

Implications of Recent Clinical Trials of Postmenopausal Hormone Therapy for Management of Cardiovascular Disease

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ABSTRACT: Estrogen therapy, originally used for the treatment of menopausal vasomotor symptoms, had by 1990 become a mainstay for the prevention of coronary heart disease (CHD) in postmenopausal women. The recommendations for use of estrogen in CHD were based on epidemiologic, animal, and laboratory data. However, a series of clinical trials published from 1998 onward have failed uniformly to confirm a CHD benefit. When the disappointing results of the secondary prevention trials were announced, there was widespread anticipation of more promising results from the primary prevention trials of the Women's Health Initiative (WHI). The WHI trials in generally healthy women also did not provide evidence of benefit, and the use of HT for disease prevention is now discouraged. In response, some commentators have incorrectly stated that the WHI was not a true primary prevention trial. A more appropriate way to frame the question is whether the effects of HT on cardiovascular disease (CVD) differ by age or years since menopause. Some preliminary data suggest that more recently menopausal women starting HT could be at lower risk of CHD (but not stroke) than women more distant from the menopause. However, even if ongoing studies provide evidence that HT can slow the initiation of early atherosclerosis in younger women, this is unlikely to translate into a reconsideration of the use of HT for the prevention of disease, because the long-term effects on cardiovascular events are unknown and unknowable, HT has other adverse effects, and there are more effective and safer ways of preventing cardiovascular disease.

KEYWORDS: estrogen; progestin; postmenopausal hormone therapy; cardiovascular disease; women

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INTRODUCTION

Conjugated equine estrogens (CEEs) were first approved in the United States for menopausal symptoms and hormone replacement therapy in 1942, but only came into widespread use in the 1960s and early 1970s after publications and speaking tours by gynecologist Dr. Robert Wilson. He espoused the notion that menopause is a state of hormone deficiency akin to castration, and that the estrogen needed to be “replaced” to ensure health and happiness.¹ The “feminine forever” fountain-of-youth premise of his book is captured in the title, and in passages such as “In the entire realm of medicine, there are few forms of therapy with a more consistent record of beneficence.” His ideas were widely promoted in the popular press. The increasing use of hormone “replacement” therapy occurred despite warning signals from the Coronary Drug Project in men, a set of lipid-lowering trials in which the high-dose CEE arms were stopped early because of increased risk of thrombosis and cardiovascular disease.² In addition, there was emerging knowledge from observational studies in young women that use of the oral contraceptive pill was associated with increased risk of thrombosis, stroke, and coronary heart disease (CHD).³ In 1975 a set of papers in the *New England Journal of Medicine* showed a strong association between unopposed estrogen use and risk of endometrial cancer, after which prescriptions plummeted, only to resume during the late 1970s when it was demonstrated that the addition of a progestin would protect against endometrial cancer.^{4,5} The return to large-scale use during the 1980s and 1990s was increasingly for indications other than menopausal symptoms: prevention of osteoporosis and cardiovascular disease. Evidence for the hypothesis that estrogen could prevent osteoporosis was strong and based on observational data, mechanistic studies, and small clinical trials of bone mineral density. Evidence for prevention of cardiovascular disease also appeared to be reasonably strong, including observational data, small trials of lipids and other intermediate outcomes, and animal studies.^{6,7} The Food and Drug Administration had approved prevention of osteoporosis as an indication, but not that for CHD. The heavily promoted hypothesis that estrogen could prevent chronic disease had another effect: prescriptions were more often written for older women well beyond the menopause, and for longer periods of time.

THE INFLUENCE OF OBSERVATIONAL STUDIES SHOWING AN ASSOCIATION OF HORMONE THERAPY WITH REDUCED RISK OF CHD

During the 1990s it was the conventional wisdom that estrogen would prevent CHD. Several authoritative bodies recommended this off-label use, especially

for women at high risk, that is, women who already had had a heart attack.⁸⁻¹¹ This thinking was based on observational studies suggesting that risk reduction in hormone users was at least as great, and possibly even greater, in women with prior heart disease as in healthy women.^{6,11} There was less evidence for estrogen in combination with a progestin, and some uncertainty as to whether the risk reduction would be of a similar magnitude.¹² The upshot was that by the early 1990s, the great majority of internists, family doctors, cardiologists, and gynecologists in the United States were prescribing estrogen for prevention of heart disease. Though it was recognized that estrogen could also increase the risk of breast cancer, the twin benefits of potential reduction in heart disease and fractures were thought to outweigh the risk of breast cancer.¹²

The most persuasive data in support of the putative benefit for coronary disease was that from several dozen observational studies; however, such studies are subject to a variety of systematic biases that could lead them to overestimate benefit, if any.^{13,14} In general, women who elect to take hormone therapy, or for whom therapy is prescribed, tend to be better educated and healthier to start with. Those that remain on therapy in the longer term are a highly selected group of compliant women who have not suffered any adverse effects. Because the practice guidelines and the prescription patterns of physicians were well ahead of the evidence, there was a clear need for randomized controlled clinical trials to test whether or not hormone therapy might indeed be of benefit to women with and without existing cardiovascular disease.

