Hormone replacement therapy (HRT) has long been a staple of management of the postmenopausal life phase. Over time, and after estrogen therapy was modified to include progestin, an increasing number of observational reports suggested that HRT conferred benefits well beyond those of managing or minimizing hot flashes, mood swings, and vaginal dryness. In short, HRT was believed to improve women’s health and even extend life. One of the most significant theorized benefits was protection against cardiovascular and cerebrovascular events. Other benefits—protection against osteoporosis, reduction in incontinence symptoms, and improved cognition—have also been linked with HRT. The validity of these theories depended largely on observational studies and anecdotal reports, and only lightly (or not at all) on randomized clinical trial data. Nevertheless, significant clinical data refuting HRT’s proposed benefits has been available for several years. Findings from these investigations, including new results from two very large trials, show that beyond managing traditional menopause symptoms, HRT has little or no role in protection against certain diseases or conditions associated with aging. Indeed, long-term use of HRT may be contraindicated in most older women with intact uteruses.


As women approach menopause, most of them grapple with the issue of whether to take hormone replacement therapy (HRT) to manage menopausal symptoms. Women are living an average of 30 years after menopause begins and during those subsequent decades are at risk for chronic medical conditions such as osteoporosis, coronary heart disease (CHD), cancer, and dementia. HRT was increasingly thought to be the treatment of choice for managing the symptoms of menopause, as well as preventing or delaying some of these chronic diseases.

Indeed, despite a dearth of randomized, clinical trial data supporting the health benefits of HRT, approximately 38% of postmenopausal American women use or have used it. Several large observational studies, including the Nurses’ Health Study, appeared to support the use of HRT for prevention of cardiovascular disease. Results of these observational studies, however, are potentially biased due to the differences in baseline characteristics of the women taking HRT compared with those who were not. Women taking HRT were better educated, had better access to medical care, led healthier lifestyles, and were more likely to use the prescribed medications appropriately, thereby creating the “healthy woman effect.” The difference in the studies’ outcomes could be attributed to the “healthy woman effect” rather than HRT.

Several recent randomized, controlled trials have refuted the role of HRT for cardiovascular disease prevention and have shown that it may raise a woman’s risk for a cardiovascular event and invasive breast cancer, particularly during the first few years of HRT use. Hormone replacement therapy’s efficacy for other chronic conditions, such as dementia, incontinence, and osteoporosis, has also faced similar challenges.

This article reviews the clinical trial data investigating use of HRT as prevention or protection against the development of cardiovascular and cerebrovascular disease, incontinence, osteoporosis, dementia, and depression; it also examines data regarding the association between HRT and quality of life. Overall, 150 studies—dating back 35 years—were reviewed.

**Coronary heart disease**

One factor that sparked the enthusiasm for HRT in recent years was the
belief that it offered possible cardio-
protection, a biologically plausible the-
ory. Randomized, controlled trials have 
shown that estrogen replacement ther-
apy lowers serum LDL cholesterol and 
raises serum HDL cholesterol—both 
of which decrease the risk of CHD—
but raises serum triglycerides. Estro-
gen also lowers serum lipoprotein(a) 
levels, improves endothelial vascular 
function, and reverses postmenopausal 
increases in fibrinogen and plasmino-
gen-activator inhibitor type 1. Despite 
these favorable effects on cardiovas-
cular risk factors, however, clinical tri-
als have failed to show a reduction in 
coronary events or deaths due to CHD 
in women using HRT.

Many observational studies, in-
cluding the Nurses’ Health Study, had 
suggested that estrogen replacement 
therapy decreased the risk of coronary 
events. This potential benefit, how-
ever, was never confirmed in clinical 
trials. The Heart and Estrogen/Pro-
estin Replacement Study (HERS) was 
a double-blind, placebo-controlled, 
randomized clinical trial designed to 
determine if estrogen plus progestin 
therapy would alter the risk for CHD 
events in postmenopausal women with 
established CHD. Overall, 2,763 
women (average age, 66.7) with CHD 
were followed for 4.1 years. The pri-
mary outcome was the occurrence of 
nonfatal MI or CHD death. No sig-
nificant between-group differences in 
primary outcomes were reported. The 
lack of effect occurred despite a net 
11% lower serum LDL cholesterol and 
a 10% higher serum HDL cholesterol 
level in the treatment group. There 
were 52% more CHD events in the 
treatment group in year 1 but fewer 
CHD events in the treatment group in 
years 3 and 4. More women in the 
treatment group suffered venous 
thromboembolic events and sympto-
matic gall bladder disease requiring 
intervention.

