

Postmenopausal Hormone Replacement Therapy for the Primary Prevention of Chronic Conditions: A Summary of the Evidence for the U.S. Preventive Services Task Force

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Acknowledgements

This summary of the evidence was prepared for the Agency for Healthcare Research and Quality (contract #290-97-0018, task order no. 2) to be used by the U.S. Preventive Services Task Force. Erin LeBlanc MD, MPH, Jill Miller MD, and Lina Takano MD, MS were fellows in a Women's Health Fellowship at the Portland Veterans Affairs Medical Center when this work was conducted. Task Force members Janet Allan, PhD, RN, and Steven Teutsch, MD, MPH, served as liaisons. Mark Helfand, MD, MS, and David Atkins, MD, MPH provided scientific expertise. Oregon Health & Science University Evidence-based Practice Center staff who contributed to this project included Kathryn Krages,

EPC administrator, Susan Wingenfeld, administrative assistant, and Patty Davies, MA, librarian.

Epidemiology

Hormone replacement therapy (HRT), either estrogen alone or estrogen combined with progestin, is used in the United States and worldwide to treat symptoms of menopause and to prevent chronic conditions such as osteoporosis. It is one of the most commonly prescribed drugs in the United States. A survey conducted in 1995 of postmenopausal women aged 50 to 75 showed that nearly 38% of women were using HRT at the time of the survey.¹ Recently published studies, however,

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Reprints are available from the AHRQ Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse (www.guideline.gov).

The USPSTF recommendations based on this evidence review can be found in Postmenopausal Hormone Replacement Therapy—Primary Prevention of Chronic Conditions: Recommendations and Rationale, which is available on the AHRQ Web site.

This chapter first appeared on the AHRQ Web site August 21, 2002 (www.preventiveservices.ahrq.gov).

suggest that HRT use is associated with potential harms that were not previously appreciated, causing many to reconsider the appropriateness of its use for prevention.

To determine the current status of benefits and harms of HRT use, we conducted systematic searches of the literature on HRT use among postmenopausal women, its effectiveness for the primary prevention of chronic conditions, and its association with harmful outcomes. Several reports and publications provide additional details of these reviews on the effects of HRT on cardiovascular disease,^{2,3} thromboembolism,^{4,5} breast cancer,⁶ osteoporosis,⁷ cognition and dementia,^{8,9} as well as overall benefits and harms.¹⁰ This report serves as a summary of the evidence with the objective of aiding the U.S. Preventive Services Task Force (USPSTF) in updating its recommendations on HRT scheduled for release in October 2002.

Use of HRT for the treatment of symptoms of menopause and for the treatment of preexisting conditions are outside the scope of the USPSTF recommendation, and this literature was not reviewed. All papers included in this review met inclusion criteria and were rated for quality (See “Inclusion/Exclusion Criteria” below). We focused on health outcomes such as myocardial infarction rather than intermediate outcomes such as lipid levels. To provide an overview of benefits and harms, we conducted several meta-analyses and used these results, as well as those from selected published papers, to calculate numbers of events prevented or caused by HRT for specific outcomes in a hypothetical population of postmenopausal women.

Prior Recommendations

In 1996, the USPSTF recommended counseling all perimenopausal and postmenopausal women about the potential benefits and harms of HRT.¹¹ They determined that there was insufficient evidence to recommend for or against HRT for all women, but thought that individual decisions should be based on patient risk factors, an understanding of the probable benefits (for example, the prevention of myocardial infarction or fracture) and harms (for

example, endometrial cancer with unopposed estrogen or breast cancer), and personal preferences.

Analytic Frameworks and Key Questions

The analytic frameworks in Figures 1 and 2 show the target populations, interventions, and health outcome measures we examined for the overall question of the benefits and harms of HRT used by postmenopausal women to prevent chronic conditions. Numbered arrows in the figures correspond to key questions specifically covered in this report (Figure 3). We were concerned with HRT as chemoprevention for primary prevention and therefore focused on the use of either estrogen alone (unopposed) or estrogen combined with progestins (combined) in healthy, postmenopausal women.

Methods

Literature Search Strategy

Methods of searching the literature, selecting abstracts, reviewing, abstracting, and rating studies, and conducting meta-analyses were standardized for all topics. Because the literature for each topic varied, each review was also subject to topic-specific modifications in methods. Detailed methods for each topic are presented elsewhere.²⁻¹⁰

In conjunction with a medical librarian, we conducted topic-specific searches using MEDLINE (1966-2001), HealthSTAR (1975-2001), and the Cochrane Controlled Trials Register (<http://www.cochranelibrary.com>); dates of searches varied with some topics. Additional articles were obtained by consulting experts and by reviewing reference lists of pertinent studies, reviews, and editorials. We used only published data in meta-analyses.

Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were developed by the investigators for each topic. In general, studies were included if they contained a comparison group

