Risk Factors for Stroke

Philip A. Wolf

Boston University School of Medicine, Boston, Massachusetts, USA

Stroke is the third leading cause of death in the United States and the major cause of adult neurological disability. In 1991, approximately 500,000 Americans had a stroke and more than 142,000 died from stroke. In that year, there were more than 3,000,000 stroke survivors in the United States (1). Stroke mortality varies widely in different countries around the world, and these differences provide evidence that environmental influences are important in the development of stroke. Among 33 industrial countries, the United States has one of the lowest stroke death rates while Eastern European countries and Portugal have among the highest rates. Other indicators supporting the importance of environmental influences in stroke incidence or mortality include: geographic variation in stroke deaths; variability according to specific geographic regions; variation in rates by sex and race; and changes in stroke occurrence over time. Death rates for stroke in the United States have declined steadily since 1915. This decline has been consistent in that it has occurred in all age groups, in both races and sexes, and in all regions. The rate of decline before 1968 averaged 1% per year. This was before the advent of modern medicine—effective antihypertensive agents did not become available until the 1960s—and many believe the decline in stroke mortality mirrored the decline in death rates generally. The evidence strongly supports a link to improved hygiene, nutrition, and public health rather than to improved medical care. From 1972 to 1992 in the United States, the pace of decline of mortality from stroke accelerated, falling more than 5% per year or 60% in two decades. Similar declines have also occurred in most other westernized industrial nations. Although the mechanism for this decline in death rates is not entirely clear, recent data suggest it is due largely to a decrease in stroke severity, although a declining stroke incidence has occurred in some populations.

Data on all strokes, not only the fatal cases cited on death certificates, are available from the prospective epidemiologic study of general populations such as in Framingham, Massachusetts. These data were collected systematically over 36 years of follow-up of more than 5,000 men and women, aged 30 to 62 years, who were free of cardiovascular disease at entry to the study in 1950. After 36 years of follow-up in the Framingham Study, there were 693 cases of stroke and transient ischaemic attacks. The average annual incidence of all strokes combined increased with age and doubled in successive decades. In contrast to myocardial infarction, the incidence
of brain infarction was nearly equal in men and women and the two-decade lag in the incidence of myocardial infarction in women is not seen for brain infarction. Furthermore, incidence of brain infarction was only 30% greater in men than in women, in contrast to the four-fold increased incidence of myocardial infarction.

During the past 25 years, several key risk factors for stroke have been identified. However, because the pathologic processes underlying the various stroke types differ, it is not surprising that risk factors for infarction may differ from risk factors for hemorrhage. Furthermore, precursors of intraparenchymatous bleeding need not be identical to those for subarachnoid hemorrhage. There is also reason to believe that risk factors for stroke due to atherosclerosis of the carotid and vertebral arteries may differ in their impact when compared to lacunar stroke resulting from disease of the deep penetrating arteries. It is likely that the risk factor profile for embolic stroke will also be different. For this reason, study of stroke requires identification of specific stroke subtypes, a difficult and laborious enterprise requiring expert neurological evaluation of each patient at the time of stroke and the availability of properly timed brain imaging studies. Nevertheless, certain predisposing factors, particularly raised blood pressure, have been found to be common to most stroke types.

Whereas innovations in medical and surgical treatments to reduce the damage from stroke offer promise, it seems likely that prevention will continue to be the most effective strategy in reducing the impact of cerebrovascular disease. To achieve this requires the relative impact of stroke risk factors to be determined. Furthermore, evidence that modification of these risk factors will reduce stroke incidence must come from clinical trials which have demonstrated the effectiveness of control of a number of these risk factors. This topic has been the subject of recent comprehensive reviews (2,3).

It is clear that hypertension is the major risk factor for stroke. Risk rises as level of blood pressure rises at all ages in men and women, and in whites and blacks. Elevations of systolic blood pressure are important; in the elderly, in whom diastolic hypertension is far less common, isolated systolic hypertension (a blood pressure level of ≥160 mm Hg systolic and ≤95 mm Hg diastolic) is associated with a doubling of stroke incidence. Recently, even isolated borderline systolic hypertension (a blood pressure level of 140–159 mm Hg systolic and ≤90 mm Hg diastolic) has been related to a 50% increase in stroke risk. Control of diastolic hypertension in middle and advanced age has incontrovertibly been shown to reduce stroke incidence. The Systolic Hypertension in the Elderly Program showed that reduction of raised systolic blood pressure in persons above the age of 65 reduced fatal and nonfatal stroke by nearly 50% with no penalty in depression, dementia, falls, or fractures.