Results from the HERS II follow up 
showed that after 6.8 years, HRT did not 
reduce the risk of cardiovascular events 
in women with CHD. In this study, 
CHD death was insignificantly in-
creased in patients treated with hor-
mone therapy (hazard ratio=1.09). An-
other HERS II follow up reported that 
after 6.8 years, adjusted hazard esti-
mates (HE) in women with CHD treated 
with HRT were significantly increased for 
venous thromboembolism (HE=3.04), 
significantly increased for biliary tract 
surgery (HE=1.35), insignificantly in-
creased for total mortality (HE = 1.11), 
significantly increased for any cancer 
(HE=1.24), and insignificantly reduced 
for any fracture (HE=0.97).

Recent clinical trial data show that, beyond managing traditional menopausal 
symptoms, hormone replacement therapy (HRT) has little or no role in protection 
against diseases or conditions associated with aging.

Illustration for Geriatrics by Jeff Suntala/Phoenix Advertising Art, Inc.
Neither estrogen alone nor combination estrogen/progestin therapy have been found to slow the progression of coronary atherosclerosis (monitored by coronary angiogram) in women with established CHD. The Estrogen Replacement and Atherosclerosis (ERA) trial was a double-blind, placebo-controlled, randomized clinical trial, with 309 women (average age, 65.8; CHD verified by angiogram) randomized to receive estrogen, estrogen plus prog- estin, or placebo. Follow-up coronary angiography at 3.2 years showed no between-group differences in progression of coronary atherosclerosis.\textsuperscript{7}

**Incontinence symptoms improved in 26% of the placebo group; \textbf{20.9%} in the hormone group**

Randomized, controlled data about the role of estrogen plus progestin in the primary prevention of CHD were recently reported from the Women's Health Initiative (WHI) study.\textsuperscript{8} The WHI investigators reported that the estrogen plus progestin component of the study—16,608 postmenopausal women aged 50 to 79, with intact uteruses—was stopped after 5.2 years of follow-up. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more episodes of pulmonary embolism, and 8 more invasive breast cancers. Absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events in the global index was 19 per 10,000 person-years.\textsuperscript{8}

Results from the Multiple Outcomes of Raloxifene Evaluation (MORE) trial showed that raloxifene therapy for 4 years in postmenopausal osteoporotic women (mean age 67) significantly reduced the risk of cardiovascular events in a subset of study patients with increased cardiovascular risk.\textsuperscript{9} There was no evidence showing that raloxifene caused an early increase in risk of cardiovascular events.

Whether raloxifene affects the risk of cardiovascular events in postmenopausal women with established CHD or with multiple risk factors for acute CHD events is currently being studied prospectively in the Raloxifene Use for The Heart (RUTH) trial, which has enrolled 10,101 postmenopausal women; results, however, will not be available for several years.\textsuperscript{10}

**Cerebrovascular disease**

Some observational studies have suggested that estrogen replacement therapy may reduce a woman's risk for stroke and death from stroke although the evidence is less consistent than that for protection against CHD.\textsuperscript{11,12} The Women's Estrogen for Stroke Trial was a double-blind, randomized, placebo-controlled, multicenter trial of estrogen replacement for the secondary prevention of cerebrovascular events. The primary endpoint was death from any cause or nonfatal stroke. The study included 664 women (average age, 71) who were followed for 2.8 years. Estrogen therapy did not reduce the risk of death or nonfatal stroke. Compared with those taking placebo, women assigned to estrogen therapy were 2.9 times more likely to die from stroke, and nonfatal strokes were associated with slightly worse neurological and functional deficits.\textsuperscript{13}

**Incontinence**

Estrogen is known to improve urethral mucosa, smooth muscle, and adrenergic tone. It is commonly prescribed both systemically and locally to treat postmenopausal urinary incontinence. Of the 1,525 women who reported incontinence at least once per week at the start of the HERS trial, 768 were randomized to HRT and 757 to placebo.\textsuperscript{14} During 4.1 years of follow up, incontinence symptoms improved in 26% of the placebo group compared with 20.9% of the hormone group; 38.8% of women in the hormone group reported worsening of incontinence compared with 27% in the placebo group (p=0.01). The between-group differences were evident as early as 4 months into the study and persisted throughout its duration. The differences persisted even when analysis was restricted to change-in-severity of stress incontinence or urge incontinence episodes. The results were also similar in analyses restricted to subgroups of women with different levels of incontinence severity (eg, 1 to 7 or more incontinence episodes per week at baseline).

**Osteoporosis**

Estrogen inhibits postmenopausal bone loss. Many observational studies and randomized, controlled trials have suggested that estrogen preserves and increases bone mineral density (BMD) in postmenopausal women. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, 875 women (aged 45 to 64) were randomized to receive placebo, conjugated equine estrogen (CEE), three different combinations of CEE, and progesterone.\textsuperscript{15} After 3 years, women in the placebo group had lost 1.8% of total BMD at the spine and 1.7% at the hip, whereas those on active regimens gained BMD at both sites—from 3.5 to 5% at the spine and up to 1.7% at the hip.

