Hormone Replacement Therapy and Stroke
Clinical Trials Review

Lawrence M. Brass, MD

Abstract—Bench research suggests that postmenopausal hormonal therapy is associated with beneficial effects on the brain and vascular system. Observational data suggest that postmenopausal hormone replacement therapy is associated with a 25% to 50% lower rate of cardiovascular disease; however, observational data for hormonal therapy is associated with the potential for significant biases. Clinical trial data are needed. There are 3 major clinical trials that inform us about stroke and postmenopausal hormone replacement therapy. Two trials focused on secondary prevention: the Heart and Estrogen/progesterone Replacement Study (HERS) and the Women’s Estrogen for Stroke Trial (WEST). One examined primary prevention: the Women’s Health Initiative (WHI). All indicate that postmenopausal hormone therapy is not effective for reducing the risk of a recurrent stroke or death among women with established vascular disease or for prevention of a first stroke. Similar results exist for cardiovascular disease. The results of these trials are now reflected in national guidelines. Hormone therapy should not be initiated to prevent vascular disease among postmenopausal women. As a result of these trials, the portion of postmenopausal women using hormone replacement therapy in the United States has fallen by more than half over the past decade. (Stroke. 2004;35[suppl 1]:2644-2647.)

Key Words: clinical trials ■ estrogen ■ hormone replacement therapy ■ prevention ■ stroke

Stroke in Women
Stroke in women is a major public health problem. The incidence of stroke is strongly age-dependent.1 In most age groups, the incidence of stroke is slightly higher in men than in women; however, women tend to live longer than men. This more than compensates for the difference in incidence, and more women have strokes each year than men. Overall, ≈55% of strokes occur in women, and women account for nearly 60% of all stroke-related deaths.

Women appear to be protected from heart disease and stroke before menopause. This is thought to be because of the protective effects of ovarian hormones, and this effect could provide clues on new paradigms to prevent stroke and ischemic vascular disease.2

Hormone Replacement Therapy is Not the Same as Oral Contraceptives
This presentation focuses on postmenopausal hormone therapy. Oral contraceptive medications are not the same as postmenopausal hormone therapy. With hormone replacement therapy, a woman is in a hypoestrogenemic state. The goal is to return to euestrogenemia. With oral contraceptive medication, the goal is to suppress physiological functions among women with normal ovarian function.

Current users of oral contraceptives may be at slightly increased risk for ischemic stroke; however, with newer, low-dose oral contraceptives the absolute increase in risk, if one exists, is very small.3,4

Estrogen’s Vascular Effects
Estrogen has diverse actions throughout the body. Many of these would appear to be beneficial for stroke prevention and recovery after stroke.2,5–9 These include vasodilatation and improved vascular reactivity, angiogenic effects, antithrombotic effects, beneficial effects on lipids, and enhanced neurogenesis and axonal sprouting after injury.

Estrogen as a Therapy for Stroke: Observational Studies
The idea of using estrogen as a stroke therapy is based on 5 major lines of evidence.2 First, the bench research cited above. Second, the observation that ischemic stroke caused by atherosclerosis is uncommon in women before menopause; this is thought to be because of the protective effects of ovarian hormones. Third, animal data suggest that hormone replacement therapy may have beneficial effects for prevention of vascular disease. Fourth, human studies document beneficial effects in risk factors. Last, the majority of epidemiological studies of cardiac disease suggest that women who use hormone replacement therapy have 25% to 50% lower rates of cardiovascular disease. The epidemiologic data looking at hormone replacement and stroke are less clear.
than for cardiovascular disease. Fewer studies exist, and they are conflicting.

In spite of great enthusiasm for hormone replacement therapy based on the observational (epidemiologic) data, it was recognized that there was the potential for significant bias.\textsuperscript{10} In the United States, women who use hormone replacement therapy are more likely to go to their doctor, to know their risk factors, and to take medications. In addition, hormone replacement users are more likely to be better educated, and of higher socioeconomic status. All of these are associated with lower rates of stroke. Accounting for these effects can be difficult in epidemiologic studies.\textsuperscript{11,12} There was a need for clinical trial data to address the question.

There are 3 major clinical trials that inform us about stroke and postmenopausal hormone replacement therapy. Two trial focus on secondary prevention: the Heart and Estrogen/ progesterone Replacement Study (HERS) and the Women’s Estrogen for Stroke Trial (WEST). One examined primary prevention: the Women’s Health Initiative (WHI).

