple, borderline, risk factor abnormalities.

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