Figure 1. Potential benefits of Hormone Replacement Therapy Analytic Framework 1

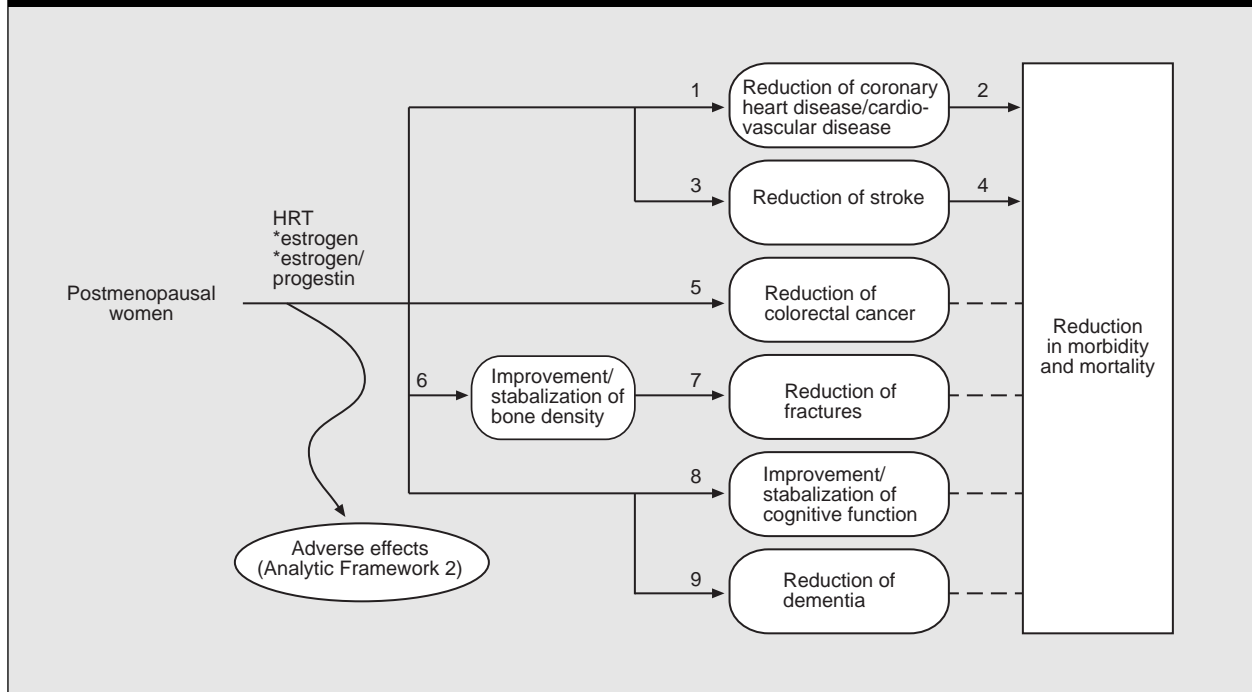
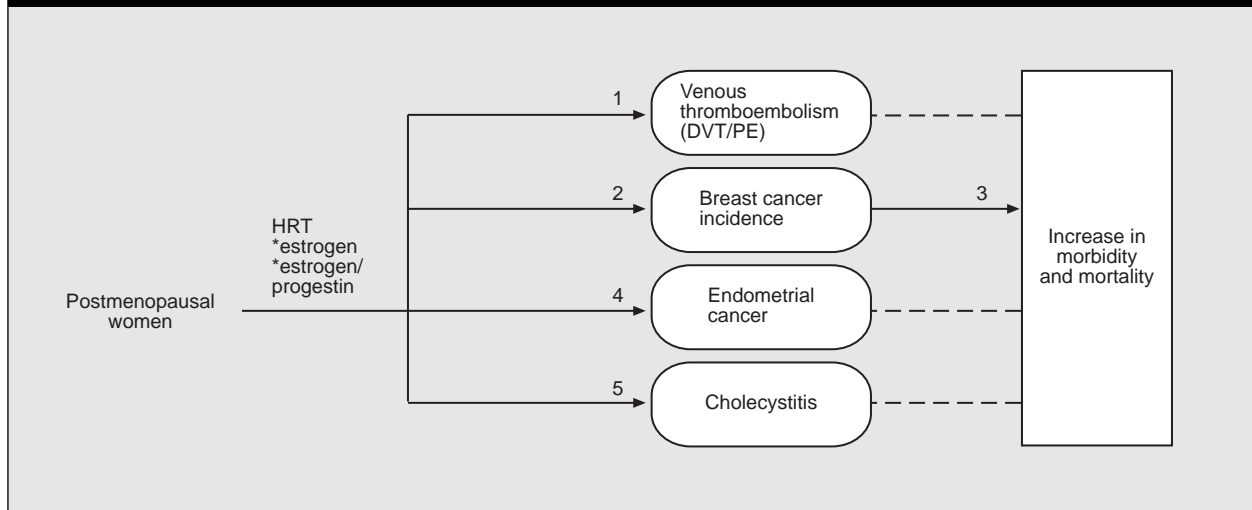


Figure 2. Potential harms of Hormone Replacement Therapy Analytic Framework 2



Note: DVT indicates deep-vein thrombosis; PE, pulmonary embolus.

Figure 3. Key Questions**Potential benefits**

Does HRT reduce risks for:

1. Coronary heart disease and cardiovascular disease incidence?
2. Coronary heart disease and cardiovascular disease mortality?
3. Stroke incidence?
4. Stroke mortality?
5. Colorectal cancer?
6. Low bone density?
7. Fractures?
8. Decline in cognitive function?
9. Dementia?

Potential harms

Does HRT increase risks for:

1. Venous thromboembolism (deep vein thrombosis and pulmonary embolism)?
2. Breast cancer incidence?
3. Breast cancer mortality?
4. Endometrial cancer?
5. Cholecystitis?

of HRT nonusers and reported data relating to HRT use and clinical outcomes of interest. Studies were excluded if the population was selected according to prior events or presence of conditions associated with higher risks for targeted outcomes. Hormone replacement therapy use was classified as unopposed estrogen replacement (estrogen only) or combined (estrogen plus progestin) when specified. When data were available, we reported effects of formulation, dose, and duration. In studies with multiple publications from the same cohort or population, only data from the most recent publication were included in the meta-analyses. We used adjusted statistics when reported.

Two reviewers independently rated each study's quality by using criteria specific to different study designs developed by the USPSTF and categorized them as good, fair, or poor.¹² When reviewers disagreed, a final rating was reached through consensus.

In addition to the systematic literature review, we included 2 recently published randomized controlled trials (RCTs) with pertinent findings. The Women's

Health Initiative (WHI), a primary prevention trial, reported results of 16,608 healthy postmenopausal women after 5.2 years of daily combined HRT or placebo.¹³ We also cite the noncardiac outcomes of the Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II),¹⁴ a trial of daily combined HRT in 2,321 postmenopausal women with preexisting coronary heart disease after 6.8 years.^{15,16}

Data Extraction and Synthesis

Meta-analyses were conducted for some of the topics because either previous meta-analyses had not been published, or they were outdated or inadequate. We used adjusted relative risk (RR) estimates when available or calculated them when possible. Under the modeling assumptions made by each study, the logarithm of the relative risk (logRR) had a normal distribution. Standard errors (SEs) for logRR were calculated from reported confidence intervals (CIs) or *P* values. The logRR and standard errors provided the data points for the meta-analyses. Heterogeneity was assessed with study-level stratification factors in the regression models. Fixed and random-effects models were fit on the data by using the Bayesian data analytic framework.¹⁷ We report only the random-effects model because the results of the 2 models were similar in all cases. Inference on the parameters was done via posterior probability distributions. The data were analyzed with WinBUGS software,¹⁸ which uses a method of Markov chain Monte Carlo called Gibbs sampling to simulate posterior probability distributions.