Whether that benefit translates into reduced risk of fractures remains questionable because clinical trial data investigating this association are lacking. There are limited data from randomized, controlled trials using fractures as an endpoint. Two small randomized, placebo-controlled, clinical trials have examined the effect of estrogen replacement and HRT, respectively, on prevention of primary\textsuperscript{16} or secondary\textsuperscript{17} vertebral osteoporotic fractures. In the HERS\textsuperscript{4} and ERA\textsuperscript{7} trials, no significant differences were observed in fracture rates in the placebo and treatment groups. In the WHI study, women randomized to hormonal therapy had 5

20 Geriatrics August 2002 Volume 57, Number 8
fewer hip fractures per 10,000 person-years. Because of a lack of data documenting a decreased risk of fracture associated with its use, in 1999 the Food and Drug Administration rescinded the indication of estrogen therapy as a treatment for osteoporosis. Extensive data support the efficacy of bisphosphonates in prevention and treatment of postmenopausal osteoporosis. In the absence of upper GI contraindications in a cognitively intact person who can follow the instructions, bisphosphonates are positive choices.

Cognition
It has been hypothesized that postmenopausal HRT may prevent cognitive decline and dementia. In a systematic review of 9 randomized controlled trials and 8 cohort studies examining the role of estrogen and cognition, women with menopausal symptoms exhibited improvement in verbal memory, vigilance, reasoning, and motor speed but no enhancement of other cognitive functions. No benefits were observed in asymptomatic women.

No data support the role of estrogen for treatment of Alzheimer’s dementia. Evidence from neuropathologic studies, animal behavioral studies, and human investigations suggests that estrogen may be beneficial in improving cognition and mood in Alzheimer’s dementia (AD). In one trial, 120 women who had hysterec-
tomy, mild-to-moderate AD, and a Mini Mental Status Exam score between 12 and 20, were randomized to receive estrogen or placebo. After 1 year, 80% of women taking estrogen and 74% taking placebo exhibited worsening on the Clinical Global Impression of Change (CGIC) 7-point and Dementia Rating Scale scales.

Quality of life and depressive symptoms
There is widespread belief that postmenopausal HRT improves quality of life in women, yet few randomized clinical trials have investigated this theory. The HERS trial compared the effect of HRT versus placebo on quality-of-life parameters among study participants. During 3 years of follow-up, women who received HRT experienced greater declines in physical function and a trend toward increased symptoms of fatigue compared with women who received placebo; women on HRT did, however, experience an improvement in depressive symptoms. Women who had no vasomotor symptoms (84.3%) at baseline experienced greater declines in physical function and energy with HRT than those taking placebo; no changes were noted for mental health or depressive symptoms. Although baseline quality-of-life parameters were worse among 15.7% of women who reported vasomotor flushing, HRT in these women was associated with improvement in mental health and reduction in depressive symptoms without significant effects on physical function or energy level.

Risks associated with estrogen therapy
Long-term use of estrogen alone in women with intact uteruses increases the risk of endometrial hyperplasia and endometrial cancer 8 to 10 fold. The Estrogen Replacement and Atherosclerosis trial showed that 19% of study participants on estrogen alone developed simple hyperplasia and 26% developed complex hyperplasia compared with 0 to 5% in women on estrogen plus progestin.

Postmenopausal women taking estrogen are at significantly higher risk of thromboembolic events. For instance, HERS data showed that compared with those on placebo, more women in the hormone group experienced deep vein thrombosis and pulmonary emboli (34 versus 12; relative hazard ratio [RH], 2.89; 95% CI, 1.50-5.58). In the WHI study, 8 more episodes of pulmonary embolism per 10,000 person-years were attributable to estrogen plus progestin.

Observational studies also show that the incidence of symptomatic gallstones requiring cholecystectomy is increased in postmenopausal women taking estrogen. The HERS trial showed a significantly higher incidence of symptomatic gallbladder disease in the HRT group compared with placebo group. (84 versus 62; RH, 1.38; 95% CI, 1.00-1.92), with 89% requiring cholecystectomy.

Data from observational studies suggest that the risk of having breast cancer diagnosed is increased with long-term (>5 years) use of estrogen. This effect is reduced after cessation of estrogen and largely disappears after approximately 5 years.

Conclusion
Given the lack of evidence from randomized clinical trials regarding the positive effects of HRT on variables such as cardiovascular status, bone mineral density, and quality of life, its use should be discouraged as a means of preventing or minimizing certain diseases, conditions, or events that are common among postmenopausal women. Until new data show that modified dosing or refined HRT regimens can reduce the risk of cardio- and cerebrovascular events and fracture, reduce incontinence, and improve cognition and quality of life, HRT should be considered carefully, monitored closely, and maintained for shorter rather than longer durations. As the current data show, HRT is most effective for relief of menopausal symptoms such as hot flashes, mood swings, and vaginal dryness.

References

continued


