Aging women sustain a large burden for stroke, an observation frequently overlooked in our popularized view of cancer as the killer of women. Accordingly, potential benefits and hazards of hormone replacement therapy (HRT) are of increasing interest to female patients at risk for stroke and cerebrovascular disease. Estrogen has been particularly well studied in animal and cell injury models of cerebral ischemia with nearly uniform favorable results, i.e., cell salvage from ischemic death pathways. Nevertheless, our ability to translate these favorable data from the bench into positive clinical trials has been quite limited. Furthermore, recent data from large, randomized, clinical trials question the use of HRT for either the primary or secondary prevention of coronary heart disease and stroke. This review will evaluate experimental and clinical evidence for estrogen’s efficacy, or lack thereof, and mechanisms of action in cerebral ischemia and stroke.

**Estrogen Appears Strongly Neuroprotective in Stroke Models**

Animal studies clearly indicate that biologic sex and endogenous sex steroids influence experimental stroke outcome. Histological damage is less in female animals than in age-matched males after focal cerebral ischemia, and the source of this protection is linked to female reproductive steroids.1–3 Furthermore, emerging data suggest that molecular mechanisms of ischemic damage may not necessarily impact identically in male and female brains. For example, ischemic outcome in transgenic mouse strains can be sex-dependent, even when the deleted (or overexpressed) gene is not linked to reproduction.4

Estrogen has been widely shown to acutely protect brain from experimental stroke.5–8 These observations have been consistent across animal models, breeder source, and genetic strain, including strains with genetic hypertension or diabetes. Estrogen treatment to physiologically relevant plasma levels improves histological, physiological, and behavioral outcomes after transient middle cerebral artery occlusion, global forebrain ischemia, photothrombotic injury, and subarachnoid hemorrhage. Presumably estrogen treatment reduces injury in adult animals of both sexes and, somewhat more relevant to women’s health, in reproducitively senescent, middle-aged female rats. There is a paucity of data in higher-order animal species, and this is an important gap when extrapolating animal data to human disease.

Postinjury treatment has been less well studied; however, two recent reports show that estrogen therapy can work when instituted during injury progression. The therapeutic range for chronic estrogen appears narrow, with beneficial effects decreasing as dose and consequent plasma levels increase upwards within and beyond the physiological range. It is likely that careful dosing with monitoring of plasma levels provides a link to estrogen’s neuroprotective potential. It should also be noted that 17-β estradiol has been the most commonly studied agent, in part because it is the major biologically active estrogen in mammals. Furthermore, estrogen compounds have typically been studied in a controlled but isolated fashion, without inclusion of progesterone. The lack of data with combined HRT (widely prescribed for treatment of perimenopausal symptoms in women) is a second important gap in transitioning from the bench to the stroke unit.

**A Pleiotropic Hormone With Multiple Cellular and Molecular Mechanisms**

Estrogens act at multiple sites in injured brain and use diverse signaling processes.9–11 As a unifying hypothesis, it seems reasonable that the very breadth of estrogen’s actions in brain is beneficial because it is a multifunctional molecule and therefore a form of combination therapy. One of estrogen’s multiple protective mechanisms is the enhancement of postischemic cerebral reperfusion and limitation of vascular endothelial dysfunction. Neurons and glia are also targets (Table). Lastly, mechanisms that are not specific to cell type are likely important, because many estrogens have potent, concentration-dependent lipid antioxidant activity. Limited data address whether either subtype of estrogen receptor (ER-α and ER-β) is necessary to the hormone’s vasoprotective or neuroprotective properties.12–14 and this issue is under active investigation.

**Observational Studies of Hormone Replacement Therapy**

More than 30 epidemiological studies have reported a reduced risk of cardiovascular disease among postmenopausal women who use ERT.15 Typically, the risk of cardiovascular disease is reduced by 30% to 50%.16–19 However, observational studies have the potential for significant biases. In HRT studies, there may be susceptibility bias (ie, that estrogen is prescribed to, and used by, women who are more affluent, better educated, thinner, more likely to exercise, have better access to medical care, and...
more likely to be adherent to treatment regimens). Recent randomized, placebo-controlled clinical trials have addressed the issue of HRT effectiveness under conditions of restricted susceptibility bias.

### Secondary Prevention After Myocardial Infarction

The Heart and Estrogen-progestin Replacement Study (HERS) was the first prospective, double-blind, randomized, placebo-controlled trial of HRT in women with known coronary heart disease (CHD). The primary end points were new CHD events (myocardial infarction or CHD death). Women were randomized to receive either placebo or a daily hormone replacement therapy (0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate). Among postmenopausal women with CHD, HRT did not reduce risk of subsequent coronary events. Stroke, a secondary end point, was not reduced with HRT.

### Secondary Prevention After Stroke

The direct clinical data available to assess estrogen’s value in cerebrovascular disease are limited and conflicting. Postmenopausal estrogen use has been associated with increased and decreased risks and no net benefit for stroke prevention. The NIH-sponsored Women’s Estrogen for Stroke Trial (WEST) compared 17β-estradiol (1 mg/d) to placebo in postmenopausal women with a recent history of transient ischemic attack or ischemic stroke. The primary aim of the study was to determine whether unopposed estrogen therapy reduces risk of death or recurrent stroke in women enrolled within 90 days of transient ischemic attack or nondisabling stroke. In the WEST, estradiol replacement did not reduce risk of recurrent stroke or death (relative risk, 1.1 in the estradiol group; 95% CI, 0.8 to 1.4). Furthermore, those subjects randomized to estrogen therapy had a higher risk of fatal stroke relative to the placebo cohort (relative risk, 2.9; 95% CI, 0.9 to 9.0). Among women with recurrent stroke, there was a suggestion of a worse outcome. Complete or near complete recovery (as measured by NIH stroke scale of 0 or 1) was 19% in the estradiol treatment group compared with 33% in the placebo group (P=0.12).

