Hormone Therapy for the Prevention of Chronic Conditions in Postmenopausal Women: Recommendation Statement

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*Members of the Task Force at the time this recommendation was finalized. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm.

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This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on hormone therapy for the prevention of chronic conditions in postmenopausal women and the supporting scientific evidence and updates the the Task Force's 2002 recommendations on hormone replacement therapy(1). The updated statement is based on the results of the Women's Health Initiative randomized controlled trial as well as the information in the 2002 summary of the evidence on this topic, which is available on the USPSTF Web site (www.preventiveservices.ahrq.gov). Explanations of the ratings and of the strength of overall evidence are given in Appendix A and Appendix B, respectively. The recommendation statement is also available in print from the Agency for Healthcare Research and Quality (AHRQ) Publications Clearinghouse (call 1-800-358-9295, or e-mail ahrqpubs@ahrq.gov). and is posted on the Web site of the National Guideline Clearinghouse™ (www.guideline.gov).

Recommendations made by the USPSTF are independent of the U.S. Government. They should not be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

Summary of Recommendations

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women. D recommendation.

The USPSTF found good evidence that the use of combined estrogen and progestin results in both benefits and harms. Benefits include reduced risk for fracture (good evidence) and colorectal cancer (fair evidence). Combined estrogen and progestin has no beneficial effect on coronary heart disease and may even pose an increased risk (good evidence). Other harms include increased risk for breast cancer (good evidence), venous thromboembolism (good evidence), stroke (fair evidence), cholecystitis (fair evidence), dementia (fair evidence), and lower global cognitive function (fair evidence). Because of insufficient evidence, the USPSTF could not assess the effects of combined estrogen and progestin on the incidence of ovarian cancer, mortality from breast cancer or coronary heart disease, or all-cause mortality. The USPSTF concluded that the harmful effects of

combined estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women.

The U.S. Preventive Services Task Force (USPSTF) recommends against the routine use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy. D recommendation.

The USPSTF found good evidence that the use of unopposed estrogen results in both benefits and harms. The benefits include reduced risk for fracture (good evidence). Harms include increased risk for venous thromboembolism (fair evidence), stroke (fair evidence), dementia (fair evidence), and lower global cognitive functioning (fair evidence). There is fair evidence that unopposed estrogen has no beneficial effect on coronary heart disease. Because of insufficient evidence, the USPSTF could not assess the effects of unopposed estrogen on the incidence of breast cancer, ovarian cancer, or colorectal cancer as well as breast cancer mortality or all-cause mortality . The USPSTF concluded that the harmful effects of unopposed estrogen are likely to exceed the chronic disease prevention benefits in most women.

Clinical Considerations

The balance of benefits and harms for a woman will be influenced by her personal preferences, her risks for specific chronic diseases, and the presence of menopausal symptoms. A shared decisionmaking approach to preventing chronic diseases in perimenopausal and postmenopausal women involves consideration of individual risk factors and preferences in selecting effective interventions for reducing the risks for fracture, heart disease, and cancer. Other USPSTF recommendations for prevention of chronic diseases (screening for osteoporosis, high blood pressure, lipid disorders, breast cancer, and colorectal cancer; and counseling to prevent tobacco use) are available at: www.preventiveservices.ahrq.gov.

- The USPSTF did not consider the use of hormone therapy for the management of menopausal symptoms, which is the subject of recommendations by other expert groups. Women and their clinicians should discuss the balance of risks and benefits before deciding to initiate or continue hormone therapy for menopausal symptoms. For example, for combined estrogen and progestin, some risks (such as the risks for venous thromboembolism, coronary heart disease [CHD], and stroke) arise within the first 1 to 2 years of therapy, and other risks (such as the risk for breast cancer) appear to increase with longer-term hormone therapy. The populations of women using hormone therapy for symptom relief may differ from those who would use hormone therapy for prevention of chronic disease (eg, age differences). Other expert groups have recommended that women who decide to take hormone therapy to relieve menopausal symptoms use the lowest effective dose for the shortest possible time.
- Although estrogen alone or in combination with progestin reduces the risk for fractures in women, other effective medications (eg, bisphosphonates and calcitonin) are available for treating women with low bone density to prevent fractures. The role of chemopreventive agents in preventing fractures in women without low bone density is unclear. The USPSTF addressed screening for osteoporosis in postmenopausal women in 2002(2).
- Unopposed estrogen increases the risk for endometrial cancer in women who have an intact uterus. Clinicians should use a shared decision-making approach when discussing the possibility of using unopposed estrogen in women who have not had a hysterectomy(3).

