Risk Factors in Stroke Due to Cerebral Infarction

A STATEMENT FOR PHYSICIANS PREPARED BY A SUBCOMMITTEE AND APPROVED BY THE EXECUTIVE COMMITTEE OF THE COUNCIL ON CEREBROVASCULAR DISEASE OF THE AMERICAN HEART ASSOCIATION

CHAIRMAN OF THE SUBCOMMITTEE: WILLIAM B. KANNEL, M.D.,
MEMBERS: F. WILLIAM BLAISDELL, M.D., RAY GIFFORD, M.D.,
WILLIAM MESS, M.D., FLETCHER MCDOWELL, M.D., JOHN S. MEYER, M.D.,
CLARK H. MILLIKAN, M.D., LEWIS E. RENTZ, D.O.,
AND RAYMOND SELTSER, M.D.

Introductory Comment
In 1968 the Council on Cerebrovascular Disease of the American Heart Association authorized the appointment of a subcommittee to produce a statement concerning "risk factors for Stroke." After working for over a year the Subcommittee reported that, because of inadequate data concerning "all or several of the factors," they had been unable to produce a statement satisfactory to each Subcommittee member. Some were reluctant to set down a policy statement until every loophole was plugged—a task made extraordinarily difficult by the complexity of Stroke and the fact that prospective studies of large population groups are necessary for the acquisition of some needed data. Another problem was that of interpreting the phrase risk factors. Does this phrase imply that eliminating or minimizing a "risk factor" (for example, maintaining a successful control of hypertension) automatically reduces the risk of Stroke for that individual? This therapeutic consideration may await an answer for years, although it must be admitted that the term "risk factors for Stroke" does suggest that careful treatment of one or several risk factors can help to prevent Stroke. In any event, the Subcommittee was admonished by its chairman, Dr. William Kannel, to consider the task a never-ending one; that data are now available indicating that certain phenomena are more commonly followed by Stroke and that these phenomena (culprits) should be publicly identified as elements or risk factors for Stroke. The Subcommittee decided to work first with the profile of the candidate at risk of a cerebral infarction—and so state. The Subcommittee realistically writes: "Any statement arrived at will be subject to periodic revision as more information is accumulated!" Obviously, new data may make changes necessary! Under Dr. Kannel's talented and dedicated leadership the Subcommittee produced the statement which follows.

vascular diseases of the brain are now the third leading cause of death in the U.S.A. and account for a major amount of disability. About 50% of victims of strokes due to cerebral infarction remain permanently handi-
capped. Rehabilitation and treatment of cerebral infarction once it has occurred are obviously less rewarding than attempts at prevention.

Cerebral infarction associated with occlusive cerebrovascular atherothrombosis comprises more than 60% of strokes. The statement which follows concerns the profile of the candidate at risk of a cerebral infarction. However, the precursors of cerebral embolus of cardiac origin, intracerebral hemorrhage, and subarachnoid hemorrhage, and other less common varieties of stroke, also deserve attention and will be dealt with elsewhere.

There is reason to believe that cerebral infarction is not an inevitable accident of nature, as the term “vascular accident” implies, but rather the end result of the evolution of a chain of events set in motion for some decades before the episode strikes. Epidemiological investigations of the manner in which strokes arise and evolve in general population samples have begun to identify highly susceptible persons and the factors which predispose, providing estimates of the risk associated with each factor singly and in combination. In effect, a portrait of the prime candidate for a cerebral infarction is slowly emerging.

Risk factors for cerebral infarction are not yet as well delineated as for coronary heart disease. Any statement arrived at will be subject to periodic revision as more information is accumulated. While certain factors are positively related to the chance of suffering an ischemic stroke, proof of efficacy of the control of these risk factors may be years away.