Sensitivity analysis was performed with different prior distributions, combining only studies with similar methods and excluding poor-quality studies and those with important biases or limitations. Sensitivity analysis varied according to the needs of each meta-analysis.

We also evaluated studies for selection bias by using funnel plots¹⁹ and investigated the sensitivity of the analysis to studies possibly missed because of publication bias by trim and fill.^{20,21} Results were unaffected, although this technique does not entirely rule out potential publication bias.

Estimates of Benefits and Harms

We calculated the number of events prevented or caused by HRT per year of use in 10,000 women by using relative risks for clinical outcomes derived from the reviewed studies and meta-analyses. We also used population-based estimates of incidence and mortality.²²⁻²⁹ We stratified event rates by 10-year age intervals because incidence rates for some outcomes are strongly age-related. Data sources for incidence and mortality rates did not allow further breakdown by race, preexisting disease, risk factors, or other variables and varied in quality. These estimates, therefore, do not consider special subgroups and would be most applicable to the general population of postmenopausal women.

We used the best evidence available to determine the relative risk for each outcome.³⁰ Some estimates were derived from extensive literature reviews and meta-analysis; others, from a single study representing the only or best literature available. We sought data from RCTs when available. When evaluating observational studies, we looked carefully at the potential for confounding and took measures to reduce its influence by including only studies that controlled for important confounders, selecting outcomes less prone to confounding, or factoring the potential for confounding into our overall conclusions. In general, observational studies allowed examination of issues of duration and currency of use and examined end points that are difficult to study in RCTs because they are infrequent or develop slowly.

Results

Cardiovascular Disease

Studies of HRT and the primary prevention of cardiovascular disease (CVD) report various outcomes. Some studies examined coronary heart disease (CHD) and stroke as separate categories, while others combined them into an overall cardiovascular disease category. We describe these as they were reported in the original sources. We evaluated results by type of use as they were defined in each study: current users are those using estrogen

at the time of assessment, past users are those who used estrogen previously but not at the time of assessment, ever users include those who used estrogen both at the time of assessment and previously, and never users have not used estrogen at any time. We also created a category, all use, that combined all mutually exclusive types of use (ever, past, and current) for purposes of pooling studies in the meta-analysis. Our review and meta-analysis focuses on the studies we rated good or fair-quality using USPSTF criteria. Characteristics of poor-quality studies included little or no control for confounding, nonrepresentative cohorts, poor definition of outcomes, poor characterization of exposure, and bias in control selection.

Overall Cardiovascular Disease

Eight observational studies evaluated overall CVD mortality.³¹⁻³⁸ The summary relative risk for CVD mortality was significantly reduced among those using HRT at the time of assessment (RR, 0.64; 95% CI, 0.44-0.93) but not among ever, past, or any users (Table 1). Two cohort studies,^{31,32} 1 case-control study,³⁹ and data from a published meta-analysis⁴⁰ reported CVD incidence. The summary relative risk with any use was 1.28 (95% CI, 0.86-2.00) (Table 1). Results were similar for those who were using estrogen at the time of assessment, those who used estrogen previously but not at the time of assessment, and those who had ever used estrogen.

Coronary Heart Disease

Five studies evaluated the risk for CHD mortality.^{32,34,35,41,42} Combined data from these studies indicated that mortality was significantly reduced among those using HRT at the time of assessment (RR, 0.62; 95% CI, 0.40-0.90), but not among any, past, or ever users (Table 1).

The association between HRT use and CHD incidence was evaluated in 3 cohort studies^{22,31,32}; 9 case-control studies⁴³⁻⁵¹; and 1 small randomized, controlled trial.³³ Combined data indicated that CHD incidence was also reduced among those using HRT at the time of assessment (RR, 0.80; 95% CI, 0.68-0.95), but not among any, past, or ever users (Table 1). Further analysis of studies adjusting for

Table 1. Summary of cardiovascular disease meta-analyses

| | Relative Risk According to Use of Hormone Replacement Therapy (95% CI)* | | | |
|--|---|------------------|------------------|------------------|
| | Current | Past | Ever | Any |
| Mortality | | | | |
| Total cardiovascular disease** | 0.64 (0.44-0.93) | 0.79 (0.52-1.09) | 0.81 (0.58-1.13) | 0.75 (0.42-1.23) |
| Coronary heart disease | 0.62 (0.40-0.90) | 0.76 (0.53-1.02) | 0.81 (0.37-1.60) | 0.74 (0.36-1.45) |
| Stroke | | | 0.81 (0.71-0.92) | |
| Incidence | | | | |
| Total cardiovascular disease | 1.27 (0.80-2.00) | 1.26 (0.79-2.08) | 1.35 (0.92-2.00) | 1.28 (0.86-2.00) |
| Coronary heart disease | 0.80 (0.68-0.95) | 0.89 (0.75-1.05) | 0.91 (0.67-1.33) | 0.88 (0.64-1.21) |
| Coronary heart disease adjusted for socioeconomic status | 0.97 (0.82-1.16) | 1.07 (0.90-1.27) | 1.11 (0.84-1.53) | 1.04 (0.79-1.44) |
| Overall stroke | | | 1.12 (1.01-1.23) | |
| Thromboembolic stroke | | | 1.20 (1.01-1.40) | |
| Subarachnoid stroke | | | 0.80 (0.57-1.04) | |
| Intracerebral stroke | | | 0.71 (0.25-1.29) | |

*Current users are those using estrogen at the time of assessment, past users are those who used estrogen previously but not at the time of assessment, ever users includes current and past users, and never users have not used estrogen at any time. We also created a category, all use, that combines all mutually exclusive types of use (ever, past, and current) for purposes of pooling studies in the meta-analysis.

**Includes multiple cardiovascular outcomes such as coronary heart disease, stroke, sudden cardiac death, and congestive heart failure.

socioeconomic status by using measures of social class such as education or income indicated no significant reductions in risk for any of the groups who used HRT (Table 1). Similar results were found when the analysis was stratified by studies adjusting for alcohol consumption and/or exercise, in addition to other major risk factors, suggesting confounding by these factors.

