

Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2005 U.S. Preventive Services Task Force (USPSTF) recommendation statement on hormone therapy for the prevention of chronic conditions in postmenopausal women.

Methods: The USPSTF commissioned a review of the literature to update evidence about the benefits and harms of using menopausal hormone therapy to prevent chronic conditions, as well as whether the benefits and harms of hormone therapy differ by population subgroups defined by age; the presence of comorbid medical conditions; and the type, dose, and method of hormonal delivery.

Population: This recommendation applies to postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to women who are considering hormone therapy for the management

of menopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to women younger than 50 years who have had surgical menopause.

Recommendation: The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. (Grade D recommendation).

The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. (Grade D recommendation).

Ann Intern Med. 2013;158:* * * FILL THIS IN * * *. www.annals.org
For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published at www.annals.org on 23 October 2012.

The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific clinical preventive services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

SUMMARY OF RECOMMENDATIONS AND EVIDENCE

The USPSTF recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. This is a D recommendation.

The USPSTF recommends against the use of estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. This is a D recommendation.

This recommendation applies only to postmenopausal women who are considering hormone therapy for the pri-

mary prevention of chronic medical conditions. This is not a recommendation about the use of hormone therapy to treat menopausal symptoms, such as hot flashes or vaginal dryness; the USPSTF did not review the evidence related to this possible indication because it falls outside of the mission and scope of the USPSTF. This recommendation also does not apply to women younger than 50 years who have had surgical menopause.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

RATIONALE

Importance

The average U.S. woman who reaches menopause is expected to live another 30 years. During her remaining

See also:

Print

Summary for Patients

Figure. Menopausal hormone therapy for the primary prevention of chronic conditions: clinical summary of U.S. Preventive Services Task Force recommendation.

Annals of Internal Medicine



**MENOPAUSAL HORMONE THERAPY FOR THE PRIMARY PREVENTION OF CHRONIC CONDITIONS
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

Population	Postmenopausal women	Postmenopausal women who have had a hysterectomy
Recommendation	Do not prescribe combined estrogen and progestin for the prevention of chronic conditions. Grade: D	Do not prescribe estrogen for the prevention of chronic conditions. Grade: D

Risk Assessment	This recommendation applies to the average-risk population. Risk factors for a specific chronic disease or individual characteristics that affect the likelihood of a specific therapy-associated adverse event may cause a woman's net balance of benefits and harms to differ from that of the average population.	
Preventive Medications	<p>Although combined estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d) decreases the risk for fractures in postmenopausal women, there is an accompanying increased risk for serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, deep venous thrombosis, and pulmonary embolism.</p> <p>Estrogen therapy (specifically, oral conjugated equine estrogen, 0.625 mg/d) decreases the risk for fractures and has a small effect on the risk for invasive breast cancer, but it is also associated with important harms, such as an increased likelihood of stroke, deep venous thrombosis, and gallbladder disease.</p> <p>Neither combined estrogen and progestin therapy nor estrogen alone reduces the risk for coronary heart disease in postmenopausal women.</p>	
Balance of Benefits and Harms	The chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women.	The chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for osteoporosis and the use of preventive medications for breast cancer, as well as other relevant interventions for the primary or secondary prevention of chronic diseases in women, such as medications for cardiovascular disease and screening for coronary heart disease, high blood pressure, lipid disorders, colorectal cancer, breast cancer, and dementia. These recommendations are available at www.uspreventiveservicestaskforce.org .	

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

life span, the estimated risk for a chronic medical condition is approximately 30% for coronary heart disease (CHD) (1), 22% for dementia (2), 21% for stroke (3), 15% for hip fracture (4), and 11% for breast cancer (5).