Ingredients of the Profile of Stroke-Proneness
1. Transient ischemic attacks; previous cerebral infarction
2. Hypertension
3. Cardiac abnormalities:
   ECG abnormalities—left ventricular hypertrophy
   myocardial infarction
   cardiac dysrhythmias—particularly atrial fibrillation
   Cardiac enlargement on x-ray—particularly if accompanied by ECG-LVH
   Congestive heart failure
4. Clinical evidence of atherosclerosis:
   angina
   myocardial infarction
   intermittent claudication
   arterial bruises—especially carotid absent pulses
5. Diabetes mellitus—any evidence of impaired glucose tolerance
6. Elevated blood lipids—cholesterol, beta lipoprotein and possibly endogenous triglyceride and pre-beta lipoprotein

Risk of a cerebral infarct mounts precipitously the more of these stroke precursors present. Other less well-documented possible risk factors in thrombotic stroke include:
1. The cigarette habit
2. Erythrocytosis—high hematocrit
3. Gout—hyperuricemia

Guidelines for Estimating Risk from Elements of the Stroke Profile

Transient Ischemic Attacks
Persons with temporary, reversible focal neurological deficits of less than 24 hours’ duration appear to be at high risk of completed strokes, and at least one-third can be expected to have a lethal or incapacitating stroke within five years. Some common transient complaints in such persons are: (1) sudden loss of vision in one eye with complete recovery in several minutes; (2) sudden weakness, paresthesia or sensory loss in an arm and leg with recovery after several minutes to 24 hours; (3) intermittent difficulty in speech or written communication; (4) intermittent severe ataxia; (5) episodic double vision; and (6) episodic dimness or bilateral loss of vision with gradual recovery over several minutes to a half hour.

Occasional correctable precipitating causes may include: cardiac dysrhythmias, transitory hypotension, hypoglycemia, polycythemia, transitory shunts (subclavian steal), kinking and external compression of vessels, and severe anemia. More common causes, possibly surgically correctable or amenable to medical therapy, are emboli from proximal atherosclerotic lesions and extracranial vascular insufficiency. The critical hemodynamic factor responsible for transient ischemic attacks in some patients remains uncertain and the mechanisms of vasospasm, hypotension and especially microemboli in persons with atherothrombotic stenotic vessels have all been
RISK FACTORS IN STROKE

evoked. The last is currently the pathogenic mechanism best supported by clinical and experimental evidence. There is some evidence from therapeutic trials to suggest that anticoagulant therapy can relieve transient cerebral ischemic symptoms and, more importantly, may reduce the risk of completed strokes. Evidence for the latter is still inconclusive.

There is recent evidence from a Joint Study of Extracranial Arterial Occlusion that in transient ischemic attacks without neurological residual, surgical management of selected patients reduces the frequency of transient attacks, and may lessen the likelihood in surgical survivors of a completed ischemic stroke on the operated side.

HYPERTENSION

In addition to possible acceleration of atherogenesis in the large cerebral vessels, hypertension may precipitate some cerebral infarctions by segmental derangement of small internal capsule or pontine arteries, or by producing impaired cardiac function. It is the commonest, most potent risk factor to emerge from prospective epidemiological investigation of stroke. Even modest degrees of hypertension, as indicated by casual blood pressure determination, at all ages, in either sex, are associated with a substantial increase of cerebral infarction. When accompanied by evidence of cardiac impairments such as ECG-LVH or congestive heart failure, the ischemic stroke risk from hypertension becomes ominously enhanced.

Since the hypertensive state is for decades an asymptomatic condition, it should be sought out periodically and placed under management well in advance of target organ involvement.

Moderate hypertension also carries a substantial risk of coronary heart disease, peripheral vascular disease, and congestive failure. The advisability of lowering blood pressure in patients with cerebrovascular disease or those prone to it has long been debated, but there is evidence accumulating to demonstrate that the benefits outweigh the possible hazards. Also, prudent control of severe hypertension may actually improve cerebral blood flow. A more aggressive approach to prophylaxis against ischemic stroke involving particularly early control of hypertension and often associated cardiac impairment would appear indicated if a substantial reduction in incidence of cerebral infarction is to be achieved. Awaiting the appearance of overt evidence of impaired cardiac function and fixed diastolic hypertension and other target organ involvement before intervening in persons with elevated pressures would appear unjustified.

CARDIAC IMPAIRMENTS

One possible mechanism by which hypertension may precipitate cerebral infarction is by causing impairment of cardiac function. Also, development of cardiac impairment from whatever cause in the hypertensive subject further enhances risk of thrombotic strokes. Persons with congestive failure have about a threefold increased risk. ECG evidence of left ventricular hypertrophy is associated with a threefold increase in risk after accounting for associated hypertension and other causes of ECG-LVH. When the ECG abnormality appears, the hypertensive subject has nine times the average risk of cerebral infarction. Cardiac enlargement on x-ray is associated with a tripling of risk and doubles the risk of hypertension alone. Those that go on to cerebral infarction generally develop ECG evidence of LVH. ECG evidence of coronary heart disease is associated with almost a fivefold increase in risk.