The WHI reported an increased risk for CHD events (hazard ratio [HR], 1.29; 95% CI, 1.02-1.63), including nonfatal myocardial infarction (HR, 1.32; 95% CI, 1.02-1.72) among estrogen users.¹³ Coronary heart disease mortality and rates of coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty were not increased. Results from HERS II indicated no significant decreases in rates of primary or secondary CHD events among estrogen users.¹⁶

Stroke

Hormone replacement therapy and stroke mortality were evaluated in 8 cohort studies and 1 case control study.^{32,34,36,37,41,42,52-54} After combining data from these studies, the summary relative risk for stroke mortality was 0.81 (95% CI, 0.71-0.92) among HRT users (Table 1). Two cohort studies, each of good quality, evaluated long-term use of estrogen and risk for stroke mortality and identified no significant association.^{41,42} The majority of studies did not differentiate between unopposed and combined estrogen regimens.

Combining 9 studies of stroke incidence resulted in a summary relative risk of 1.12 (95% CI, 1.01-1.23), indicating a small increase in stroke in association with HRT use (Table 1).^{22,31,32,39,50,52,53,55-57} Results of a sub-analysis indicate a significant increase in risk for thromboembolic stroke (RR, 1.20; 95% CI, 1.01-1.40)^{54,55,57,58} but not

subarachnoid hemorrhage (RR, 0.80; 95% CI, 0.57-1.04)^{57,59,60} or intracerebral hemorrhage (RR, 0.71; 95% CI, 0.25-1.29)^{50,55,57,61} among women who had ever taken HRT.

One cohort and 1 case-control study evaluated the effect of long-term use (≥ 5 years) of estrogen and the risk for stroke and neither showed an association.^{22,57} The Nurses Health Study reported a significant dose-response relationship between stroke and HRT use, with graded risks of 0.54 (95% CI, 0.28-1.06), 1.35 (95% CI, 1.08-1.68), and 1.63 (95% CI, 1.18-2.26) for estrogen doses of 0.3 mg, 0.625 mg, and 1.25 mg or more, respectively.²² A 45% higher risk for stroke among women taking combined regimens compared with women who had never used HRT was also shown in the Nurses Health Study (RR, 1.45; 95% CI, 1.10-1.92)²²; the association between stroke and unopposed estrogen use also was increased (RR, 1.18; 95% CI, 0.95-1.46), though was not statistically significant.

The WHI reported an increased risk for nonfatal strokes, although the confidence interval crossed 1.0 in adjusted analysis (HR, 1.50; 95% CI, 0.83-2.70).¹³ HERS II reported no increase in stroke or transient ischemic attacks.¹⁶

Thromboembolism

Twelve abstracts met inclusion criteria and contained primary data (3 randomized controlled trials,^{15,62,63} 8 case-control studies,^{29,64-70} and 1 cohort study⁶⁰). No studies were designed to report venous thromboembolic events (ie, deep vein thrombosis and/or pulmonary embolism) as primary outcomes. Studies varied in quality with the most important limitations including lack of controlling for key confounders such as smoking, not reporting dose or duration of estrogen use, differences in characteristics of patients and controls, small numbers of cases, and variation in outcome assessment. Despite differences in design and quality, the studies had consistent results, with 11 of 12 reporting relative risk point estimates above 1.0, and 6 of these with confidence intervals above 1.0.

When studies were combined by meta-analysis, results indicated that use of HRT at the time of the studies was associated with an increased risk for

venous thromboembolism (RR, 2.14; 95% CI, 1.64-2.81). Estimates did not significantly change when pooling studies by type of study design, quality rating, or whether subjects had preexisting coronary artery disease. Using a baseline risk of 1.3 events per 10,000 woman-years based on a study with 10,000 controls, an additional 1.5 events per 10,000 women each year would be expected.²⁹ Six studies that reported risk according to duration of use found the highest risks in the first 1 to 2 years (combined RR for first year was 3.49; 95% CI, 2.^{15,29,65,67-69}

Some studies reported the effects of dose and regimen, although the numbers of study participants were small. Three studies reported a higher risk for increased doses of estrogen (>0.625 mg conjugated) compared with lower doses.^{29,65,67} A higher risk (odds ratio [OR], 2.2-5.3) for estrogen combined with progestin compared with estrogen alone was reported by 3 studies.^{29,65,68} A comparison of oral (OR, 4.6; 95% CI, 2.1-10.1) and transdermal (OR, 2.0; 95% CI, 0.5-7.6) estrogen was reported by only 1 study.⁶⁵

Both the WHI and HERS II reported statistically significant 2-fold increases in thromboembolic events among estrogen users with trends toward higher rates early in the course of use.^{13,15}

Breast Cancer

Our search identified studies that evaluated breast cancer incidence or mortality as primary or secondary outcomes in association with HRT use. Those meeting inclusion criteria included 8 meta-analyses,⁷¹⁻⁷⁸ 15 case-control studies,⁷⁹⁻⁹³ and 15 cohort studies.⁹⁴⁻¹⁰⁹

The WHI results indicated increased breast cancer risk for women using estrogen combined with progestin after 5.2 years of use (HR, 1.26; 95% CI, 1.00-1.59).¹³ Trend data indicated increasing risk for breast cancer with increasing duration of use. Studies identified by our literature search support these findings. Current estrogen users have an increased risk for breast cancer according to most recent good-quality studies including 3 meta-analyses (relative risks range from 1.21 to 1.40).⁷¹⁻⁷³ Risk increases with longer duration of use (relative risks range from 1.23 to 1.35 based on all 6 meta-

analyses that evaluated this relationship).⁷¹⁻⁷⁷ Few studies and no meta-analyses specifically evaluated estrogen combined with progestin, although some recent studies suggest increased risk above that of unopposed estrogen,^{78-81,94} while others do not.⁸²⁻⁸⁵

In contrast to studies of current users, the majority of studies of women who have ever used HRT, including 14 of 18 observational studies and 7 of 8 meta-analyses, reported no increase in risk for breast cancer (relative risks range from 0.85 to 1.14 from 8 meta-analyses).^{40,71-77}

No meta-analyses have evaluated breast cancer mortality. All 6 recent cohort studies that evaluated breast cancer mortality showed either no effect or decreased mortality among those who had ever used HRT, or among those who used HRT in the short-term (<5 years) (relative risks ranging from 0.5 to 1.0).^{78,95-99} Risk by duration of use was evaluated in 5 studies of mixed quality that evaluated mortality in different ways, including by tumor node status and family history.^{78,95,96,98,99} Two good-quality studies that reported results for use longer than 5 years have conflicting results.^{78,98}

Colon Cancer

A published meta-analysis of 18 observational studies of colorectal cancer and HRT indicated a 20% reduction in colon cancer among those who had ever used HRT compared with those who had never used HRT (RR, 0.80; 95% CI, 0.74-0.86) and a 34% reduction among those using HRT at the time of assessment (RR, 0.66; 95% CI, 0.59-0.74).¹¹⁰ Duration of HRT use did not influence risk estimates. Results were similar for rectal cancer. These results were based entirely on observational studies that included estrogen users who were healthier, less obese, more physically active, and had healthier diets than nonusers, and who may have been at a lower risk for developing colorectal cancer based on these factors.