**Heart and Estrogen/Progesterone Replacement Study**
The HERS looked at hormone replacement therapy after myocardial infarction among postmenopausal women. There were 2763 women randomized to either equine estrogens and a progestin (medroxyprogesterone) or placebo and followed for up to 5 years (mean 4.1 years). There was no net reduction in the primary endpoint of nonfatal or coronary heart disease death.\textsuperscript{13} Although there was no overall benefit, there was evidence for a significant temporal trend within those randomized to hormone therapy. There were more events early (within the first year) and fewer in years 4 and 5. It was suggested that this result could indicate that women who were already on treatment might be beyond an initial period of danger (ie, could continue therapy). This promising trend was not found in subsequent studies.

In the HERS, there was no benefit of the equine estrogens and a progestin for stroke. In a subsequent report focused on stroke, hormone therapy was not associated with the risk of nonfatal stroke, fatal stroke, or transient ischemic attacks.\textsuperscript{14}

**Women’s Estrogen for Stroke Trial**
The WEST looked at hormone replacement therapy after ischemic stroke and transient ischemic attacks (TIA) among postmenopausal women.\textsuperscript{15} There were 664 women randomized to either 17β-estradiol (the most abundant human estrogen in women) or placebo. The use of a progestin was minimized because the WEST trialists’ interpretation of the literature was that there was little evidence for a vascular projective effect of progestins. The majority of data suggesting an effect suggested a deleterious one.\textsuperscript{16}

The goal in designing the WEST was to find the hormone regimen with the greatest chance of having an effect in preventing recurrent vascular events. The recurrent ischemic events (nonfatal and fatal) following stroke far outnumber even the most pessimistic estimates of potential hormone-induced cancers. For women without a uterus, unopposed estrogen was used. For those with an intact uterus, estrogen therapy was opposed annually with progesterone.

Women were followed for up to 4 years. The mean follow-up was 2.8 years. The primary endpoint was stroke and death. Secondary endpoints included transient ischemic attacks and nonfatal myocardial infarction.

There was no net benefit for the primary endpoint. In a secondary analysis, there was an increased risk of stroke-related death (which included fatal stroke or death within 30 days of a stroke). Based on this result and the results of the HERS, a post hoc analysis was performed. In the WEST, as with the HERS, there was evidence for an increased early risk among those randomized to hormone replacement therapy. During the first 6 months following randomization, there were 3 fatal strokes and 18 nonfatal strokes in the group randomized to estradiol, compared with 1 fatal stroke and 8 nonfatal strokes in the placebo group (relative risk, 2.3; 95% CI, 1.1 to 5.0).

There was also evidence that women randomized to estradiol had more severe (recurrent) strokes. Among those with recurrent (nonfatal) strokes, complete or near complete recovery (as defined by a National Institutes of Health Stroke Scale score of 0 or 1) was half as likely to occur among those randomized to estrogen therapy compared to placebo (19% versus 33%, P=0.12).

**Women’s Health Initiative**
The first report of results from the WHI was for the group of women with an intact uterus.\textsuperscript{17} In this primary prevention trial there were 16,608 healthy postmenopausal women, aged 50 to 79 years. Only 7.7% reported prior cardiovascular disease. In these women, combination therapy (conjugated equine estrogen and medroxyprogesterone) was used as the active treatment. The hypothesis was that hormone replacement therapy would reduce the risk of ischemic vascular events (benefit) and this effect would be greater than a potential increase in cancer (risk). The primary outcome was coronary heart disease (nonfatal myocardial infarction and coronary heart disease death). Invasive breast cancer was the primary adverse outcome. A global index was used to help better assess the balance between risk and benefit. It included the 2 primary outcomes along with stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death (not because of coronary heart disease).

The trial was stopped early (after 5.2 years of follow-up) by the study’s data and safety monitoring board because invasive breast cancer exceeded the stopping boundary. In addition, ischemic events were increased (not decreased) among those women randomized to hormone replacement therapy. The global index also indicated a net adverse effect of hormonal therapy (of 19 per 10,000 person-years). There were beneficial effects seen (6 fewer colorectal cancers and 5 fewer hip fractures per 10,000 person-years); however, these were countered by an increase in other events (7 more coronary events, 8 more strokes, 8 more pulmonary emboli, and 8 more invasive breast cancers per 10,000 person-years).\textsuperscript{17}

The second report (published after the Princeton Conference presentation) was for women who had a hysterectomy. Among these women, estrogen alone (conjugated equine estrogen) was used as the active therapy. The results were
similar to the trial of estrogen plus progestin. The increased risk of stroke was 1.39 (95% CI, 1.10 to 1.77).18

What Does This Mean for Clinical Care?
These clinical trials did not demonstrate any beneficial effect of hormonal therapy for stroke prevention. If anything, there appears to be an adverse effect associated with postmenopausal hormone therapy although the absolute increase may be small. In the WHI, there was an absolute excess risk (in their global index) of 19 per 10 000 person-years.