Discussion

The median age of menopause in women in the United States is 51 years (range 41-59 years), but ovarian production of estrogen and progestin begins to decrease years before the cessation of menses. The average woman in the United States who reaches menopause has a life expectancy of nearly 30 years. The probability that a menopausal woman will develop various chronic diseases during her lifetime has been estimated to be 46% for CHD, 20% for stroke, 15% for hip fracture, 10% for breast cancer, and 2.6% for

endometrial cancer(4). In North America, an estimated 7% to 8% of people 75 to 84 years of age have dementia, and more than 90% of cases of colorectal cancer occur after the age of 50(5).

Benefits of Hormone Therapy

Osteoporosis and Fractures

Good evidence from observational studies and randomized clinical trials demonstrates that estrogen therapy increases bone density and reduces the risk for fractures. The combined estrogen-progestin arm of the Women's Health Initiative (WHI) trial(6), a fair-quality study, found significant reductions in total fracture risk (hazard ratio [HR], 0.76; adjusted 95% confidence interval [CI], 0.63-0.92) among healthy women taking estrogen and progestin. This arm of the WHI trial also showed reductions for hip and vertebral fracture, although these did not achieve statistical significance(6). (In its analysis, the USPSTF used nominal 95% CIs for the primary outcomes and adjusted 95% CIs for all secondary outcomes.)

The estrogen-only arm of the WHI trial also reported decreased risk for hip and vertebral fracture, which also did not reach statistical significance(7). A meta-analysis of 22 trials of estrogen reported an overall 27% reduction in non-vertebral fractures (relative risk [RR], 0.73; [95% CI, 0.56-0.94]), although the quality of individual studies varied(8). The Heart and Estrogen/progestin Replacement Study (HERS) and its unblinded follow-up study, HERS II(9), a fair-quality trial of combined estrogen-progestin for the secondary prevention of heart disease that reported many other outcomes, found no reduction in hip, wrist, vertebral, or total fractures with hormone therapy (relative hazard [RH] for total fractures, 1.04; 95% CI, 0.87-1.25). Overall, a good-quality body of evidence supports the efficacy of hormone therapy in increasing bone density and decreasing fracture risk.

Colorectal Cancer

Results from the WHI study(6) and HERS(9) showed a trend toward reduced incidence of colon cancer (HR, 0.63; adjusted 95% CI, 0.32-1.24 and RH, 0.81; 95% CI, 0.46-1.45, respectively), but the trend did not reach statistical significance. The estrogen-only arm

of the WHI trial showed neither benefit nor harm for colorectal cancer risk (HR, 1.08; adjusted 95% CI, 0.63-1.86) (7). A meta-analysis of 18 observational studies of postmenopausal women reported a 20% reduction in colon cancer (RR, 0.80; 95% CI, 0.74-0.86) and a 19% reduction in rectal cancer (RR, 0.81; 95% CI, 0.72-0.92) among women who had ever used combined estrogen-progestin or estrogen alone compared with women who had never used hormone therapy(10). This decrease in risk was more apparent when current users were compared with those who had never used hormone therapy (RR, 0.66; 95% CI, 0.59-0.74). Overall, the evidence suggesting a trend toward reduction of colorectal cancer risk with combined hormone therapy should be interpreted cautiously until controlled trials clarify whether therapy has either no benefit or modest benefit.

Harms of Hormone Therapy

Breast Cancer

The estrogen-progestin arm of the WHI study was terminated after an average of 5.2 years of followup because "evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and pulmonary embolism, outweighed the evidence of benefit for fractures and possible benfit for colon cancer(6)." This study showed an increased invasive breast cancer incidence (HR, 1.26; nominal 95% CI, 1.00-1.59). However, no effect on breast cancer mortality was observed. Comparable increases in breast cancer incidence were observed among women taking estrogen and progestin over 6.8 years of follow-up in HERS(9). The U.K. Million Women Study, a fair-quality study, showed an increased risk for breast cancer in current users of combined estrogen-progestin (RR, 2.00; 95% CI, 1.91-2.09) compared with those who had never used hormone therapy(11). Results from two good-quality cohort studies conflict on the effects of long-term hormone therapy on breast cancer mortality(12,13). Overall, there is a good-quality body of evidence indicating that combined estrogen-progestin increases breast cancer risk. It is unclear whether the combination of estrogen-progestin confers a greater breast cancer risk than estrogen alone. In studies of estrogen alone, the results are conflicting: the Million Women Study showed an increased risk for breast cancer in

current users of estrogen only (RR, 1.30; 95% CI, 1.22-1.38) compared with those who had never used it (11); but the estrogen-only arm of the WHI trial showed a trend toward breast cancer prevention (HR, 0.77; nominal 95% CI, 0.59-1.01)(7).