Benefits and Harms of Preventive Medication
Combined Estrogen and Progestin

Many health outcomes potentially associated with the use of hormone therapy in postmenopausal women have been examined. The USPSTF found convincing evidence that estrogen and progestin therapy (specifically, oral conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d) is of moderate benefit in reducing the risk for fractures in postmenopausal women. However, the USPSTF found adequate evidence that its use is also associated with moderate harms, including an increase in the risk for stroke, dementia, gallbladder dis-

ease, and urinary incontinence. There is convincing evidence of a small increase in the incidence of invasive breast cancer and adequate evidence of a small increase in breast cancer deaths. There is also convincing evidence that estrogen and progestin therapy is associated with a small increased risk for deep venous thrombosis (DVT) and pulmonary embolism. Convincing evidence shows that the use of estrogen and progestin therapy does not have a beneficial effect on CHD and probably increases the risk for its occurrence. Table 1 provides absolute risk difference estimates for the benefits and harms of estrogen and progestin therapy.

Estrogen Alone

The use of estrogen without progestin has generally been restricted to women who have had a hysterectomy

Table 1. Estimated Event Rate Differences Associated With the Use of Oral Estrogen and Progestin in Postmenopausal Women Compared With No Treatment

Outcome	Event Rate Difference per 10 000 Person-Years	
	Events Prevented, n (95% CI)	Events Caused, n (95% CI)
Benefits		
Total fractures	46 (29 to 63)	–
Hip fracture	6 (1 to 10)	–
Harms		
Stroke	–	9 (2 to 15)
Deep venous thrombosis	–	12 (6 to 17)
Pulmonary embolism	–	9 (4 to 14)
Invasive breast cancer incidence	–	8 (3 to 14)
Gallbladder disease	–	20 (11 to 29)
Dementia	–	22 (5 to 39)
Self-reported urinary incontinence	–	872 (591 to 1153)

because unopposed estrogen use increases the risk for endometrial cancer in women with an intact uterus. The USPSTF found convincing evidence that estrogen (specifically, oral conjugated equine estrogen, 0.625 mg/d) is of moderate benefit in reducing the incidence of fractures. There is adequate evidence that the use of estrogen alone results in a small reduction in the risk for developing or dying of invasive breast cancer. However, the USPSTF found adequate evidence that its use is also associated with moderate harms, including the risk for stroke, gallbladder disease, and urinary incontinence, as well as a small increase in the risk for DVT. There is convincing evidence that estrogen does not have a beneficial effect on CHD. Table 2 provides absolute risk difference estimates for the benefits and harms of estrogen therapy.

Table 2. Estimated Event Rate Differences Associated With the Use of Unopposed Oral Estrogen in Postmenopausal Women Without a Uterus Compared With No Treatment

Outcome	Event Rate Difference per 10 000 Person-Years	
	Events Prevented, n (95% CI)	Events Caused, n (95% CI)
Benefits		
Invasive breast cancer incidence	8 (1 to 14)	–
Breast cancer deaths	2 (1 to 3)	–
Total fractures	56 (37 to 75)	–
Hip fracture	7 (1 to 12)	–
Harms		
Stroke	–	11 (2 to 20)
Deep venous thrombosis	–	7 (1 to 14)
Gallbladder disease	–	33 (20 to 45)
Self-reported urinary incontinence	–	1271 (883 to 1660)

USPSTF Assessment

The USPSTF concludes with high certainty that the chronic disease prevention benefits of combined estrogen and progestin do not outweigh the harms in most postmenopausal women.

The USPSTF concludes with moderate certainty that the chronic disease prevention benefits of estrogen are unlikely to outweigh the harms in most postmenopausal women who have had a hysterectomy.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies only to postmenopausal women who are considering hormone therapy for the primary prevention of chronic medical conditions. It does not apply to women who are considering hormone therapy for the management of menopausal symptoms, such as hot flashes or vaginal dryness. It also does not apply to women younger than 50 years who have had surgical menopause.

Assessment of Risk

This recommendation applies to the average-risk population. Risk factors for a specific chronic disease or individual characteristics that affect the likelihood of having a specific therapy-associated adverse event may cause a woman’s net balance of benefits and harms to differ from that of the average population.

Use of Preventive Medication

Although combined estrogen and progestin therapy decreases the risk for fractures in postmenopausal women (about 46 fractures of any type prevented per 10 000 person-years), there is an accompanying increased risk for serious adverse events, such as stroke, invasive breast cancer, dementia, gallbladder disease, DVT, and pulmonary embolism (Table 1). It does not decrease a woman’s risk for CHD, and results from the Women’s Health Initiative (WHI) randomized, controlled trial show a trend toward an increased likelihood of having a cardiac event (hazard ratio [HR], 1.22 [95% CI, 0.99 to 1.51]) (6, 7).