The WHI is the first RCT to report similar outcomes, although results were not significant when adjusted analysis was used.¹³ Risk was not reduced among HRT users in HERS II.¹⁴

Endometrial Cancer

A meta-analysis of 29 observational studies reported a significantly elevated relative risk for endometrial cancer for unopposed estrogen users compared with nonusers (RR, 2.3; 95% CI, 2.1-2.5).¹¹¹ Increased risk was associated with increasing duration of use, and risk remained elevated 5 or more years after discontinuation of unopposed estrogen therapy. Users of unopposed conjugated estrogen had a greater increase in risk than users of synthetic estrogens. Mortality from endometrial cancer was not significantly elevated (RR, 2.7; 95% CI, 0.9-8.0).

A meta-analysis of 7 studies evaluating the effects of combined HRT regimens (estrogen with progestin) on endometrial cancer incidence reported a relative risk of 0.8 (95% CI, 0.6-1.2).¹¹¹ Three cohort studies indicated a decreased risk for endometrial cancer (RR, 0.4; 95% CI, 0.2-0.6),¹¹²⁻¹¹⁴ and 3 case-control studies showed an increase in risk (RR, 1.8; 95% CI, 1.1-3.1).¹¹⁵⁻¹¹⁷ Neither the WHI nor HERS II reported an increase in endometrial cancer when a daily combined HRT regimen was used.^{13,14}

Osteoporosis

For bone density outcomes, RCTs consistently indicated improved bone density with estrogen use. A published Cochrane systematic review reported combined results of 57 RCTs enrolling postmenopausal women for more than 1 year that compared HRT with placebo or calcium/vitamin D use.¹¹⁸ Findings were similar between prevention and treatment trials, opposed and unopposed regimens, oral and transdermal forms of estrogen, and types of progestins. Results differed, however, with different doses and duration of estrogen use. Use of usual doses (eg, 0.625 mg of conjugated estrogen) resulted in greater bone density increases at lumbar, femoral neck, and forearm sites than use of lower doses (0.3 mg). Two-year trials resulted in greater increases than 1-year trials.

For fracture outcomes, a meta-analysis of 22 trials of estrogen reported an overall 27% reduction in

nonvertebral fractures (RR, 0.73; 95% CI, 0.56-0.94).¹¹⁹ Although the meta-analysis itself met USPSTF criteria for a good-quality rating, 21 trials included in the meta-analysis did not meet inclusion criteria for our review because they used unpublished data; did not verify fractures radiographically; or included traumatic fractures, women with preexisting osteoporosis, or those who were hospitalized or had secondary causes of osteoporosis.

We identified 4 trials^{13,14,120-122} that met inclusion criteria and reported fracture outcomes. A primary prevention trial enrolled a subgroup of a large prospective osteoporosis study based in Finland.¹²⁰ In this study, early postmenopausal women without osteoporosis were randomly assigned to 1 of 4 treatment groups. New, symptomatic, radiographically confirmed nonvertebral fractures were recorded during a mean 4.3 years of follow-up. Compared with the groups given placebo, the risk for fracture was significantly lower for the group using estrogen/progestin alone (RR, 0.29; 95% CI, 0.10-0.90), but not for the group using estrogen/progestin and vitamin D, or the group using vitamin D alone when adjusted for baseline bone density and prior fractures. Another primary prevention trial randomized early postmenopausal women in Denmark to oral HRT or placebo. After 5 years, the relative risk for all types of fractures was 0.82 (95% CI, 0.53-1.29) and for forearm fractures it was 0.40 (95% CI, 0.16-1.01).¹²¹ The WHI is the first RCT to demonstrate reduction of hip fracture risk with estrogen use, although the confidence interval crosses 1.0 when adjusted analysis is used.¹³ Risk for other osteoporotic fractures was significantly reduced (HR, 0.77; 95% CI, 0.63-0.94). No risk reduction for hip or other types of fractures was evident in HERS¹²² or HERS II.¹⁴

Six good-quality cohort studies were also identified,¹²³⁻¹²⁸ and 3 of 4 studies reported 20% to 35% reductions in adjusted relative risks for hip fractures among those who had ever used HRT (combined RR for 4 studies, 0.76; 95% CI, 0.56-1.01).¹²⁴⁻¹²⁷ Cohort studies also reported reduced risks for wrist (RR, 0.44; 95% CI, 0.23-0.84),^{123,125} vertebral (RR, 0.60; 95% CI, 0.74-0.86),¹²⁵ and

nonvertebral fractures.¹²³ Cohort studies included large numbers of women, often recruited from community-based populations, and followed them for longer periods than did the RCTs.

Cognitive Function and Dementia

Twenty-nine studies met inclusion criteria, including 9 RCTs¹²⁹⁻¹³⁷ and 8 cohort studies¹³⁸⁻¹⁴⁵ describing the effects of HRT on cognitive decline and 2 cohort^{146,147} and 10 case-control studies¹⁴⁸⁻¹⁵⁷ providing estimates for dementia risk.

Studies measuring the effects of estrogen on cognition in women without preexisting dementia were not combined quantitatively because of their heterogeneity. These studies used more than 40 different tests among them and administered these tests in nonstandardized ways. They also differed in their study design and patient populations. Results indicated that women with menopausal symptoms experienced improved verbal memory, vigilance, reasoning, and motor speed, but no enhancement of other cognitive functions. Generally, no benefits were observed in asymptomatic women.