Coronary Heart Disease

In the WHI study, women who took combined estrogen-progestin daily, compared with women taking placebo, had an increased risk for CHD (fatal and non-fatal myocardial infarctions), which became evident shortly after initiation of the study (HR, 1.29; nominal 95% CI, 1.02-1.63)(6). However, mortality from CHD was not significantly increased among the women taking combined hormone therapy daily. One meta-analysis of observational studies showed a statistically significant reduction in CHD (RR, 0.80; 95% CI, 0.68-0.95) among current hormone therapy users, but not among those who had used hormone therapy in the past or among those who had never used it(14). This meta-analysis also showed that CHD mortality in observational studies was reduced among current hormone therapy users (RR, 0.62; 95% CI, 0.40-0.90) but was not reduced among those who had used hormone therapy in the past. However, among studies that controlled for socioeconomic status (social class, education, or income), no CHD benefit was seen among current hormone therapy users, suggesting that the observed difference may be due to confounding by socioeconomic status and other lifestyle factors (eg, exercise or alcohol use) rather than use of hormone therapy. Thus, selection bias (in this case, the tendency of healthier women to use hormone therapy) appears to explain the apparent protective effect of estrogen against CHD seen in observational studies. The estrogen-only arm of the WHI trial showed no decreased risk for CHD(7).

Stroke

A meta-analysis of 9 observational primary prevention studies suggests that hormone therapy is associated with a small increase in stroke incidence (RR, 1.12; 95% CI, 1.01-1.23), due primarily to an increase in thromboembolic stroke (RR, 1.20; 95% CI, 1.01-1.40)(14,15). The risk for subarachnoid bleeding and hemorrhagic stroke was not increased, and the overall stroke mortality was marginally reduced (RR, 0.81; 95% CI, 0.71-0.92). These results are consistent with findings from the WHI, which reported increased incidence of stroke in women taking combined estrogen-progestin daily (HR,

1.41; adjusted 95% CI, 0.86-2.31)(6). The estrogen-only arm of the WHI trial, which was terminated after an average of 6.8 years of followup, showed a trend toward increased stroke risk with unopposed estrogen use (HR, 1.39; adjusted 95% CI, 0.97-1.99)(7).

Venous Thromboembolism (Deep Venous Thrombosis and Pulmonary Embolism)

In a meta-analysis of 12 studies (3 randomized controlled trials, 8 case-control studies, and 1 cohort study), hormone therapy (estrogen alone or in combination with progestin) was associated with an increased risk for venous thromboembolism (RR, 2.14; 95% CI, 1.64-2.81)(16,17). Five of 6 studies that examined the effects of hormone therapy over time reported that the risk was highest within the first year of use (RR, 3.49; 95% CI, 2.33-5.59). These results are consistent with the findings in the estrogen-progestin arm of the WHI(6), which reported a 2-fold increased rate of venous thromboembolic disease, including deep venous thrombosis and pulmonary embolism, in women taking combined estrogen-progestin daily. The estrogen-only arm of the WHI trial showed a trend toward increased risk for venous thromboembolism with unopposed estrogen use (HR, 1.33; adjusted 95% CI, 0.86-2.08)(7).