Estrogen-only therapy is associated with a reduction in the risk for fractures (about 56 fractures of any type prevented per 10 000 person-years), as well as a small reduction in the risk for invasive breast cancer (about 8 fewer cases per 10 000 person-years) and for dying of the disease (about 2 fewer deaths per 10 000 person-years) (Table 2). The biological mechanism underlying the apparent protective effect of estrogen alone, as compared with the harmful effect of estrogen and progestin combined, on the development of invasive breast cancer in postmenopausal women is unclear. However, estrogen-only therapy is also associated with important harms, such as an increased likelihood of stroke, DVT, and gallbladder disease. It does not reduce the risk for CHD (WHI results: HR, 0.95 [CI, 0.78 to 1.15]) (6, 7).

In addition to other harms, combined oral estrogen and progestin and oral estrogen-only therapy have both been shown to be associated with an increased incidence of stress, mixed, or any urinary incontinence in previously asymptomatic women after 1 year (8). This outcome was measured by a self-administered questionnaire; additional randomized trials that focus on urinary incontinence as a primary study end point and use urodynamic testing as part of the assessment strategy would be useful to further clarify the effect of hormone therapy on urinary symptoms.

U.S. Food and Drug Administration (FDA)-approved indications for hormone therapy in postmenopausal women are limited to the treatment of menopausal symptoms and the prevention of osteoporosis. A black box warning indicates that estrogen with or without progestin should be prescribed at the lowest effective dose and for the shortest duration of use consistent with treatment goals and risks for the individual woman (9).

Timing of Intervention

No randomized trials have prospectively evaluated the effect of the timing of initiation of hormone therapy relative to menopause onset on associated benefits and harms. Post hoc subgroup analyses suggest an increased probability of harm with increasing age at initiation and longer duration of use, but these findings are not consistent across all trials and generally do not reach statistical significance (6, 7).

Other Approaches to Prevention

Women have different characteristics and risk factors, such as age, family history, and comorbid medical conditions, that affect their likelihood of developing a given chronic disease; they may also differentially value preventing specific outcomes. As such, any choice of therapy should be based on the intersection of a woman's clinical situation, preferences, and values to maximize benefits over harms.

In the case of fractures, other effective interventions for treating women with low bone density include weight-bearing exercise, bisphosphonates, and calcitonin (the USPSTF addressed screening for osteoporosis in 2011 [10]). In women at high risk for breast cancer, the use of tamoxifen or raloxifene could potentially be a preventive strategy in selected situations, depending on the woman's underlying risk for stroke and thrombotic events (11). In addition to breast cancer chemoprevention and screening for osteoporosis, the USPSTF has issued recommendations on other relevant interventions for the primary or secondary prevention of chronic diseases in women, including medications for cardiovascular disease and screening for CHD, high blood pressure, lipid disorders, colorectal cancer, breast cancer, and dementia. All are available at www.uspreventiveservicestaskforce.org.

OTHER CONSIDERATIONS

Research Needs and Gaps

The average age of women participating in WHI was approximately 64 years, largely past the point of menopause onset. Given that most women who currently use hormone therapy are transitioning through menopause, new research to help better define whether there is a differential balance of benefits and harms based on age at initiation (including surgical or premature menopause), duration of use, and dose or delivery mechanism would be useful. Although some subgroup analyses of previously conducted trials have been performed for these factors, they have been limited by lack of power and have largely been post hoc (exploratory, not confirmatory) in nature. Additional research to better understand the apparently contradictory finding that combined hormone therapy increases the risk for invasive breast cancer incidence and possibly breast cancer death, whereas estrogen alone exerts a small but statistically significant protective effect on these outcomes, is also warranted.