Our meta-analysis of 12 observational studies with dementia outcomes¹⁴⁶⁻¹⁵⁷ suggested that HRT was associated with a decreased risk for dementia (summary OR, 0.66; 95% CI, 0.53-0.82). However, these studies commonly used self-reported outcomes for controls and proxy for cases, used interviewers who were not blinded to the outcome, did not control for education, and included only those using estrogen at the time of assessment. Possible biases and lack of control for potential confounders limit interpretation of these studies. Studies did not contain enough information to adequately assess the effects of progestin use, various estrogen preparations or doses, or duration of therapy.

Neither the WHI nor HERS II reported effects of HRT on cognition and dementia.^{13,14} We considered the relationship between HRT and dementia to be an uncertain benefit because of lack of RCT evidence and the methodologic limitations and inconsistencies among observational studies.

Cholecystitis

The relationship between HRT and cholecystitis is well-described in a publication from the Nurses Health Study, a good-quality cohort study.²⁸ When compared with those who had never used HRT, those who were using HRT for the short-term at the time of assessment had an age-adjusted relative risk for cholecystitis of 1.8 (95% CI, 1.6-2.0). This risk increased after 5 years of use and remained elevated at this rate for women who had used HRT for 10 years or more. Among those who used HRT in the past, the risk decreased to between 1.4 and 1.7 but still remained significantly elevated as compared with those who had never used HRT.

Other studies support these findings,^{64,79,158-160} although some do not.¹⁶¹⁻¹⁶⁵ The HERS II trial reported an increase in biliary tract surgery among HRT users compared with those receiving placebo during 6.8 years of follow-up (RR, 1.44; 95% CI, 1.10-1.90).¹⁴ This outcome has not yet been reported by the WHI. Another study evaluated data from 800,000 women in Canada to explore the relationship of a variety of medications with gallbladder and other diseases.¹⁶⁶ In this study, estrogen users were significantly more likely than users of other medications to have cholecystectomy and primary appendectomy.

Benefits and Harms Outcomes Table

Our review of the evidence and the results of our meta-analyses, as well as recent results from the WHI, provided risk estimate assumptions for a table summarizing the benefits and harms of HRT (Table 2). We obtained incidence rates for target conditions from population-based sources and calculated the number of events prevented or caused by HRT per year in 10,000 postmenopausal women. We calculated outcomes twice, once using results of this literature review and meta-analysis and once using recent results of the WHI. We predominantly used incidence rates because our review of evidence indicated that either HRT did not significantly

protect against mortality for specific outcomes (stroke and breast cancer) or mortality outcomes were not studied (fractures, colon cancer, and thromboembolism).

For most clinical outcomes, we used relative risk estimates from those who had ever used HRT as opposed to those who were using HRT at the time of assessment or those who had used HRT in the past. The groups who had ever used HRT were the most consistently reported across studies and would be expected to bias results less than those who were using HRT at the time of assessment. Cholecystitis and thromboembolism were associated with HRT use at the time of assessment; rates for those who had ever used HRT were not provided, the relative risk estimates for those who were taking HRT at the time of assessment was used. For some outcomes, such as cholecystitis and breast cancer, risk increases with duration of use. To reflect these changing risks, we calculated events for short-term (<5 years) and long-term (≥5 years) users. Data support an increased risk for thromboembolic events in the first year of use, but because most HRT users intend a longer course to prevent chronic conditions, we calculated first-year and overall event rates.

We did not calculate endometrial cancer outcomes because the association between unopposed estrogen and endometrial cancer is well known and the standard of care is to provide combined therapy for women who have not had a hysterectomy. Combined therapy is not associated with increased risk for endometrial cancer. Eight published meta-analyses⁷¹⁻⁷⁸ of breast cancer incidence provided different risk estimates. To reflect this range of risk, we calculated a potential range of cases of endometrial cancer caused by HRT use.

Table 3 summarizes these results by 10-year age groups for women aged 55 to 84. Event rates for benefits and harms are generally lower in younger women and higher in older women. Except for CHD, rates are similar when WHI hazard ratios rather than relative risks from our review are used.

Table 2. Outcomes table assumptions

| Condition (reference) | This review RR or OR (95% CI) | Results of WHI* HR (95% CI) | Incidence or mortality rates by age group | | | | | | | | |
|--|----------------------------------|--------------------------------|---|----------|----------|----------|----------|-----------|----|----|----|
| | | | 55-64 | | 65-74 | | 75-84 | | | | |
| | | | 55-59 | 60-64 | 65-69 | 70-74 | 75-79 | 80-84 | | | |
| Benefits | | | | | | | | | | | |
| Hip fracture (23) | 0.76 (0.56-1.01) | 0.66 (0.33-1.33) | 0.00089 | 0.001528 | 0.002372 | 0.005305 | 0.010184 | 0.017315 | | | |
| Wrist fracture (24) | 0.44 (0.23-0.84) | NA | 0.006053 | | 0.00671 | | 0.008113 | | | | |
| Vertebral fracture (25) | 0.60 (0.36-0.99) | 0.66 (0.32-1.34) | 0.0068 | 0.0093 | 0.0123 | 0.0161 | 0.0205 | 0.0252 | | | |
| Colorectal cancer (27) | 0.80 (0.74-0.86) | 0.63 (0.32-1.24) | 0.000712 | 0.001121 | 0.001568 | 0.002274 | 0.002951 | 0.003838 | | | |
| Uncertain Benefits | | | | | | | | | | | |
| Dementia incidence (26) | 0.66 (0.53-0.82) | NA | 0.005** | | 0.01 | | | 0.02** | | | |
| Harms | | | | | | | | | | | |
| Coronary heart disease incidence (22) | 0.91 (0.67-1.33) | 1.29 (1.02-1.63) | 0.00174 | 0.00264 | 0.00308 | | | 0.00398** | | | |
| Overall stroke incidence (22) | 1.12 (1.01-1.23) | 1.41 (0.66-2.31) | 0.00064* | 0.00121 | 0.00229 | | | 0.00469** | | | |
| Thromboembolism incidence (≤1 year) (29) | 3.49 (2.33-5.59) | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Thromboembolism incidence (overall) (29) | 2.14 (1.64-2.81) | 2.11 (1.26-3.55) | 0.00013 | | 0.00013 | | | 0.00013 | | | |
| Breast cancer incidence (<5 years) (27) | 1.0 - 1.14 | NA | 0.002963 | 0.003473 | 0.004044 | 0.004555 | 0.004833 | 0.004681 | | | |
| Breast cancer incidence (≥5 years) (27) | 1.23 - 1.35 | 1.26 (1.00-1.59) | 0.002963 | 0.003473 | 0.004044 | 0.004555 | 0.004833 | 0.004681 | | | |
| Cholecystitis (<5 years) (28) | 1.8 (1.6-2.0) | NA | 0.00357 | | 0.00357 | | | 0.00357 | | | |
| Cholecystitis (≥5 years) (28) | 2.5 (2.0-2.9) | NA | 0.00357 | | 0.00357 | | | 0.00357 | | | |

*Nominal CIs are indicated for main outcomes of the trial (breast cancer, CHD), adjusted CIs for secondary outcomes.