These results are now reflected in national guidelines. Hormone therapy should not be initiated to prevent vascular disease among postmenopausal women.19,20 As a result of these trials, the portion of postmenopausal women using hormone replacement therapy in the United States has fallen by more than half over the past decade.21

Where Do We Go From Here?
Although some might argue that these trials set to rest the question of postmenopausal hormonal therapy for stroke prevention, I would not agree. Critically important questions remain. What happened in the clinical trials such as the HERS, the WEST, and the WHI? Why were the results of these clinical trials different than the observational studies and bench research, which strongly suggested beneficial effects of estrogen for vascular disease? Do women really have higher rates of vascular disease with hormone replacement therapy? If there is an increase in vascular events associated with postmenopausal hormone therapy, then why does this occur? If an increased risk does occur, can we selectively turn off or prevent the adverse effects of hormonal therapy and allow potentially beneficial effects to emerge? There are 2 broad approaches to address this last question. First, block the adverse effects of hormonal therapy. Second, selectively stimulate those estrogen receptors associated with desirable actions. There are also data suggesting these hypotheses should be explored.

For the first of these mechanisms (blocking adverse events), there is some evidence that adverse events of hormonal therapy can be blocked. In the HERS, the risk for venous thromboembolism was increased among those women randomized to active therapy. Among those randomized to hormonal therapy the rate of venous thromboembolism was 50% lower among women who reported using aspirin during the trial compared with those who did not.22 A similar protective effect was not seen for arterial events in the HERS; however, there was a trend for a reduction in myocardial infarction, stroke, or vascular death in the WEST among women randomized to estrogen therapy who were taking antiplatelet therapy at the time of randomization. These exploratory analyses suggest that more effective means of blocking the prothrombotic effects of hormonal therapy might allow a net beneficial to emerge.

A second approach is a more selective stimulation of estrogen receptors. Estrogens are pure agonists. Antiestrogens are antagonists. Selective estrogen receptor modulators (SERMs) can exert both agonist and antagonistic effects on different classes of estrogen receptors.23 Different classes of estrogen receptors are associated with different actions. This approach is already being used in the treatment of osteoporosis with selective estrogen receptor modulators such as raloxifene and tamoxifen.23,24 These agents have agonistic effects on bone, lipids, and some vascular risk factors, and they have estrogen antagonistic effects on the breast and uterus.25

In the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial, a study of women with osteoporosis, a subgroup analysis was done. Of the 7705 postmenopausal women included in the study, 1035 were classified as being at high risk for cardiovascular disease. There was a two thirds lower rate of stroke among those women classified as high risk for cardiovascular disease who were randomized to raloxifene compared with placebo. A similar reduction was seen for cardiovascular events.26 Additional information, specifically for vascular disease, will be forthcoming from the Raloxifene Use for The Heart (RUTH) Study,25,27 which was designed to determine whether raloxifene lowers the risk of coronary events and the risk of invasive breast cancer in women at risk for a major coronary event. Stroke is included as a secondary endpoint.

Summary
Postmenopausal hormone therapy is not effective for reducing the risk of a first stroke. Postmenopausal hormone therapy is not effective for reducing the risk of a recurrent stroke or death among women with established vascular disease.

Among women taking hormone replacement therapy, there may be an increased risk of fatal stroke. There may also be a more severe impairment following a recurrent stroke among women using hormone replacement therapy.

It may be possible to block the adverse effects of hormonal therapy on the vascular system and selectively stimulate those effects more likely to be of benefit for prevention of ischemic vascular disease.

There are appropriate indications for the use of postmenopausal hormone therapy. Stroke prevention is not one of them. The trials reviewed here also inform clinical care for those women who do use postmenopausal hormone therapy. The reported rates of stroke, myocardial infarction, and vascular death allow for a more realistic assessment of the risks and benefits of hormone therapy among postmenopausal women.

References
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