Cognition and Dementia

While earlier studies showed a beneficial effect of hormone therapy on cognition, these studies had marked heterogeneity and variation in assessment of outcomes. For example, 9 randomized controlled trials examining the effect of hormone therapy on cognition in women showed improvement in verbal memory, vigilance, reasoning, and motor speed; however, these trials may have biased results, since they were conducted with women experiencing menopausal symptoms at baseline. A meta-analysis of 12 observational studies (1 of good quality, 3 of fair quality, and 8 of poor quality) showed a reduction in the risk for dementia among postmenopausal women taking hormone therapy (RR, 0.66; 95% CI, 0.53-0.82)(18). Because of issues of internal and external validity from these previous studies, the more recent, fair-quality WHI memory studies are more likely to represent the effects of hormone therapy use in the healthy postmenopausal population. The WHI memory study showed decreased global cognitive function (measured by the

modified Mini-Mental State Examination) in women taking estrogen alone and in the pooled group of women taking estrogen alone or estrogen-progestin(19). The WHI memory study also showed an increased risk for probable dementia or mild cognitive impairment in both the estrogen-alone (HR, 1.38; 95% CI, 1.01-1.89) and estrogen-progestin (HR, 1.44; 95% CI, 1.04-1.99) arms of the trial(20). The overall evidence supports harmful effects of hormone therapy on cognitive function, although the clinical relevance of this difference in cognitive function is unclear.

Endometrial and Ovarian Cancer

Results of a meta-analysis of 29 good-quality observational studies of endometrial cancer reported a relative risk of 2.3 for users of unopposed estrogen compared with nonusers(21). Risks increased with increasing duration of use (RR, 9.5 for 10 years of use), and the risk for endometrial cancer remained elevated 5 or more years after discontinuation of unopposed estrogen therapy. Estrogen and progestin did not increase the risk for endometrial cancer in HERS(5) or in the WHI(6).

Data on the association between the use of hormone therapy and the risk for ovarian cancer are inconsistent. Two good-quality cohort studies reported increased risks for ovarian cancer or ovarian cancer mortality among women who had taken hormone therapy for 10 years or more(22,23). However, a third study found no effect of hormone therapy on ovarian cancer mortality(24). One study suggested higher risk with unopposed estrogen than with estrogen-progestin therapy(22), but data are insufficient to resolve the effects of different formulations or doses of hormone therapy on ovarian cancer risk. Neither the WHI nor HERS reported risk for ovarian cancer.

Cholecystitis

Results from the Nurses' Health Study, a good-quality cohort study, reported an increased risk for cholecystitis among current hormone therapy users and long-term users (>5 years) compared with nonusers(25). Risk for cholecystitis remained elevated among past users. An increase in biliary tract surgery during 6.8 years of follow-up was reported among women taking estrogen plus progestin compared with those taking placebo in

HERS(9,26); the WHI has not reported on outcomes for biliary tract disease among women taking hormone therapy.

Conclusion

Combined estrogen-progestin may reduce the risk for fractures and colorectal cancer but has no beneficial effect on CHD. The use of combined estrogen-progestin may lead to increased risk for breast cancer, venous thromboembolism, stroke, cholecystitis, dementia, and lower global cognitive function. The excess absolute combined risks for CHD and breast cancer that can be attributed to hormone therapy are low; for example, according to WHI results, there would be 7 more CHD events, 8 more strokes, 8 more pulmonary embolisms, and 8 more cases of invasive breast cancer each year for every 10,000 women taking hormone therapy. The absolute risk reduction for every 10,000 women would be 6 fewer colorectal cancers and 5 fewer hip fractures. The evidence is insufficient to determine the effects of hormone therapy on the incidence of ovarian cancer, mortality from breast cancer or CHD, or all-cause mortality. Evidence about the effects of different dosages, types, and delivery modes of hormone therapy remains insufficient. Overall, the harmful effects of combined estrogen and progestin are likely to exceed the benefits of chronic disease prevention for most women.

Since unopposed estrogen increases a woman's risk for endometrial cancer, it has been used in postmenopausal women without a uterus to prevent chronic disease. While estrogen alone may decrease a woman's risk for fractures, it has no beneficial effect on CHD. The use of estrogen alone may lead to increased risk for thromboembolism, stroke, dementia, and lower global cognitive function. The evidence is insufficient to determine the effects of unopposed estrogen on the incidence of breast cancer, ovarian cancer, or colorectal cancer as well as breast cancer mortality or all-cause mortality. Overall, the harmful effects of unopposed estrogen are likely to exceed the chronic disease prevention benefits in most women.

Recommendations of Other Groups

The American College of Obstetricians and Gynecologists(27), American Heart Association(28), North American Menopause Society(29), and Canadian Task Force on Preventive Health Care(30,31) recommend against use of HT for the prevention of chronic diseases in postmenopausal women.