**Data based on extrapolated values.

Note: NA indicates not available; WHI, Women's Health Initiative.

Table 3. Outcomes table: hormone replacement therapy use in 10,000 women—benefits and harms per year

| | Number of events prevented or caused per year | | | | | |
|---|---|-----|-------------|-----|-------------|------|
| | Age 55-64 | | Age 65-74 | | Age 75-84 | |
| | This review | WHI | This review | WHI | This review | WHI |
| Benefits (prevention) | | | | | | |
| Hip fractures | 3 | 4 | 9 | 13 | 33 | 47 |
| Wrist fractures | 34 | – | 37.5 | – | 45 | – |
| Vertebral fractures | 32 | 27 | 57 | 49 | 91 | 78 |
| Cases of colon cancer | 2 | 3 | 4 | 7 | 7 | 12.5 |
| Uncertain Benefits | | | | | | |
| Cases of dementia | 17* | – | 34 | – | 68* | – |
| Harms (caused) | | | | | | |
| Coronary heart disease events | 0 | 6 | 0 | 9 | 0 | 11.5 |
| Strokes | 1* | 4* | 3 | 9 | 6* | 19* |
| Thromboembolic events during first year | 3 | – | 3 | – | 3 | – |
| Thromboembolic events overall | 1.5 | 1.4 | 1.5 | 1.4 | 1.5 | 1.4 |
| Breast cancer cases (<5 years' use) | 0 to 2.5 | – | 0 to 6 | – | 0 to 7 | – |
| Breast cancer cases (≥5 years' use) | 7 to 11 | 8 | 10 to 15 | 11 | 11 to 17 | 12 |
| Cholecystitis cases (<5 years' use) | 25 | – | 25 | – | 25 | – |
| Cholecystitis cases (≥5 years' use) | 53.5 | – | 53.5 | – | 53.5 | – |

*Estimates based on extrapolations.

Note: WHI indicates Women's Health Initiative.

Discussion

Conclusions

Table 4 summarizes the quality of evidence for each key question addressed in this review. According to our analysis of observational studies and results of the WHI, using HRT to prevent CHD and CVD does not reduce these events. However, HRT use does not increase mortality from CHD and CVD based on these studies. Stroke incidence, specifically thromboembolic stroke—but not stroke mortality—is increased with HRT use according to our meta-analysis and results of the WHI. Prevention of colorectal cancer is also supported by the WHI and observational studies, although this evidence is weaker because WHI

findings are not significant when the analysis is adjusted and observational studies are biased. Prevention of osteoporotic fractures is supported by results of the WHI and several consistent, good-quality observational studies of fractures and RCTs of bone density, an important intermediate outcome and risk factor for fracture. HRT effects on cognition were reported only in women with symptoms of menopause. Prevention of dementia is supported only by observational studies with important methodological limitations.

Several harms of HRT use are supported by an increasingly strong body of evidence. Our meta-analysis, the WHI, and HERS II are consistent in reporting a 2-fold increase in thromboembolic events with HRT use. Risk is highest in the first year of use. Observational studies support the WHI

Table 4. Summary of evidence

| Key questions | Evidence codes* | Quality of evidence** |
|-----------------------------------|-----------------|--|
| Potential benefits | | |
| Does HRT reduce risks for: | | |
| 1. CHD and CVD incidence? | I, II-2 | Fair-good: most studies are observational and have important biases; when confounders are considered, apparent benefits for current users are not supported; trial data from WHI indicates increased risk further undermining validity of observational studies. |
| 2. CHD and CVD mortality? | I, II-2 | Fair-good: results based on observational studies with biases; both observational and trial data indicate no increase or decrease in risk. |
| 3. Stroke incidence? | I, II-2 | Fair-good: results based on observational studies with biases; observational and trial data suggest increased risk. |
| 4. Stroke mortality? | I, II-2 | Fair-good: observational studies indicated reduced risk for stroke mortality, although trial data did not support this finding. |
| 5. Colorectal cancer? | I, II-2 | Poor-good: results are based on observational studies that were primarily designed for other outcomes; findings from the WHI are not significant when the analysis is adjusted. |
| 6. Low bone density? | I | Good: many good-quality RCTs are consistent and demonstrate benefit; limited by short duration of trials, bone density is an intermediate outcome. |
| 7. Fractures? | I, II-2 | Fair-good: RCTs- few trials available, none is definitive because of limitations of methods although benefit is supported. Cohort studies- several good-quality cohort studies are consistent and demonstrate benefit; limited by healthy user bias. |
| 8. Decline in cognitive function? | I, II-2 | Fair-poor: studies enlist different patient populations and measure many different outcomes; results for symptomatic women are different from asymptomatic women. Duration of studies is too short to be meaningful. Difficult to draw any conclusions because outcome measures are so diverse. |
| 9. Dementia? | II-2 | Fair-poor: although the meta-analysis supports a protective effect, methodologic limitations and biases exist in individual studies (e.g., healthy user effect, use of proxy interviews, historical data obtained from subjects with dementia). |
| Potential Harms | | |
| Does HRT increase risks for: | | |
| 1. Venous thromboembolism? | I, II-2 | Poor-good: RCTs- venous thromboembolism is a secondary outcome, groups were randomized for cardiac outcomes, method of outcome assessment was not reported. Case-control- quality ratings range from poor to good; analysis based on small numbers of cases, important confounders such as smoking not considered in some studies. The consistency of the findings for an increased risk support the relationship. |

Continued on page 14

Table 4. Summary of evidence (cont.)

