Despite major progress in treatment and prevention, stroke remains the leading cause of disability and the third leading cause of death, surpassed only by heart disease and cancer, in the United States. An estimated 500,000 to 600,000 first and 100,000 recurrent strokes occur each year, and ≈160,000 of these are fatal. Among stroke survivors, the burden of long-term disability is great. In the Framingham Heart Study, 71% had impairments that affected their ability to work in their previous capacity and 31% needed help in caring for themselves. Stroke rates in women increase sharply with age, doubling in each successive decade after the age of 55 years. Stroke incidence is substantially lower in younger women than in age-matched men, but it tends to equalize in the two sexes in the postmenopausal years. Thus, stroke is a major health problem for postmenopausal women and one that merits aggressive preventive strategies.

A number of preventive strategies have been proven effective in reducing the risk of stroke. A review of 14 prospective, randomized, controlled trials demonstrated a 42% risk reduction for stroke when the diastolic blood pressure was reduced by 5 to 6 mm Hg, and the Systolic Hypertension in the Elderly Program (SHEP) study showed that treating isolated systolic hypertension in the elderly reduced stroke by 36%. Similarly, pharmacological intervention with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin agents), aspirin, and warfarin in patients with decreased left ventricular function or evidence of left ventricular thrombi after myocardial infarction has proven effective in stroke prevention. Oral anticoagulation and antiplatelet therapy also reduce the risk of stroke in patients with atrial fibrillation, and carotid endarterectomy is effective in preventing stroke in persons with asymptomatic carotid stenosis with 60% to 99% occlusion. Lifestyle modifications, including smoking cessation, moderation of alcohol consumption, and increased physical activity, can also reduce the risk of stroke.

The question of whether hormone replacement therapy (HRT) is useful in preventing stroke and other forms of cardiovascular disease has been asked in a number of observational studies, and the answers have been inconsistent. In a national sample of postmenopausal women, Finucane and colleagues found a relative risk of 0.69 for stroke incidence and 0.37 for stroke mortality in HRT users after adjustment for risk factors. Similarly, in a prospective study of 8891 postmenopausal retirement community residents, a relative risk of 0.63 for mortality due to cerebrovascular disease was observed among estrogen users. Further observational support for a protective role of HRT in stroke prevention came from a study of 23,000 Swedish women in whom the relative risk for stroke was 0.79 in women using unopposed estrogen formulations and 0.61 in those using combination therapy with progestins. Other observational studies failed to demonstrate a benefit for HRT in stroke prevention. Grodstein and colleagues examined the relation between cardiovascular disease and HRT in 59,000 women enrolled in the Nurse’s Health Study, and they found no significant difference in stroke incidence between users of combined hormones or estrogen alone and nonusers. Likewise, they found no significant difference in mortality due to stroke between HRT users and nonusers. Folsom and colleagues also found stroke mortality rates were similar, regardless of HRT, in 40,000 postmenopausal women who were followed for 6 years as part of the Iowa Women’s Health Study. In contrast, these large, prospective, observational studies found that HRT use was associated with marked reductions in the incidence of coronary heart disease (CHD). In this issue of Circulation, Simon and colleagues report the results of the first randomized, controlled, clinical trial to examine the effects of postmenopausal HRT on stroke and transient ischemic attack, the Heart and Estrogen Replacement Study (HERS). Stroke and transient ischemic attack were prespecified secondary outcomes of HERS, which was a secondary CHD prevention study performed in postmenopausal women. The results of this study provide no evidence that postmenopausal HRT has a significant effect on stroke risk in postmenopausal women with CHD.

The HERS trial randomized a total of 2763 women with CHD to receive 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or placebo daily, in addition to usual CHD treatments. The mean age of the participants was 66.7 years. Hypertension was present in 68% of participants at baseline, and 13% were current smokers. Eighty-eight percent were white, 23% had diabetes, and 79%...
were using aspirin.13,14 Risk factor profiles and cardiovascular drug treatment regimens were similar in HRT and placebo groups.

In their analysis of the HERS data, Simon et al13 found 165 strokes in 149 participants during the course of the study. The strokes were ischemic in 85% of the cases, hemorrhagic in 8%, and unclassified in 6%. Seventy-nine women experienced transient ischemic attacks. There was no significant difference in the risk of stroke or transient ischemic attack between women receiving HRT and those receiving placebo. HRT had no discernible effect on the risk of fatal versus nonfatal stroke or on the risk of hemorrhagic versus ischemic stroke. Likewise, there was no association with the risk for all combined cerebrovascular events. In contrast to the original HERS report, which found a significant time trend toward benefit of HRT on CHD events after an early period of excessive CHD and venous thromboembolic events, Simon et al13 found no relation between the use of HRT and cerebrovascular events over time.13

