In this issue, the U.S. Preventive Services Task Force (USPSTF) recommends against using hormone therapy for the prevention of chronic conditions in postmenopausal women (1). These recommendations address only the use of hormones to prevent disease and not their use for symptom management in early menopause. On the basis of a systematic review of evidence published through November 2011 (2), the USPSTF concluded with moderate to high certainty that the harms of hormone therapy outweigh the benefits when it is used for chronic disease prevention. However, in the short interval between finalization and publication of the recommendations, new evidence emerged that raised questions about them. DOPS (Danish Osteoporosis Prevention Study), a multicenter randomized trial, reported that hormone therapy given to early postmenopausal women reduced the risk for a combined end point of death, myocardial infarction, and heart failure and caused no increase in breast cancer or stroke among women who used it for more than 10 years (3).

The use of hormone therapy for chronic disease prevention in postmenopausal women gathered momentum throughout the 1980s and 1990s as evidence accumulated about potential beneficial effects of estrogen on cardiovascular disease. Laboratory studies identified cardioprotective pathways mediated by estrogen receptors (4), animal studies suggested a protective role of estrogens on atherosclerosis (5), clinical trials showed beneficial effects on cardiovascular risk factors (6), and strong observational evidence supported an inverse association between hormone therapy and cardiovascular events (7). By the mid-1990s, almost 38% of U.S. postmenopausal women aged 50 to 74 years were using hormone therapy (8)—many of them believing that it would prevent cardiovascular disease and cause no harm.

Those beliefs were shaken a decade ago with the publication of the WHI (Women’s Health Initiative) (9, 10) and critical reevaluation of observational studies (11). The WHI investigators randomly assigned 16 608 women aged 50 to 79 years to receive conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, or placebo, and they assigned 10 739 similarly aged post hysterectomy women to receive conjugated equine estrogens alone or placebo. Both trials were stopped early, the former because of increased risks for breast cancer, coronary heart disease, stroke, and pulmonary embolism (9) and the latter because of increased risk for stroke (10). In cumulative analyses that included intervention and postintervention phases, combined therapy showed a statistically nonsignificant increased risk for coronary heart disease (hazard ratio [HR], 1.11 [95% CI, 0.94 to 1.31]) (12), whereas estrogen alone had little effect on coronary heart disease risk (HR, 0.95 [CI, 0.82 to 1.11]) (13).

Although the WHI heavily influenced clinical practice recommendations, including the most recent ones from the USPSTF (2), it stirred debate. Some argued that the lack of cardiovascular benefits seen in the WHI could have been due to the selection of women who had experienced menopause many years previously and that beneficial effects would have been seen if hormone therapy had been started shortly after menopause (the “timing hypothesis”). Subset analyses of WHI lent support to this hypothesis. After 11 years of follow-up in the estrogen-only trial, women aged 50 to 59 years at enrollment had a reduced risk for coronary heart disease (HR, 0.59 [CI, 0.38 to 0.90]) and total myocardial infarction (HR, 0.54 [CI, 0.34 to 0.86]) with estrogen compared with placebo, in contrast to neutral or increased risks in older women (the P values for interaction by age were 0.05 and 0.007, respectively) (13). Interaction by time since menopause was also apparent, but less pronounced, in the estrogen plus progestin trial (14). Because of lower absolute risks for coronary heart disease, stroke, venous thrombosis, and other clinical events, the attributable risks from hormone therapy were lower in younger than older women. Regardless, the WHI could not definitively address the balance of benefits and risks of hormone therapy in newly menopausal women.

Now, DOPS provides direct evidence of the effect of hormone therapy in early postmenopausal women (3). During 1990 to 1993, the DOPS investigators randomly assigned 1006 women aged 45 to 58 years with last menstrual bleeding 3 to 24 months before study entry to hormone therapy or no treatment. Hormone therapy for women with an intact uterus was 2 mg of synthetic 17β-estradiol for 12 days per month, 2 mg of 17β-estradiol plus 1 mg of norethisterone acetate for 10 days per month, and 1 mg of 17β-estradiol for 6 days per month. Women who had had a hysterectomy received 2 mg of 17β-estradiol daily. The reported primary cardiovascular end point was the combination of death or hospitalization for myocardial infarction or heart failure. The planned duration of treatment was 20 years, but investigators advised participants to discontinue hormone therapy after 10 years of follow-up because of the WHI findings. At 10 years, hormone therapy had reduced the risk for the cardiovascular end point compared with no treatment (HR, 0.48 [CI, 0.26 to 0.87]). There were no statistically significant increased risks for breast cancer (HR, 0.58 [CI, 0.27 to 1.27]) or for hospitalization for either deep venous thrombosis (HR, 2.01 [CI, 0.18 to 22.16]) or stroke (HR, 0.77 [CI, 0.35 to 1.70]) with hormone therapy. Conclusions after 6 years of postintervention follow-up were similar to those at 10 years.

Given the DOPS findings of cardiovascular benefits and no apparent harms, should the USPSTF reconsider its recommendations against using hormone therapy to prevent chronic conditions? We think not. DOPS was originally designed to evaluate hormone therapy for the primary prevention of osteoporotic fracture (15). Although several
outcomes were monitored and adjudicated, a composite outcome comprising death or hospitalization for myocardial infarction or heart failure was not a prespecified primary outcome denoting overall cardiovascular effect. The inclusion of heart failure hospitalization in the composite measure seems odd because prior argument about cardiovascular effects of hormone therapy focused on coronary heart disease. Even so, only 49 "cardiovascular" events at 10 years and 86 events at 16 years were seen. The findings on these events were statistically significant but imprecise. Trials with small numbers of outcome events can result in extreme findings, which are often attenuated or even reversed in larger trials.

The DOPS findings about other outcomes are also uncertain. Confidence intervals around risk estimates for breast cancer, deep venous thrombosis, and stroke were wide because of limited numbers of events and overlapped respective estimates from the WHI. Most available evidence shows that oral hormone therapy increases the risk for venous thrombosis. Interpreting the DOPS HR of 2.01 and associated 95% CI of 0.18 to 22.16 for this outcome as proof that hormone therapy does not increase the risk for thrombosis is a mistake. Likewise, understanding the DOPS findings about breast cancer in the context of other available evidence is difficult because of insufficient power to differentiate effects of different hormone therapy regimens. Finally, DOPS was an open-label trial. Participants knew whether they were receiving hormone therapy, which may have resulted in differential use of health care services or clinician diagnostic bias for certain outcomes.

The DOPS investigators interpret their findings as clear support of the timing hypothesis, but the limitations of the trial make it fall short of proof. The USPSTF recommendations remain sound. Although hormone therapy continues to have a role in the management of symptoms in early menopause (16), women should demand more definitive evidence before getting their hearts set on using hormone therapy for chronic disease prevention.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-2834.

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