DISCUSSION

Burden of Disease

Hormone therapy has been considered as a potential preventive intervention for several chronic conditions among postmenopausal women, including CHD, dementia, and osteoporosis. In 2008, 14% of U.S. women aged 60 to 79 years and 21% of women aged 80 years or older were living with CHD (12), and 16% of women aged 71 years or older were living with some form of dementia (13). In the same year, approximately 189 000 women died of CHD (12), and 58 000 died of Alzheimer disease (14). Eleven percent of U.S. women aged 65 years or older report a diagnosis of osteoporosis, and 6% report ever having a hip fracture (4).

Scope of Review

Key questions in the current review include the benefits and harms of menopausal hormone therapy when used to prevent chronic conditions, as well as whether the benefits and harms of hormone therapy differ by population subgroups defined by age; the presence of comorbid medical conditions; and the type, dose, and method of hormonal delivery. Evidence included in the current review was limited to published randomized, controlled trials of menopausal hormone therapy versus placebo.

Benefits and Harms of Preventive Medication

Nine placebo-controlled randomized trials evaluated the efficacy of hormone therapy for the prevention of chronic conditions (6, 7). Of these, the fair-quality WHI was the only trial powered to evaluate the effectiveness of hormone therapy for the primary prevention of multiple chronic conditions. It compared oral conjugated equine estrogen, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or oral conjugated equine estrogen, 0.625 mg/d,

alone with placebo in women aged 50 to 79 years. The Women's Health Initiative represents the largest trial with the longest duration of follow-up and is most applicable to the target population for this recommendation (average-risk postmenopausal women living in the United States). The estimated rates of benefits and harms of hormone therapy presented in this recommendation (Tables 1 and 2) are derived from WHI results; findings from other available trials are generally consistent with those of WHI in the observed direction of effect.

Cardiovascular Events

The primary outcome of interest in WHI was the rate of CHD (defined as CHD death plus total myocardial infarction rate). Although observational evidence previously suggested a protective effect of hormone therapy on CHD, these findings were not replicated in WHI. Combined estrogen and progestin therapy showed a trend toward an increased risk for CHD after 5 years of follow-up, which persisted through 8.6 years (HR, 1.22 [CI, 0.99 to 1.50]). For the overall enrolled population, there was no reduction in the risk for CHD with estrogen alone after nearly 8 years of follow-up (HR, 0.95 [CI, 0.78 to 1.15]) (6, 7). Subgroup analysis did reveal a potential reduction in CHD in women aged 50 to 59 years (HR, 0.59 [CI, 0.38 to 0.90]) but not in women aged 60 to 69 or 70 to 79 years (15); this finding warrants confirmation in future studies.

Women's risk for stroke is statistically significantly increased with the use of postmenopausal hormone therapy. The estrogen-only group in WHI was stopped early because of the observed increased stroke rate (HR, 1.36 [CI, 1.08 to 1.71]); the estrogen and progestin group reported similar findings (6, 7).

Fractures

Compared with placebo, estrogen and progestin decreased the rates of hip (HR, 0.67 [CI, 0.47 to 0.95]), vertebral (HR, 0.68 [CI, 0.48 to 0.96]), and total fractures (HR, 0.76 [CI, 0.69 to 0.83]) in WHI after 8.6 years of follow-up. Estrogen alone showed similar reductions in risk at about 8 years of follow-up (6, 7).

Cognitive Function

Before WHI, observational evidence suggested that hormone therapy might be associated with a reduction in the risk for dementia or other forms of cognitive impairment. Results from the WHI Memory Study—which ran concurrently with and used participants aged 65 to 79 years from the main WHI trial—do not support this conclusion. After approximately 4 years of follow-up, a statistically significant increase in the risk for probable dementia was seen in the estrogen plus progestin group (HR, 2.05 [CI, 1.21 to 3.48]). No statistically significant difference was seen in the rate of probable dementia between women

receiving estrogen alone versus placebo (HR, 1.49 [CI, 0.83 to 2.66]). No statistically significant difference was seen in the incidence of mild cognitive impairment for women using either combined hormone therapy (HR, 1.07 [CI, 0.74 to 1.55]) or estrogen alone (HR, 1.34 [CI, 0.95 to 1.89]) (6, 7). Both combined estrogen and progestin and estrogen alone were associated with a statistically significant increase in risk compared with placebo when a composite outcome of probable dementia or mild cognitive impairment was used (HR, 1.44 [CI, 1.04 to 1.99] and 1.38 [CI, 1.01 to 1.89], respectively), although this was not the primary outcome of the trial (16).