Cigarette smoking increases stroke risk and smoking cessation is followed within 1 year or 2 by a substantial reduction in the risk. Risk continues to fall for several years, and stroke incidence in lapsed smokers reaches the level of persons who have never smoked in 4 or 5 years. This beneficial effect of smoking cessation has no clear upper age limit, leading to the slogan, "It's never too late to quit."
Diabetics have been known to be at increased stroke risk, with the level of risk rising with the severity of the diabetes. Recent clinical trials have shown that tight control of blood glucose levels among insulin-dependent diabetics is associated with reduced occurrence of retinopathy and neuropathy. This suggests the other adverse vascular consequences also may be reduced with better control of the blood glucose (4).

During the past 5 years, evidence has emerged that implicates diet, vitamins, and other personal life habits in stroke risk. To focus on nutritional factors contributing to stroke—the subject of this symposium—it is useful to begin with a review of the data concerning intracerebral hemorrhage and malnutrition in post-World War II Japan. A surprising but consistent finding was the strong relationship between low total serum cholesterol and the increased incidence of intracerebral hemorrhage initially noted in Japan in the 1950s. Those Japanese, particularly in rural areas, had very low serum cholesterol concentrations by western standards, i.e. <160 mg/dl, and also had a markedly increased incidence of intracerebral hemorrhage. Initially, no cause and effect relationship was seriously considered. However, it has become clear that as nutrient intake of fat, particularly animal fat, has increased and sodium chloride intake has fallen, there has been a corresponding increase in total serum cholesterol (5). For example, among men and women age 40 to 49 years, total serum cholesterol levels rose from 155 mg/dl in 1963–1966 to 175 mg/dl in 1972–1975 and to 181 mg/dl in 1980–1983. Total serum protein levels and relative weight rose significantly during these 20 years, while systolic and diastolic blood pressures declined. Accompanying these profound changes in risk-factor levels were similar remarkable declines in the incidence of intracerebral hemorrhage, which fell by 65% in men ($p < 0.05$) and by 94% in women ($p < 0.001$) between 1964–1968 and 1979–1983 (5).

This relationship between nutrient intake, total serum cholesterol, and intracerebral hemorrhage incidence is not unique to Japan. Studies in Hawaiian Japanese and in Caucasian American men confirmed the link between total serum cholesterol and intracerebral hemorrhage. In the United States, the Multiple Risk Factor Intervention Trial (MRFIT) of 350,977 male screenees aged 35 to 57 years at screening and followed for 6 years for mortality yielded 83 fatal intracerebral hemorrhages and 55 deaths from subarachnoid hemorrhage. In the lowest serum cholesterol category, <160 mg/dl, the risk factor adjusted relative risk of intracranial hemorrhage was considered to be 1.0; relative risk at all higher levels of serum cholesterol was lower, at approximately 0.32. When deaths from intracranial hemorrhage were examined by entry blood pressure, the age-adjusted rates were significant only in those screenees with low cholesterol whose diastolic pressure was >90 mm Hg. Death rates per 10,000 were 23.07 in the lowest serum cholesterol category, <160 mg/dl, and ranged from 3.09 to 4.83 per 10,000 in the four highest categories. The interaction of high diastolic blood pressure and low serum cholesterol in promoting intracerebral hemorrhage suggested to some investigators that extremely low serum cholesterol levels weakened the endothelium of intracerebral arteries with resultant hemorrhage in the presence of hypertension.
However, cholesterol is not a definite risk factor for ischemic stroke, although the MRFIT data suggest that it may be. Recent findings from the Honolulu Heart Study in Japanese men living in Hawaii, supports a long-term influence of raised total serum cholesterol on thromboembolic stroke but not a short-term effect. No such findings were noted in Framingham nor in a large scale meta-analysis of 45 prospective observational cohorts involving 450,000 individuals with 5 to 30 years of follow-up (6). In addition, there was no significant or substantial reduction in total stroke incidence (odds ratio 0.98, 95% confidence interval 0.80 to 1.19) in a meta-analysis of eight cholesterol reduction trials (7).