Are these findings that HRT did not prevent stroke in the HERS trial cohort surprising? These results are surprising when one considers the well-documented vasoprotective role of estrogen. HRT regimens that include estrogens produce favorable effects on serum lipid concentrations, coagulation and fibrinolytic systems, antioxidant systems, and the production of vasoactive molecules such as nitric oxide and prostaglandins.15 Furthermore, animal studies have demonstrated a neuroprotective role for estrogen in models of cerebral ischemia. In a rat model of cerebral infarction, Simpkins and colleagues16 found a reduction in infarct size accompanied by mortality reduction in ovariecctomized rats pretreated with estrogen compared with untreated ovariecctomized controls. Other investigators have noted a neuroprotective effect of estrogen administered after a cerebral ischemic insult.17 Postulated mechanisms of these neuroprotective effects include inhibiting the excitatory amino acid propagation of ischemic damage (eg, glutamate), reducing the oxidative damage associated with ischemia and reperfusion, inducing the expression of neurotrophic growth factors, enhancing vasodilatation, and recruiting collateral circulation during cerebral artery occlusion. Both α and β types of estrogen receptors, which are thought to mediate many of the vascular effects of the hormone, are present in the brain.18 All of these mechanisms are supported by evidence from in vitro experiments and animal studies of estrogen effects on cerebral ischemia.18,19 The HERS trial and the analysis by Simon et al13 did not attempt to determine whether HRT modulated the course of established stroke or improved stroke outcomes. HERS was neither designed nor powered to assess recovery or functional status in women who experienced stroke while in the trial. Thus, it is not possible to assess a potential neuroprotective role of HRT in established stroke using the HERS database.

However, the failure of HRT to prevent stroke in the HERS cohort is not surprising considering the complex pathophysiology of stroke, a heterogeneous clinical syndrome with multiple etiologies, risk factors, and pathophysiological mechanisms. Three principal causes of stroke are ischemia, intracranial hemorrhage, and subarachnoid hemorrhage. Ischemic disease, which accounted for the vast majority (85%) of strokes in HERS, can be due to emboli, large vessel atherosclerotic disease, or small vessel disease leading to lacunar infarcts.1 HRT is not known to have a favorable effect on arterial thromboembolic events, although some hormone preparations, including those administered in HERS, reduce plasminogen activator inhibitor and fibrinogen levels and inhibit platelet activation and, thus, would be expected to protect against thrombus formation.20

The effects of HRT on atheromatous disease are complex and apparently contradictory. Despite the beneficial effects on cardiovascular disease risk factors such as dyslipidemia and fibrinogen levels, on endothelial function, and on lesion development in animal models of vascular injury and atherosclerosis, HRT has been shown to be ineffective in slowing the progression of coronary atherosclerosis and in preventing coronary events in women with established disease.21 Whether the failure of hormones to protect the diseased vessel is related to the reduced expression of estrogen receptors in atherosclerotic arteries,22 to proinflammatory effects that offset their cardioprotective actions,23,24 or to other factors remains to be determined.

Lacunar infarcts, which may account for a large proportion of strokes, are related to small vessel disease in the brain. Hypertension is a major risk factor in the pathogenesis of this form of vascular disease and the single most important modifiable risk factor for ischemic stroke.1 Uncontrolled hypertension (blood pressure > 160 mm Hg systolic or > 95 mm Hg diastolic) is associated with a 4-fold increase in stroke risk. A history of hypertension was present in 68% of HERS participants, and it was associated with a 67% increased risk of stroke, independent of other risk factors, in Simon et al’s analysis.13 Data on the quality of blood pressure control in the HERS cohort during the course of the trial are not available, and the effects of HRT on blood pressure were not assessed in HERS. Published data indicate that the HRT preparation used in HERS has a neutral effect on blood pressure in apparently healthy normotensive postmenopausal women.20 The effects of this and other hormone preparations on blood pressure in hypertensive postmenopausal women, in the presence or absence of concomitant antihypertensive therapy, have not been extensively studied, but available data suggest that no rise in blood pressure occurs in hypertensive women using HRT.25 Thus, it is unlikely that HRT had either a beneficial or deleterious effect on lacunar stroke in the HERS cohort.

On balance, the finding that HRT was not protective against stroke in a cohort of elderly (average age, 67 years) women who were many years postmenopausal and had established CHD is not surprising. Conventional HRT clearly has limitations in the secondary prevention of vascular disease and cardiovascular disease events. However, as suggested by observational studies, these limitations may not apply to its use in younger, presumably healthy women for the primary prevention of cardiovascular disease. We await the results of primary prevention trials such as the Women’s Health Initiative to answer this question.26 Further, HRT is an important intervention for many postmenopausal women who can benefit from its effects on menopausal symptoms, bone
metabolism, and other noncardiovascular conditions. The findings of HERS should not discourage the use of HRT in the primary prevention of cardiovascular disease; rather, they should stimulate future study of the effects of hormones and nonhormonal therapy on the biology of blood vessels and the pathogenesis of vascular disease, including disease of the cerebral vasculature.

References


Key Words: Editorials ■ stroke ■ hormones
Hormone Replacement Therapy and Stroke: Are the Results Surprising?
Todd Tolbert and Suzanne Oparil

Circulation. 2001;103:620-622
doi: 10.1161/01.CIR.103.5.620

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