Invasive Breast Cancer

The Women's Health Initiative was designed to evaluate the incidence of invasive breast cancer as the primary adverse event of interest for hormone therapy use. Results for combined estrogen and progestin therapy confirm a statistically significant increase in the risk for invasive breast cancer (HR, 1.25 [CI, 1.07 to 1.46]), as well as a trend toward increased breast cancer deaths (HR, 1.96 [CI, 1.00 to 4.04]) after 11 years of follow-up (6, 7).

Unexpectedly, the estrogen-only trial showed a small but statistically significant reduction in the incidence of invasive breast cancer compared with placebo after nearly 11 years of follow-up (HR, 0.77 [CI, 0.62 to 0.95]; absolute risk reduction, 8 [CI, 1 to 14]) (6, 7) and a small (about 2 fewer cases per 10 000 person-years) reduction in breast cancer mortality (HR, 0.37 [CI, 0.13 to 0.91]), as well as a reduction in the risk for all-cause mortality after breast cancer diagnosis (HR, 0.62 [CI, 0.39 to 0.97]) (17). However, the CI for the HR is wide, which makes it difficult to be certain about the exact magnitude of the risk reduction expected to accrue in the population. Subgroup analyses suggest that lower breast cancer incidence was limited to participants without a family history of breast cancer or a personal history of breast biopsy.

The underlying reason for the discrepancy in findings between women using estrogen and progestin versus estrogen only is unclear. It is important to note that the baseline characteristics of the participants in the combined estrogen and progestin trial and the estrogen-only trial differed in important ways, and these trials were not designed to permit head-to-head comparisons between the 2 regimens. As such, future research is needed to understand whether the difference is attributable to the biochemical mechanisms of progestin itself, differences in characteristics between women who have had a hysterectomy and those who have not, or other causes.

Thromboembolic Events

Both combined therapy and estrogen alone are associated with a statistically significantly increased risk for DVT (HR, 1.88 [CI, 1.38 to 2.55] and 1.47 [CI, 1.06 to 2.05], respectively). Women receiving estrogen and progestin

therapy also had a statistically significant increase in the incidence of pulmonary embolism (HR, 1.98 [CI, 1.36 to 2.87]) compared with estrogen alone (HR, 1.37 [CI, 0.90 to 2.07]) (6, 7).

Gallbladder Disease

The risks for cholecystitis and cholelithiasis are both statistically significantly increased with the use of estrogen and progestin after about 5 to 7 years of follow-up (HR for combined risk, 1.61 [CI, 1.30 to 2.00]) and with estrogen alone (HR for combined risk, 1.79 [CI, 1.44 to 2.22]) (6, 7).

Urinary Incontinence

The Women's Health Initiative found an increased risk for self-reported, new-onset stress, urge, or mixed urinary incontinence in postmenopausal women after 1 year of treatment with either combined oral hormone therapy (HR for combined risk, 1.39 [CI, 1.27 to 1.52]) or oral estrogen alone (HR for combined risk, 1.53 [CI, 1.37 to 1.71]). Symptoms of incontinence were found to persist for a subsample of estrogen and progestin users at 3 years of follow-up (6, 7). As previously noted, diagnosis was based on self-reporting rather than formal urodynamic testing, which may limit the precision of the observed estimates.

A recent systematic review of nonsurgical interventions for urinary incontinence found improvements in stress incontinence with the use of topical estrogen therapy (intra-vaginal tablets or ovules) compared with placebo; however, transdermal estrogen patches worsened both stress and any urinary incontinence (18). The reason for the discrepancy in effect between the different methods of estrogen delivery is unclear. The systematic review for the USPSTF included results for women who were continent at the time of study entry and developed incontinence during the study (that is, incident cases) as opposed to those with established incontinence.