More promising are findings from research relating low levels of dietary and plasma vitamins to raised plasma homocyst(e)ine levels. Plasma homocysteine levels in stroke patients were found to be increased compared with controls (8,9). In the sole prospective study, however, in U.S. male physicians, a small but nonsignificant association was found. The study did not rule out either no association or a moderate increase in risk, because the number of subjects was small and the subjects were at low risk of stroke by virtue of age and low risk-factor levels (10). Persons within the uppermost quartile of plasma homocysteine (≥14.4 mmol/l) had an odds ratio of 2.0 of ≥25% internal carotid artery stenosis when compared with persons in the lowest quartile (≤9.1 mmol/l) after adjustment for sex, age, plasma high density lipoprotein cholesterol concentration, systolic blood pressure, and smoking status ($p < 0.001$ for trend) (11). Plasma concentrations of folate and pyridoxal-5'-phosphate (the coenzyme form of vitamin B-6) and the level of folate intake were inversely associated with carotid artery stenosis after adjustment for age, sex, and other risk factors. In a follow-up of the First National Health and Nutrition Examination Survey (NHANES I), a plasma concentration of folate of ≤9.2 mmol/l was associated with an increased risk of ischemic stroke which was significant in blacks, who had a relative risk of 3.60 (95% CI 1.02 to 12.71) but not in whites (12). Recently, intake of fruits and vegetables has been related to reduced stroke incidence in men in Framingham (13) and in women in the Nurses Health Study (14).

Increased incidence of brain hemorrhage has been related to increased alcohol consumption and a higher rate of ischemic stroke is seen in nondrinkers. This U-shaped curve relating alcohol intake to stroke occurrence suggests that mild or moderate alcohol consumption may exert a protective effect on ischemic stroke. Such a beneficial effect has been demonstrated for myocardial infarction. Some have suggested that wine, particularly red wine, exerts a more protective effect when compared with other alcohol-containing beverages such as beer, fortified wines, or spirits. Balancing the reduction of ischemic stroke and heart disease incidence afforded by moderate alcohol consumption against the hazards of brain hemorrhage and the multitude of other adverse social and health effects of alcohol remains to be done.

Relating the intake of sodium, potassium and calcium to blood pressure and stroke risk has been addressed by other participants of this symposium in animal models and in vivo. This is clearly an area where diet has been related to stroke risk.

There are certainly other established risk factors for stroke. These include family
RISK FACTORS

history, physical activity level, blood components such as fibrinogen and the presence of other cardiovascular diseases. Cardiac conditions such as coronary heart disease, congestive heart failure, increased left ventricular mass, left atrial abnormalities such as increased left atrial size and mitral annular calcification, and particularly nonvalvular atrial fibrillation have been shown to make major independent contributions to increased stroke risk. Discussion of these cardiac contributors to stroke is beyond the scope of this chapter but has been dealt with elsewhere (2,15,16).

The investigation of the relationship of nutrient intake and diet to the incidence of stroke has been accelerating in recent years. It seems likely that consumption of certain foodstuffs, beverages, minerals, and vitamins will prove to provide protection from stroke. Epidemiologic studies should continue to provide the hypotheses for controlled clinical trials to demonstrate the effectiveness of these interventions.

REFERENCES


DISCUSSION

Dr. Bogousslavsky: I have a general question about the problem that we have with stroke epidemiology in Europe which is, if you look at the incidences reported from country to
country, there are variations of up to 50 times. For instance, if we take the yearly mortality in Swiss women, it is about 25 per 100,000, while if you look at the other extreme, in Bulgarian men, it is close to 1%. Do you think this is only a methodological problem?

Dr. Wolf: I think that people who complete death certificates for stroke and who analyze them are usually not neurologists and certainly often not people who are very interested in the specific disease, so I think some of it is methodological. We have done a study in which we compared cases known to us with what the death certificate showed and we found about a 20% error, increasing with advancing age. In other words, about 20% of patients whose death was certified as due to stroke did not have a stroke. There is great deal of variability and I suspect some of it has to do with modes of coding. For many years in the United States, if you coded stroke with hypertension, the coding algorithm gave you a diagnosis of cerebral hemorrhage. But I think there is probably also substantial variation in stroke incidence between countries; there is certainly a big difference in overall mortality between Bulgaria and Switzerland and some of this may be accounted for by stroke.

