The Veterans Administration Cooperative Study on Antihypertensive Agents. Implications for Stroke Prevention

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Hypertension and atherosclerosis are the leading causes of stroke. The risk of stroke is directly related to the height of the blood pressure.

The Veterans Administration Cooperative Study included 523 male patients. If the results of two subgroups (115 to 129 mm Hg and 90 to 114 mm Hg initial diastolic) are combined, the total incidence of stroke was 25 in the control group and six in the treated group.

In addition to widespread lack of awareness of the medical profession of the benefits of treatment, there also is a failure of detection of hypertension in large segments of our population. There is need for greater professional as well as public education concerning hypertension.

Additional Key Words: cerebrovascular disease, hypertension, epidemiology study, atherosclerosis, risk factors

Hypertension and atherosclerosis are the leading causes of stroke. Hypertension is particularly important in hemorrhagic stroke, which is more apt to result in fatality or permanent disability and also is the more frequent type of stroke seen in young and middle-aged adults. Hypertension causes cerebral vascular microaneurysms and it also aggravates and accelerates atherosclerotic changes in the larger cerebral arteries.

The risk of stroke is directly related to the height of the blood pressure. For example, the Framingham data indicate that the incidence of stroke in men age 45 to 54 years was 10/100,000 with a systolic blood pressure of 110 to 119 mm Hg and 37/100,000 with a systolic blood pressure of 160 to 169 mm Hg. With respect to diastolic blood pressure, the incidence rose from 17/100,000 with a diastolic blood pressure of 80 to 84 mm Hg to 29/100,000 at a diastolic level of 100 to 104 mm Hg. In women of similar age the difference was even greater, the incidence of stroke being three times greater in the group with the higher diastolic level.

The above epidemiological and pathological observations raise the reasonable possibility that stroke in hypertension is the direct result of the elevated blood pressure, since a direct relationship between level of blood pressure and incidence of stroke strongly suggests a causal relationship. The formation of microaneurysms and the high incidence of cerebral hemorrhage in hypertension are most directly explained by postulating that they are the consequence of a higher than normal blood pressure. The aggravation of atherosclerosis could well be the result of abnormal stresses and resultant damage to the arterial walls and to disturbed blood flow resulting from the high blood pressure. If these assumptions are correct, then reduction of blood pressure should have a beneficial effect in the prevention of stroke.

The first prospective controlled therapeutic trial was carried out by Hamilton. He administered guanethidine (plus thiazides if needed) to patients with no prior cardiovascular complications but with diastolic blood pressures in the range of 110 to 130 mm Hg. There were 61 patients in the study, 22 males and 39 females. During a five-year follow-up period, four of the untreated male patients developed strokes as compared to none in the treated group. In the female patients three of the untreated patients and three of the treated group had strokes. However, of the latter group, strokes developed only in the patients whose diastolic blood pressures were not reduced below 100 mm Hg, whereas none of the female patients whose blood pressures were lowered below this level developed a stroke.

The Veterans Administration Cooperative Study included 523 male patients with initial diastolic blood pressures of 90 through 129 mm Hg (average of two posthospitalization outpatient visits prior to randomization). Patients were randomly assigned double-blind to either active drugs consisting of hydrochlorothiazide plus reserpine plus hydralazine or to placebos of these agents. In the subgroup of 143 patients with initial diastolic blood pressures of 115...
through 129 mm Hg, the study was terminated after an average follow-up of 18 months because of the high incidence of major hypertensive complications of all types occurring in the placebo group. With respect to stroke, in the 70 placebo patients there was one patient who had a cerebral hemorrhage, three who had a cerebral thrombosis, and one who had recurring transient ischemic attacks. In the 73 treated patients only one had a cerebral thrombosis.

The remaining 380 patients with initial diastolic blood pressures averaging between 90 and 114 mm Hg were followed after randomization for an average period of 3.3 years and some were followed for more than five years. There were 19 cardiovascular deaths in the control group and eight in the treated group. In the control group, seven of the deaths were due to stroke, four to cerebral or subarachnoid hemorrhage, and three to thrombotic stroke. In the treated group there were no deaths due to hemorrhagic stroke and only one due to cerebral thrombosis.

The total incidence of stroke both fatal and nonfatal was 20 patients in the placebo group and five in the treated group, a ratio of 4 to 1. If only severely incapacitating or fatal stroke is included there were 12 such patients in the control group and only one in the treated series.

If the results of the two subgroups (115 to 129 and 90 to 114 mm Hg initial diastolic) are combined, the total incidence of stroke was 25 in the control group and six in the treated series. These results along with those of Hamilton leave little doubt that effective long-term control of hypertension markedly reduces the incidence of stroke in hypertensive patients, particularly with respect to hemorrhagic stroke. It will be noted that there were no instances of cerebral or subarachnoid hemorrhage in the treated patients and only one fatality which was associated with a cerebral thrombosis.

It would be expected that the results of these well-controlled therapeutic trials demonstrating the value of effective antihypertensive drug treatment in the prevention of stroke would be widely recognized and immediately applied by the medical profession. The available evidence, however, indicates the opposite. A recent survey by Schoenberger of the employees of large downtown banks in Chicago indicated that only 11% of the hypertensive patients found in the survey were receiving effective antihypertensive treatment. Yet, this survey was carried out after the results of Hamilton’s study and the Veterans Administration Cooperative trial had been published.

In addition to widespread lack of awareness of the medical profession of the benefits of treatment, there also is a failure of detection of hypertension in large segments of our population. In the same survey Schoenberger found that more than 40% of the individuals found to be hypertensive had no prior knowledge of their disease. Since hypertension is asymptomatic prior to appearance of cardiovascular complications, patients may go for many years without a medical examination. Furthermore, blood pressure may not be recorded routinely in patients who present themselves in doctors’ offices or dispensaries for minor illnesses.

These considerations emphasize the need for greater professional as well as public education with respect to hypertension, particularly with respect to the preventable nature of most of its complications including stroke. In addition, a more systematic effort needs to be made to screen all adults in the country periodically for the presence of hypertension. Hypertension presents a real challenge in the prevention of stroke. It will require the collaboration of the profession as well as public and private health agencies if the challenge is to be met successfully.

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