Diabetes

A secondary analysis of WHI found a decreased risk for a new diagnosis of diabetes requiring pharmaceutical treatment among women receiving estrogen plus progestin (HR, 0.79 [CI, 0.67 to 0.93]). No statistically significant association was found for estrogen use alone (HR, 0.88 [CI, 0.77 to 1.01]), although the trend was in the same direction of effect. To assess the incident diabetes rate, participants completed a semiannual questionnaire that asked, "Since the date given on the front of this form, has a doctor prescribed any of the following pills or treatments?" Choices included "pills for diabetes" and "insulin shots for diabetes." Diabetes was thus determined via self-report of a new physician diagnosis of diabetes treated with pharmacologic agents rather than through blood glucose measurement (6, 7). Given the limitations of WHI in eval-

uating this outcome, the USPSTF concludes that there is insufficient evidence to determine the effect of hormone therapy on the development of type 2 diabetes.

Colorectal Cancer

Long-term follow-up from WHI reported no statistically significant effect of combined estrogen plus progestin or estrogen-only therapy (HR, 0.75 [CI, 0.57 to 1.00] and 1.11 [CI, 0.82 to 1.50], respectively) on the risk for colorectal cancer (15, 19), but CIs are wide and do not definitively rule out a potential small benefit for combined therapy.

Other Cancer

The USPSTF found insufficient evidence to determine whether hormone therapy has an adverse effect on the risk for developing or dying of lung cancer. In WHI, neither combined estrogen and progestin therapy nor estrogen-only therapy was found to be statistically significantly associated with an increased incidence of lung cancer; however, a post hoc analysis reported that the use of combined therapy was associated with an increased risk for death from lung cancer compared with placebo (HR, 1.71 [CI, 1.16 to 2.52]) (6, 7). No statistically significant increase in lung cancer mortality was seen with the use of oral estrogen alone (20).

No statistically significant associations were found between the use of estrogen and progestin and the risk for ovarian or cervical cancer; these outcomes were not reported for estrogen alone (6, 7).

Estimate of Magnitude of Net Benefit

Although the use of hormone therapy to prevent chronic conditions in postmenopausal women is associated with several potential benefits, there are substantial, well-documented harms to consider as well. The magnitude of adverse consequences associated with postmenopausal hormone therapy is moderate; the benefits are small in the case of combined estrogen and progestin therapy and small to moderate in the case of estrogen alone. Therefore, the USPSTF concludes with high certainty that there is zero to negative net benefit for the use of combined estrogen and progestin therapy for the prevention of chronic conditions and concludes with moderate certainty that there is no net benefit for the use of estrogen alone.

How Does Evidence Fit With Biological Understanding?

The incidence of cardiovascular disease in premenopausal women is lower than in men of the same age; this difference between the sexes decreases or disappears as women age past menopause onset. Estrogen has also been associated with a reduction in low-density lipoprotein cholesterol and an increase in high-density lipoprotein cholesterol, and it is a vasodilator. Despite favorable relationships with these surrogate outcomes and suggestive observational evidence, randomized, controlled trials showed a detrimen-

tal effect of hormone therapy on the risk for stroke and CHD. Many potential explanations have been proposed for these divergent findings, including, among others, the effect of timing of administration (that is, age at initiation and time since menopause onset), variations in dose and formulation, and the thromboembolic properties of both estrogen and progestin, but the reason underlying the contradictory results is not entirely clear (21).

Another apparently paradoxical finding is that estrogen and progestin impart a small increase in the risks for developing and dying of breast cancer, whereas estrogen alone seems to slightly reduce these risks. Estrogen generally acts to stimulate breast cell proliferation and inhibit apoptosis; however, some preclinical studies have shown that, after a period of estrogen deprivation, the administration of estrogen actually induces breast cell apoptosis because of changes in breast tumor gene expression profiles. It has therefore been hypothesized that some cases of breast cancer in postmenopausal women will only survive a limited range of estrogen exposure and that substantial increases in the level of exposure (for example, exogenous estrogen use) may inhibit breast cancer growth (22).

RESPONSE TO PUBLIC COMMENTS

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 29 May to 26 June 2012. In response to the comments received, the USPSTF has clarified that this recommendation statement only applies to the use of hormone therapy in postmenopausal women for the primary prevention of chronic diseases, such as CHD or fractures. This is not a recommendation about the use of hormone therapy to treat symptoms of menopause, such as hot flashes or vaginal atrophy. The USPSTF is charged with evaluating the benefits and harms of clinical interventions intended to prevent disease; questions about treatment of symptomatic conditions are beyond its scope of work.