Atrial fibrillation is associated with a substantial increase of cerebral infarction incidence even when hypertension is taken into account and associated cardiac impairments excluded. While the presumption that these are embolic from the heart is difficult to refute, the possibility that many of these cerebral infarctions are related to occlusive arterial disease must be entertained.

OTHER MANIFESTATIONS OF ATHEROSCLEROSIS

While the tendency to lay down atheromata in the arterial intima is a general one, sites of predilection depend upon local factors such as dynamics of flow, caliber of vessels, the integrity of the intima, the metabolism of the vessel wall, and fibrin deposition among others. Atherosclerosis seems to proceed at a slower pace in cerebral vessels than in the coronaries. However, because of shared precursors, persons with one manifestation of atherosclerosis will, on the average, have more atherothrombotic brain infarctions than those without. Persons with coronary heart disease share atherogenic traits and hypertension with potential stroke
IMPAIRED GLUCOSE TOLERANCE

Diabetics have been demonstrated to have both large and small vessel disease, to have multiple lipid abnormalities and an increased propensity to hypertension. It is consequently not surprising that impaired glucose tolerance has been observed in ischemic stroke victims and potential candidates for cerebral infarction. Even modest impairment of carbohydrate tolerance has been found to be associated with an increased risk of brain infarction, and the combination of hypertension and impaired glucose tolerance is ominous. Perhaps owing to preoccupation solely with the blood sugar values, there is little significant evidence to suggest that the late vascular complications of diabetes are reduced by stringent control. More attention to the lipid disorders and particularly the associated hypertension may improve this outlook.

BLOOD LIPID ABNORMALITIES

Risk of cerebral infarction is less clearly related to antecedent blood lipid values than is coronary heart disease. Except for precocious cerebral infarction, evidence that the incidence is proportional to blood lipids is weak. However, even in coronary heart disease where the relationship is strong, the association becomes attenuated with advancing age. There is evidence that blood lipids (cholesterol and triglyceride-rich pre-beta lipoprotein) measured prior to age 50 are related to stroke incidence, the risk varying widely in proportion to the associated blood pressure.5

LIVING HABITS

A number of living habits have been incriminated in the etiology of cerebral infarction although the evidence is still inadequate to substantiate most claims. Among those implicated are the cigarette habit, sedentary living, diet, and habits leading to obesity.

Cigarette Smoking

A number of prospective epidemiological studies have demonstrated an excess of ischemic strokes among cigarette smokers, particularly in men.2 Whatever the relation between cigarette smoking and cerebral infarction, there are other ample reasons for advising people to give up the habit including lung cancer, emphysema and coronary prevention.

Obesity

Whether primarily a consequence of sloth or gluttony, overweight usually results from faulty living habits. An association between obesity and cerebral infarction has not been established. However, because obesity is often associated with hypertension, impaired glucose tolerance and lipid abnormalities, and weight reduction is often associated with some improvement in these abnormalities, it seems wise to advocate maintenance of lean body weight and correction of obesity.

Sedentary Living

Few prospective studies have convincingly implicated lack of physical activity in development of cerebral infarction. The evidence is far from conclusive and recommendations in this regard can be made only in the interest of coronary prevention and maintenance of lean body weight and general physical fitness.

Diet

There is a strong suspicion and ample experimental and international epidemiological evidence to incriminate faulty diet in lipid abnormalities and atherogenesis. However, there is still no prospective epidemiological information to directly link constituents of the diet to the incidence of stroke. It seems reasonable at present to advocate in overweight persons a reduction in calorie intake. More normal plasma lipid values may be achieved by reduction in intake of saturated fat, cholesterol and refined carbohydrate. In some hypertensive subjects it may be wise to achieve a reduced salt intake.

HIGH HEMATOCRIT AND OTHER HEMATOLOGICAL DISORDERS

When there is underlying arterial disease, relative polycythemia not infrequently is associated with cerebral infarction presumably because of increased blood viscosity, and a tendency to clot formation. There is some evidence to suggest that patients with hemoglobin values in the upper end of the normal distribution may be at higher risk than those with more normal values.9

Other hematological disorders which carry a somewhat increased risk include: hemoglobinopathies, thrombocytopenia, hemophilia.
RISK FACTORS IN STROKE

and hypoprothrombinemia. These, however, are unusual causes of cerebral infarction.