### Primary Prevention of Vascular Disease

The Women’s Health Initiative (WHI) Randomized Controlled Trial was designed to define the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Interventions included placebo versus hormone replacement therapy, conjugated equine estrogens (0.625 mg/d) with medroxyprogesterone acetate (2.5 mg/d). A separate arm of the trial is ongoing that tests estrogen without progestin. The estrogen plus progestin arm of this

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**Known or Candidate Mechanisms for Estrogen’s Action in Experimental Stroke**

<table>
<thead>
<tr>
<th>Known or Candidate Mechanisms for Estrogen’s Action in Experimental Stroke</th>
<th>Experimental Conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most directly implicated protective mechanisms</td>
<td>MCA occlusion, rat</td>
<td>43, 44</td>
</tr>
<tr>
<td>Partially preserves intra-ischemic CBF</td>
<td>Global; rat, rabbit</td>
<td>45, 46</td>
</tr>
<tr>
<td>Improves postischemic reperfusion</td>
<td>MCA occlusion, rat</td>
<td>47</td>
</tr>
<tr>
<td>Reduces intravascular leukocyte adhesion</td>
<td>Global, rat</td>
<td>48, 49</td>
</tr>
<tr>
<td>Amplifies endothelial NO and/or cyclooxygenase signaling</td>
<td>Pial vessels in situ, isolated microvessels and MCA</td>
<td>50–52</td>
</tr>
<tr>
<td>Induces eNOS translocation and activation</td>
<td>Endothelial culture</td>
<td>53, 54</td>
</tr>
<tr>
<td>Increases microvascular cGMP</td>
<td>Isolated cerebral microvessels</td>
<td>55</td>
</tr>
<tr>
<td>Increases available bcl-2 and protective bcl-2 expression</td>
<td>MCA occlusion, rat</td>
<td>56, 57</td>
</tr>
<tr>
<td>Antioxidant activity</td>
<td>Not specific to cell type</td>
<td>58, 59</td>
</tr>
<tr>
<td>Preserves endogenous brain antioxidants</td>
<td>Global, gerbil; basal, rat</td>
<td>1, 6, 60</td>
</tr>
<tr>
<td>Preserves mitochondrial function; suppresses reactive oxygen species</td>
<td>PC12 cells; primary neurons, chick embryonic</td>
<td>61, 62</td>
</tr>
<tr>
<td>Blocks glutamate and kainate injury, by MAP kinase mechanisms</td>
<td>Hippocampal, cortical culture</td>
<td>63, 64</td>
</tr>
</tbody>
</table>

| Candidate protective mechanisms | Basal cortex, hippocampus; culture of same | 65–67 |
| Increases neurotrophic factors and increases receptor expression, eg, NGF, BDNF, bFGF | Astrocytes, astroglial culture, rat | 6 |
| Suppresses gial cytokine production and reduce reactive gliosis | Dopaminergic neurons, mouse, monkey; nigral culture | 68–70 |
| Anti-apoptotic action and maintains neuronal integrity | Hippocampal granule neurons | 71 |

| Potential toxic mechanisms in selected brain areas | Hypothalamic neurons, endorphinergic or PVN neurons of preoptic area; functional basis sex development and senescence | 72–74 |
| Pro-apoptotic action in adult brain; neuronal toxicity | CA1 pyramidal cells, rat | 75 |
| Increases NMDA-receptor mediated excitatory transmission; amplifies seizure-like activity at high concentrations | | |
clinical trial was recently stopped because of the observation of increased risk of CHD, the primary outcome (estimated HR 1.29 with 95% CI of 1.02 to 1.63), and increased risk for breast cancer, the primary adverse outcome (HR 1.26 with 95% CI of 1.00 to 1.59). In the WHI, stroke was a prespecified end point. Like CHD, stroke was increased among those receiving combined estrogen/progestin therapy (HR 1.41 with 95% CI of 1.07 to 1.85).

**Current Recommendations for HRT**

These trial data do not support the use of HRT for prevention of vascular disease. Use of estrogen therapy for prevention of nonvascular conditions (eg, osteoporosis or hip fracture) must be weighted against these data suggesting a potential for increased stroke or CHD risk. Additional studies are clearly needed to investigate why there are such dramatic differences between observational studies and randomized trials of HRT.

**Conclusions**

As the population ages, the optimal use of HRT is a question of increasing public health importance. Given the preponderance of stroke in postmenopausal women, the need for increased attention to beneficial treatments for this population is obvious. Many of estrogen’s properties could be beneficial in human vascular stroke, and these properties are being actively characterized in animal and relevant cell models. Key objectives are to understand how sex and native sex steroids impact stroke pathophysiology, to evaluate mechanisms by which novel estrogen-like pharmaceutical agents provide vasoprotection and neuroprotection, and to dissect undesirable effects of estrogen from its beneficial mechanisms of action. For example, estrogens can contribute to thromboembolism, particularly at moderate to high doses. HRT may increase some families of cytokines and C-reactive protein, and these mechanisms are critical in diseases with inflammatory etiologies, such as atherosclerosis. Anti-inflammatory statin therapy reduces C-reactive protein and reduces venous thromboembolism among women using HRT. Whether recurrent arterial ischemic events respond in patients using HRT in combination with statin therapy, aspirin therapy, or other anti-inflammatory agents warrants additional study. If the beneficial effects of estrogen can be harnessed, then estrogen replacement therapy may yet emerge as an important therapy for women at risk for stroke and cerebrovascular disease.

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**References**

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341

Hurn and Brass


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