| | | |
|-----------------------------|---------|--|
| 2. Breast cancer incidence? | I, II-2 | Poor-good: increased risk with current use of long duration was supported by observational data and WHI trial; despite biases of the observational studies, the consistency of this finding provides stronger evidence for an association. |
| 3. Breast cancer mortality? | II-2 | Poor-good: observational and trial data indicate that mortality is not increased. |
| 4. Endometrial cancer? | II-2 | Poor-good: results are based on observational studies only, although results are consistent and demonstrated dose-response relationships. |
| 5. Cholecystitis? | I, II-2 | Poor-good: increased risk was reported from RCTs and observational studies, but was not a finding in every study; results demonstrated dose-response relationships. |

***Study Design Categories**

I: Randomized, controlled trials

II-1: Controlled trials without randomization

II-2: Cohort or case-control analytic studies

II-3: Multiple time series, dramatic uncontrolled experiments

III: Opinions of respected authorities, descriptive epidemiology

**Quality of evidence ratings based on criteria developed by the U.S. Preventive Services Task Force (Harris, 2001)

finding that breast cancer incidence was increased in those using HRT at the time of assessment after 5 or more years of use. Our review indicated that those who used estrogen previously but not at the time of assessment and short-term users were not at increased risk for breast cancer, and mortality was not increased for any group. Risks for endometrial cancer are increased with unopposed estrogen use but not with combined regimens. Studies are consistent in reporting increased risk for cholecystitis among those using HRT at the time of assessment which appears to increase with time.

New studies reporting associations between HRT use and ovarian cancer have been recently reported since this review was completed. Results indicate that women using unopposed estrogen for prolonged durations may have an increased risk for ovarian cancer.¹⁶⁷⁻¹⁶⁹

Limitations of the Literature

Studies of HRT, particularly observational studies, have many limitations. Women who take HRT differ from those who do not in many ways that are known or believed to alter risk. Hormone

replacement therapy users tend to be more affluent, leaner, and more educated, and they tend to exercise more often and drink alcohol more frequently than those who do not use HRT.^{31,78,170} These lifestyle factors are associated with increased risk for breast cancer and decreased risk for cardiovascular disease.^{31,170-172} Also, by definition, women who take HRT have access to health care and have a greater likelihood of being treated for other comorbid conditions that may also decrease their risks for certain clinical outcomes. Long-term HRT users are treatment-compliant, itself a factor associated with better health.^{173,174} Women often stop HRT when they become ill, a tendency that would bias studies evaluating recent or current use by underestimating HRT use in ill patients. Hormone replacement therapy is used more often by women who have undergone hysterectomy and oophorectomy, conditions associated with decreased risks for breast cancer and increased risks for osteoporosis.

There have been significant changes in clinical practice regarding the use of estrogen, including type, administration, and dose, as well as the relatively recent practice of adding progestins to estrogen therapy. For many of the years represented

in these studies, hypertension, diabetes, and heart disease were considered contraindications to the use of HRT. Practicing physicians may have been more likely to offer and prescribe HRT to women for whom the physicians' sense of overall health was higher. This type of selection bias is difficult to measure and may have led to systematic overestimates of the benefit of HRT. Also, most studies measured estrogen use at one point only or asked women if they had ever used estrogen. Thus, those who had ever used HRT and those who used HRT at the time of assessment could have used HRT for either long or short periods of time.

Our review is also limited by assumptions in Table 2 that lead to the estimated cases in Table 3. In many cases, a variety of relative risks was available for certain outcomes, and we selected a value according to our judgment of the best evidence. This judgment may differ from that of other reviewers of the evidence. Sources for population incidence and mortality rates for health outcomes varied in their reliability and may not be directly comparable. The applicability of population estimates when risks are determined for individuals is unknown. Our estimates do not account for racial and ethnic differences or important risk factors. These estimates are most valuable when relative magnitudes of benefits and harms are compared in conjunction with patient preferences.

Future Research

Additional evidence from RCTs is needed to more accurately weigh the benefits and harms of HRT. Areas of future research could include the following:

- The roles of progestins and types and doses of estrogen on outcomes are alluded to in the literature but are unresolved. Results of the WHI were based on use of a daily combined regimen in women with an intact uterus. A smaller arm of the study consisting of women with hysterectomies and using estrogen alone is continuing and apparently has not experienced statistically significant adverse outcomes. Additional studies may find that women taking unopposed estrogen have reduced risks for some outcomes, but increased risk for others.
- As selective estrogen receptor modulators (SERMs) and other estrogen-like agents are developed, direct comparisons with estrogen in addition to placebo during trials will be important. Careful monitoring and reporting of adverse events would contribute additional knowledge of the consequences of HRT use.
- Effects of HRT may differ by age or other important risk factors. Practice could be influenced if women who experience thromboembolic events, for example, are different from those who do not and could be identified prior to initiating HRT. Results from other studies indicate that women with a prior history of venous thromboembolism while taking HRT, those with the Factor V Leiden mutation, or those with hip or lower extremity fracture, cancer, hospitalization, or surgery are at increased risk for thromboembolism.
- It is unclear how age modifies the impact of estrogen. Understanding the optimal duration of effect would allow targeting of estrogen use to enhance beneficial effects and avoid harms.
- Although our review supports an association between HRT and increased risk for venous thromboembolism, as well as HRT and reduced risk for colorectal cancer, the pathophysiology of these relationships is not well understood.
- Clarification of potential increased risk for breast cancer with HRT use among subpopulations of women already considered at high-risk would help these women make decisions about HRT use.
- Studies can be designed to evaluate whether HRT has different effects in women with BRCA 1 and/or BRCA 2 tumor suppressor gene mutations. Are women with these mutations at any higher risk for breast cancer if they use HRT?

- Research on the effects of HRT on cognitive performance should focus on older, asymptomatic women instead of perimenopausal women.
- Studies of cognition need to use standardized outcome measures. The tests should not have ceiling values and need to be sensitive to very small differences because the effects of estrogen on cognition may be subtle. These tests should examine particular cognitive domains because the evidence indicates that estrogen may have neural and cognitive specificity. Future studies should include measures of the ability to care for oneself, live independently, and complete activities of daily living.
- Estrogen's cognitive and neural specificity should also be considered when interpreting the results of future research studies, including the 2 ongoing primary prevention trials of HRT and cognition, the Women's Health Initiative Study of Cognitive Aging (WHISCA)¹⁷⁵ and the Women's International Study of Long Duration Oestrogen after Menopause in the United Kingdom.¹⁷⁶

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