References

1. U.S. Preventive Services Task Force. Postmenopausal hormone replacement therapy to prevent chronic conditions: recommendations and rationale. *Ann Intern Med.* 137(10):1-48.
2. U.S. Preventive Services Task Force. Screening for osteoporosis in postmenopausal women: recommendations and rationale. *Ann Intern Med.* 137(6):526-528.
3. Sheridan SL, Harris RP, Woolf SH for the Shared Decisionmaking Workgroup, Third U.S. Preventive Services Task Force. Shared decision-making about screening and chemoprevention: a suggested approach from the U.S. Preventive Services Task Force. *Am J Prev Med.* 2004;26(1):56-66.
4. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med.* 1992;117(12):1016-1037.
5. American Cancer Society. *Cancer Facts & Figures 2004.* Available at: http://www.cancer.org/downloads/STT/CAFF_finalPWSecured.pdf . Accessed Aug 19, 2004.
6. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
7. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701-1712.
8. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. *JAMA.* 2001;285(22):2891-2897.
9. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study Follow-up (HERS II). *JAMA.* 2002;288(1):58-66.
10. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med.* 1999;106(5):574- 582.
11. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet.* 2003;362(9382):419-427.
12. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med.* 1995;332(24):1589-1593.
13. Sellers TA, Mink PJ, Cerhan JR, et al. The role of hormone replacement therapy in the risk for breast cancer and total mortality in women with a family history of breast cancer. *Ann Intern Med.* 1997;127(11):973-980.
14. Humphrey L, Takano L, Chan BK. Postmenopausal Hormone Replacement Therapy and Cardiovascular Disease. Systematic Evidence Review No.10 (Prepared by the Oregon Health & Science Evidence-based Practice Center under Contract No. 290-97-0018.) 2002. Available at: http://www.ahrq.gov/clinic/serfiles.htm#hrt-cardio. Accessed Aug 2004.

15. Humphrey LL, Chan BK, Sox HC. Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease. *Ann Intern Med.* 2002;137(4):273-284.
16. Miller J, Chan BK, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;136(9):680-690.
17. Miller J, Chan BK, Nelson H. Hormone Replacement Therapy and Risk of Venous Thromboembolism. Systematic Evidence Review No.11 Prepared by the Oregon Health & Science Evidence-based Practice Center under contract No. 290-97-0018. 2002. Available at: http://www.ahrq.gov/clinic/serfiles.htm#hrtrisk. Accessed Aug 2004.
18. LeBlanc E, Chan BK, Nelson H. Hormone Replacement Therapy and Cognition. Systematic Evidence Review No.13 (Prepared by the Oregon Health & Science Evidence-based Practice Center under Contract No. 290-97-0018.) 2002. Available at: http://www.ahrq.gov/clinic/serfiles.htm#hrtcog . Accessed Aug 2004.
19. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004;291(24):2959-2968.
20. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA.* 2004;291(24):2947-2958.
21. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol.* 1995;85(2):304-313.
22. Lacey JV, Jr., Mink PJ, Lubin JH, et al. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA.* 2002;288(3):334-341.
23. Rodriguez C, Patel AV, Calle EE, Jacob EJ, Thun MJ. Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women. *JAMA.* 2001;285(11):1460-1465.
24. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy--long-term follow-up of a Swedish cohort. *Int J Cancer.* 1996;67(3):327-332.
25. Grodstein F, Colditz GA, Stampfer MJ. Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol.* 1994;83(1):5-11.
26. Simon JA, Hunninghake DB, Agarwal SK, et al. Effect of estrogen plus progestin on risk for biliary tract surgery in postmenopausal women with coronary artery disease. The Heart and Estrogen/progestin Replacement Study. *Ann Intern Med.* 2001;135(7):493-501.
27. ACOG Task Force on Hormone Therapy.l Hormone Therapy. *Obstetrics and Gynecology*. 2004;104,4 Supplement:1S-131S.
28. American Heart Association. AHA scientific statement: evidence-based guidelines for cardiovascular disease prevention in Women. *Circulation.* 2004;109:672-693.
29. The North American Menopause Society. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society. *Menopause* 2004;11(6):589-600.

30. Abramson BL. Postmenopausal hormone replacement therapy for primary prevention of cardiovascular and cerebrovascular disease. Recommendation statement from the Canadian Task Force on Preventive Health Care. *CMAJ.* 2004;170(9):1388-1389.
31. 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 (10):1535-1537.

APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE
STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.