The USPSTF has also clarified the specific form, dosage, and route of administration of the estrogen and progestin and estrogen-only therapies used in WHI (oral conjugated equine estrogen, 0.625 mg/d, with or without oral medroxyprogesterone acetate, 2.5 mg/d) and notes that the estimates of the absolute risks and benefits it describes throughout this recommendation statement are derived primarily from this study. There is no convincing evidence to assert that the ultimate balance of benefits and harms might be substantially altered by using different approaches; however, available data are limited, and additional research would be useful to reveal whether any differences do exist.

Some commenters asked the USPSTF to provide information about the use of compounded bioidentical hormones in menopausal and postmenopausal women. According to the FDA, "bioidentical hormone replacement therapy" is a marketing term rather than a formally defined

drug classification. To date, the FDA has not approved any type or class of bioidentical hormone therapy for the prevention of chronic diseases in postmenopausal women, and the safety and effectiveness of these products have not been evaluated through the FDA's drug approval process (23). In its review of the evidence, the USPSTF did not identify any randomized trials that have studied the potential benefits or harms of bioidentical hormones for the prevention of chronic conditions in postmenopausal women.

RECOMMENDATIONS OF OTHERS

The American Heart Association and the American Congress of Obstetricians and Gynecologists recommend against the use of menopausal hormone therapy for the primary or secondary prevention of cardiovascular disease (24, 25). The Canadian Task Force on Preventive Health Care and the American Academy of Family Physicians recommend against the use of hormone therapy in postmenopausal women for the prevention of chronic conditions (26, 27); the American Academy of Family Physicians is currently in the process of updating its guideline on the subject. The North American Menopause Society advocates that individualization is of key importance in the decision to use hormone therapy and that it should incorporate women's health and quality-of-life priorities, as well as such personal risk factors as risk for venous thrombosis, CHD, stroke, and breast cancer. The society further states that hormone therapy should not be used for coronary protection in women of any age and does not recommend hormone therapy to prevent cognitive aging or dementia (28).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

Disclaimer: Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Financial Support: The USPSTF is an independent, voluntary body. The U.S. Congress mandates that the Agency for Healthcare Research and Quality support the operations of the USPSTF.

Potential Conflicts of Interest: Disclosure forms from USPSTF members can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2392.

Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

References

- Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353:89-92. [PMID: 10023892]
- Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. *Lancet Neurol*. 2007;6:1106-14. [PMID: 18031707]