GOUT AND HYPERURICEMIA

These are often associated with hypertension, abnormal lipids and overweight. On this account it would be expected that such persons would manifest precocious atherosclerosis, as has in fact been claimed. Persons with gout should be examined for the associated findings and, when present, these as well as the gout should be treated in the hope of reducing the incidence of possible vascular sequelae.

MISCELLANEOUS FACTORS

Included in this omnibus category is the possible relation of focal cerebral ischemia to the use of oral contraceptives. While the evidence is feeble and far from conclusive, impaired glucose tolerance, lipid abnormalities, hypertension and increased venous thrombotic tendency have been noted to occur in some women, the long-term consequences of which are unknown but which could result in accelerated atherogenesis and vascular occlusions. Certainly women with a history of thromboembolic disease, with transient ischemic, retinal or cerebral attacks, and with migraine, hypertension, diabetes, or any of the above stigmata predisposing to stroke should be advised to use alternative contraceptive methods.

Injudicious use of hypotensive, hypoglycemic and anesthetic agents may provoke focal cerebral ischemia in susceptible persons.

Summary

Each of the following risk factors is accompanied by more than a doubling of the risk of a cerebral infarction, and when they occur in combination the risk is further compounded: (1) hypertension of 160/95 mm Hg or greater; (2) serum cholesterol values exceeding 250 mg % or a pre-beta band on electrophoresis (in persons under age 50 only); (3) cardiac enlargement on x-ray; (4) electrocardiographic left ventricular hypertrophy; (5) evidence of coronary heart disease; (6) congestive heart failure and/or dysrhythmia; and (7) impaired glucose tolerance—two-hour postprandial blood sugar more than 160 mg % or fasting or casual blood sugar more than 120 mg %.

Dogmatic statements concerning risk factors in ischemic stroke are premature. Field trials to demonstrate the efficacy of preventive measures which appear rational are urgently needed. There is no assurance that adherence to any recommended prophylactic regimen will in fact prevent cerebral infarction in the aged. However, two concrete facts seem well founded at present. Hypertension is the most potent factor thus far identified in stroke, and the key to prevention of stroke would appear to be the early detection and control of hypertension. Also, the presence of cardiac impairment greatly adds to the increased risk in hypertensive subjects and would provide additional indication for vigorous management of hypertension and would indicate early use of cardiac glycosides.

The long-term observation for prevention of cerebral infarction should also include repeated evaluation of the vascular system for bruises about the head and neck, differences in pressure and pulse in the upper extremities and neck, and the several enumerated risk factors. This will thus entail periodic determinations of blood pressure, blood lipids, glucose tolerance, blood hemoglobin, an electrocardiogram, chest x-ray, and clinical evaluation for congestive failure. Because of the higher frequency of cerebral infarction in certain segments of the population—nonwhites and those with a strong family history of hypertension, diabetes, lipid disorders and strokes—such periodic assessments should be carried out in them at more frequent intervals and they should receive higher priority.

It must be emphasized that in the long run primary prevention, including attention to associated cardiovascular disease and hypertension, is the only hope for achieving a substantial reduction in the incidence of ischemic stroke. It is the often-associated cardiovascular disease rather than the cerebral infarction which accounts for most of the shortening of the life span in these patients. While surgery may lessen the likelihood of a stroke in those with transient ischemic attacks and extracranial vascular disease—a far from trivial benefit—it will not necessarily lengthen life. Cerebral infarction is part of a larger problem of cardiac and vascular disease including hypertensive cardiovascular disease, congestive heart failure and coronary heart disease. Attention to the precursors of these is indicated in the prophylaxis against stroke due to cerebral infarction.
References

7. U. S. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. JAMA 213: 1143-1152 (Aug 17) 1970

Reprints of this article may be obtained from your local Heart Association. Ask for Educational Material No. 551.
Risk Factors in Stroke Due to Cerebral Infarction
WILLIAM B. KANNEL, F. WILLIAM BLAISDELL, RAY GIFFORD, WILLIAM HASS, FLETCHER McDOWELL, JOHN S. MEYER, CLARK H. MILLIKAN, LEWIS E. RENTZ and RAYMOND SELTSE

Stroke. 1971;2:423-428
doi: 10.1161/01.STR.2.5.423

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1971 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/2/5/423

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at: http://stroke.ahajournals.org//subscriptions/