Dr. Ganten: I wonder whether the problems with the predictive value of the risk factors which you have discussed might result from the fact that all these risk factors are a mixed bag of pathological entities. I wonder if it is possible to subclassify, say, types of hypertension or types of diabetes and then relate this subclassification to risk, and whether you then get a clearer picture. I am especially thinking about genetics and in some of these areas there is a genetic basis on which you could base a subclassification.

Dr. Wolf: Most of the people who were diabetic were noninsulin-dependent diabetics because of the nature of our cohort (these were adults in 1950). I am not familiar with any large study. I think everyone's clinical impression is that insulin-dependent diabetics get a terrible increase in rate of stroke and clinical trials have shown that. With our noninsulin-dependent diabetics, we had a great deal of difficulty with the classification because it was not a randomized trial. Some people would be put on oral antidiabetic drugs, others not, and so on. But your point is well taken. When you say types of hypertensives, are you talking about renin levels?

Dr. Ganten: The obvious subtypes would be the converting enzyme polymorphisms. Everyone looks at these but they are rather disappointing. There are other types, however.

Dr. Wolf: We are working with a number of people to try to sort this out. It is obviously a very promising area. We have extended families—children and parents—and we have DNA on most of them. We are looking at the relationships within families—hypertensive families, hypercholesterolemic families, and so forth.

Dr. Richardson: You mentioned the indications that the incidence of stroke is increasing in the West. Does this parallel the increases in overweight and obesity? And second, I am surprised that in the assessment of the probability of risk, there were no points assigned to either overweight or indeed to level of physical activity. Is that going to be added in?

Dr. Wolf: Physical activity certainly should be. Our difficulty is that this model was based on measures that were made generally every 2 years and we, therefore, have only periodic assessments of physical activity. We are trying to incorporate that. With physical activity, it seems important to specify whether it is assessed early on or later in life. Physical activity at certain point may be predictive for, say, 10 years, but if you were very active when you were 20 and then you ceased activity completely, then when you get to 70, that earlier activity does not seem to be of any confirmed benefit as far as risk of stroke or prevention of stroke is concerned. So far as obesity is concerned, when you take into account the other risk factors that are associated with obesity such as hypercholesterolemia, high blood sugar, high blood pressure, and so on, there seems to be very little residual impact on stroke for obesity. It may
be that the pattern of obesity rather than the other type of obesity is more closely associated, but obesity per se does not seem to contribute much. That is not to say it is not important: if you tell someone who is obese to lose weight, you will reduce the risk of stroke, and that will probably be mediated by alterations in these other risk factors.

Dr. Guesry: You show the importance of reducing hypertension in reducing the risk of stroke but I wonder if this reduction in hypertension was induced by drugs alone or also by diet and lifestyle, and if so, what weighting those measures have. If it was done only with drugs, is there any difference between the different types of drugs used? One could imagine that drugs acting only on the cardiac pump, with no action on the rigid and narrowed arteries, might have a negative rather than a positive effect.

Dr. Wolf: One of the points that I should have made but didn’t was that the impact that was seen in these clinical trials was understated. By the end of the trial, a substantial proportion of the people in the treatment group weren’t taking their medicine and weren’t controlled, while a substantial proportion of people in the untreated (placebo) group were in fact being treated and controlled because their pressure exceeded a certain level, so the remarkable reduction in risk was even greater than it appears at first sight. The reduction on blood pressure was generally achieved with diuretics, followed by hydralazine and β blockers. The modern antihypertensives were in the main not used in this trial.

Dr. Crozier: In relation to your data showing that cholesterol had no effect on stroke, did you discriminate between the types of stroke, that is, thrombotic or hemorrhagic?

Dr. Wolf: Those data were on brain infarction, so those are patients without hemorrhage and who don’t have embolic infarcts; they are ischemic nonembolic strokes, though the data go back to the 1950s and 1960s and, therefore, precede CT and NMR scanning. However, on clinical grounds, the strokes were in general not hemorrhagic or cardioembolic. We were surprised at the lack of correlation with cholesterol because we thought there should be an impact. Clearly, there is a relation between coronary disease and stroke and cardiovascular disease generally, and that is undoubtedly related inversely to HDL and positively to LDL and total cholesterol. However, the stroke mechanism does not seem to be related.