3. **Sheshadri S, Beiser A, Kelly-Hayes M, Kase CS, Au R, Kannel WB, et al.** The lifetime risk of stroke: estimates from the Framingham Study. *Stroke*. 2006;37:345-50. [PMID: 16397184]
4. **U.S. Department of Health and Human Services.** Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2004. Accessed at www.surgeongeneral.gov/library/reports/bonehealth/content.html on 22 May 2012.
5. **Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, et al.** SEER Cancer Statistics Review, 1975–2008. Bethesda, MD: National Cancer Institute; 2011. Accessed at www.seer.cancer.gov/csr/1975_2008/index.html on 22 May 2012.
6. **Nelson HD, Walker M, Zakher B, Mitchell J.** Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U.S. Preventive Services Task Force recommendations. *Ann Intern Med*. 2012;157:104-13. [PMID: 22786830]
7. **Nelson HD, Walker M, Zakher B, Mitchell J.** Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions: Systematic Review to Update the 2002 and 2005 U.S. Preventive Services Task Force Recommendations. Evidence Synthesis no. 93. AHRQ Publication no. 12-05168-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
8. **Hendrix SL, Cochrane BB, Nygaard IE, Handa VL, Barnabei VM, Iglesia C, et al.** Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005;293:935-48. [PMID: 15728164]
9. **Pfizer Pharmaceuticals.** Premarin Package Insert. New York: Pfizer Pharmaceuticals; 2011. Accessed at <http://labeling.pfizer.com/showlabeling.aspx?id=131> on 22 May 2012.
10. **U.S. Preventive Services Task Force.** Screening for osteoporosis: U.S. preventive services task force recommendation statement. *Ann Intern Med*. 2011;154:356-64. [PMID: 21242341]
11. **U.S. Preventive Services Task Force.** Chemoprevention of breast cancer: recommendations and rationale. *Ann Intern Med*. 2002;137:56-8. [PMID: 12093249]
12. **Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2-e220. [PMID: 22179539]
13. **Alzheimer's Association.** 2011 Alzheimer's Disease Facts and Figures. Chicago: Alzheimer's Association; 2011. Accessed at www.alz.org/downloads/facts_figures_2011.pdf on 22 May 2012.
14. **Miniño AM, Murphy SL, Xu J, Kochanek KD.** Deaths: final data for 2008. *Natl Vital Stat Rep*. 2011;59:1-126. [PMID: 22808755]
15. **LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al; WHI Investigators.** Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA*. 2011;305:1305-14. [PMID: 21467283]
16. **Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al; Women's Health Initiative Memory Study.** Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291:2947-58. [PMID: 15213206]
17. **Anderson GL, Chlebowski RT, Aragaki AK, Kuller LH, Manson JE, Gass M, et al.** Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13:476-86. [PMID: 22401913]
18. **Shamliyan T, Wyman J, Kane RL.** Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness. Comparative Effectiveness Review no. 36. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Accessed at www.ncbi.nlm.nih.gov/books/NBK92960 on 22 May 2012.
19. **Heiss G, Wallace R, Anderson GL, Aragaki A, Beresford SA, Brzyski R, et al; WHI Investigators.** Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299:1036-45. [PMID: 18319414]
20. **Chlebowski RT, Anderson GL, Manson JE, Schwartz AG, Wakelee H, Gass M, et al.** Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. *J Natl Cancer Inst*. 2010;102:1413-21. [PMID: 20709992]
21. **Yang XP, Reckelhoff JF.** Estrogen, hormonal replacement therapy and cardiovascular disease. *Curr Opin Nephrol Hypertens*. 2011;20:133-8. [PMID: 21178615]
22. **Chlebowski RT, Anderson GL.** Changing concepts: Menopausal hormone therapy and breast cancer. *J Natl Cancer Inst*. 2012;104:517-27. [PMID: 22427684]
23. **U.S. Food and Drug Administration.** Bio-Identicals: Sorting Myths From Facts. Silver Spring, MD: U.S. Food and Drug Administration; 2008. Accessed at www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm049312.pdf on 27 August 2012.
24. **Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al.** Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243-62. [PMID: 21325087]
25. **American College of Obstetricians and Gynecologists Committee on Gynecologic Practice.** ACOG Committee Opinion No. 420, November 2008: hormone therapy and heart disease. *Obstet Gynecol*. 2008;112:1189-92. [PMID: 18978127]
26. **Wathen CN, Feig DS, Feightner JW, Abramson BL, Cheung AM; Canadian Task Force on Preventive Health Care.** Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ*. 2004;170:1535-7. [PMID: 15136543]
27. **American Academy of Family Physicians.** Hormone Replacement Therapy. Leawood, KS: American Academy of Family Physicians; 2005. Accessed at www.aafp.org/online/en/home/clinical/exam/hormonereplacement.html on 22 May 2012.
28. **North American Menopause Society.** The 2012 hormone therapy position statement of: The North American Menopause Society. *Menopause*. 2012;19:257-71. [PMID: 22367731]

APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (Baylor College of Medicine, Houston, Texas); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas);

Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Joy Melnikow, MD, MPH (University of California, Davis, Sacramento, California); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Douglas K. Owens, MD, MS (Veteran Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); Carolina Reyes, MD, MPH (Virginia Hospital Center, Arlington, Virginia); and Timothy J. Wilt, MD, MPH (University of Minnesota Department of Medicine and Minneapolis Veteran Affairs Medical Center, Minneapolis, Minnesota).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	<i>Note: The following statement is undergoing revision.</i> Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms, there is likely to be only a small benefit from this service.	Offer or provide this service only if other considerations support offering or providing the service in an individual patient.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.