Dr. Pertuiset: Do you have data on the sleep apnea syndrome as a risk factor for stroke?

Dr. Wolf: We don’t, but we will. There is a study in the United States called the Sleep Health Heart Study in which people who are reported to snore are being monitored at home, with a control group, to see how much desaturation they get and how much sleep apnea occurs. From cross-sectional studies, there appears to be a relation to level of blood pressure and other cardiac risk factors.

Dr. Kornhuber: I would like your comments on the change of severity of stroke. Do you really believe that the changing pattern in risk factors is changing the severity of stroke, or is it rather the improved treatment of stroke with intensive care and better medication that is changing the outcome? When I was looking at stroke data in Ulm and computed a severity index for all patients and an index for the risk factors, I did not find any correlation between the risk factors and severity.

Dr. Wolf: There are certain things that are clear. Stroke mortality has fallen, the prevalence of intracerebral hemorrhage has fallen but, in most populations, we are unable to find a decline in the incidence of stroke. In Göteborg, Framingham, and many other studies, there seems to be a reduction in the severity of stroke, that is, the percentage of people unconscious at the time they reach the emergency room and measures of deficit at the time of stroke, seem to be less. This may be due to a shift to smaller vessel disease or less severe stroke and there is certainly less intracerebral hemorrhage. The other thing is that it is possible that many of the strokes that we diagnose today would have gone undiagnosed in the past and might not
have been called strokes. There are many different possible factors here. In a population as a whole, you can look at blood pressure levels and at how many people are on antihypertensive agents, and even if their pressure is not controlled, their mean blood pressure is probably lower than it would be if they were not treated, and this may have some impact on stroke.

**Dr. Boing:** You showed your profile and your predictions for risk reduction. Do you have any possibility of testing this hypothesis? In other words, is it really true that when you advise people to do something, they actually reduce their risk?

**Dr. Wolf:** The risk reduction projections were based on data from clinical trials. We do not have that information. As far as the risk profile is concerned, a medical student from Copenhagen spent time with us and then went back and used the projections on the Copenhagen stroke study and they worked quite well. There were some baseline differences but other than that, the slopes were quite similar for the predictions in Copenhagen and in Framingham.

**Dr. Feller:** Is there also a relation between age and severity of the stroke?

**Dr. Wolf:** Not that I know of. There is a relation between case fatality rate and age.

**Dr. Feller:** I ask because it seems to me that there is a discrepancy between the expanding aging population—especially the over 85s, the fastest growing segment of the population—and the decrease in the rate of the stroke.

**Dr. Wolf:** If one looks at stroke death rates, they are falling for all age groups in both blacks and whites and both sexes, so if you look at any particular age group, the rates have fallen. When you make an age adjustment, which essentially makes the population a similar age, you also see that the rates are falling. Now the total number of deaths in the United States from stroke fell for many years despite the growth of an increasingly elderly population, but in 1991, that stopped at about 147,000 and now, it is up to 150,000 or 152,000, so the increasing numbers of elderly are starting to account for an increasing number of strokes. I think the death rates also stopped falling somewhere around 1990 or 1991. The rates obviously cannot keep falling indefinitely; the curve must become asymptotic, which it seems to have done now in United States. That is not to say there is no effort at stroke prevention; the population smokes, doesn't take any antihypertensives, is overweight, and eats terribly. There is a lot of room for improvement.

**Dr. Yamori:** I would like to comment on the importance of nutrition in the pathogenesis and prevention of stroke. You showed a rapid decline of the mortality rate of stroke in the United States, and we have had a similar experience in Japan. In 1970, the mortality rate from stroke was the highest in the world in Japan. We have analyzed the factors contributing to the rapid reduction in stroke mortality in Japan and found that a general improvement in nutrition, in particular, relating to moderate increases in protein intake and cholesterol levels, is correlated with the reduction in stroke. So I think improved nutrition is really effective in preventing small vessel disease and the major risk for small vessel disease is hypertension. I think in Framingham study, the pathological nature of the stroke is different in the early stage and the later stage.