THE IMPACT OF CLINICAL TRIALS OF HORMONE THERAPY TO PREVENT CHD

Because benefit was deemed to be most likely in women with existing heart disease, and because their higher background rates allowed for a smaller sample size, most of the planned trials were in women with clinical or angiographic evidence of coronary disease. The Heart and Estrogen/Progestin Replacement Study (HERS) was the first of the large-scale trials to report its results, and they were disappointing.¹⁵ Overall, combined CEE and medroxy-progesterone (MPA) did not affect the incidence of CHD events; furthermore, during the first year there was a significant increase in CHD risk. With longer follow-up the risk decreased and reversed toward the end of the original study. This pattern can be seen as one of no overall effect, but a redistribution of events within the trial period. The questions are whether the initial increase was due to some triggering of acute thrombotic events in an existing complicated lesion, and whether the later decrease in risk was due to a longer-term effect of lipid lowering, or whether it was simply a survivor effect in the less susceptible women. During the posttrial follow-up (during which almost half of the participants continued their active medication) there was no suggestion of a continued

benefit and the overall result remained neutral, supporting a conclusion that HT has no overall effect on CHD beyond the triggering of early events in susceptible women.¹⁶ The possibility that several years of HT might reduce existing atherosclerosis was dealt a further blow when a series of angiographic trials showed no benefit in reducing the progression of atherosclerosis.¹⁷⁻¹⁹

After the publication of HERS, the conventional wisdom was revised to a view that HT is not effective for secondary prevention, and there was a general expectation that the results of the Women's Health Initiative (WHI) trials of HT would yield different results. The WHI trials studied generally healthy women, though a small proportion of women with existing cardiovascular disease were included. On average, the risk profile of the cohort was better than in the general U.S. population, as evidenced by their low CHD rates (about half of that in the general population). Two parallel trials were conducted: the trial of CEE plus MPA (CEE + MPA) in women with an intact uterus enrolled 16,608 women aged 50-79 years, and the trial of CEE alone in women who had had a hysterectomy enrolled 10,739 women. The trials were planned to have a follow-up of 8.4 years, but both ended before that. The trial of CEE + MPA was terminated after an average follow-up of 5.6 years because of increased risks of breast cancer, CHD, stroke, and pulmonary embolism, which were not offset by decreased risks of hip fracture and colorectal cancer.²⁰ The trial of CEE was terminated after 7.1 years average follow-up because of increased risk of stroke, no effect on the primary outcome of CHD, no overall benefit, and little probability that the results would change with additional follow-up.²¹ A substudy of participants in both trials aged 65-79 years showed increased risks of dementia and minimal cognitive impairment.²² Other risks included those of gallbladder disease and urinary incontinence.^{23,24} Though vasomotor symptoms improved in the 12-17% of women who had moderate/severe symptoms at baseline, the overall health-related quality of life was not improved.^{25,26} There were some differences between the two trials: in the CEE + MPA, but not in the CEE trial, the CHD and breast cancer risks were increased. Colorectal cancer risk appeared to be decreased in the CEE + MPA trial only. The effects were similar for stroke, dementia, and venous thrombosis (increased risk) and for hip fracture (decreased risk).

The publication of the WHI CEE + MPA trial results in July 2002 was attended by a considerable amount of attention from the media, the public, and the medical profession. By July 2003, the U.S. prescriptions for the particular CEE + MPA formulation (Prempro) had dropped by 66% and overall HT prescriptions dropped by 38%.²⁷ The findings led to a revision of the package inserts for all HT formulations, including statements that HT should not be used for the prevention of CVD, and if used for approved indications it should be used at the lowest dose and shortest duration needed to obtain the therapeutic effect. In addition, HT was relegated to second-line status for the prevention of osteoporosis. The practice guidelines of many professional organizations were revised to include statements similar to those in the Food and Drug

Administration guidance; however, some individuals remained convinced that HT does have a cardioprotective effect if initiated early enough, and disputed that WHI truly was a primary prevention trial.^{28,29}

CAN THE OBSERVATIONAL STUDIES AND THE CLINICAL TRIALS BE RECONCILED?

The current conventional wisdom is that menopausal estrogen therapy (with or without a progestin) should not be initiated or continued for the purpose of preventing cardiovascular disease. This is diametrically opposed to the conventional wisdom prevalent at the time of planning the WHI program. However, there is an emergent wisdom that hormone therapy may offer cardiovascular protection (or at least do no harm) if started early in the menopause.³⁰ Those who subscribe to this view cite differences in study populations between observational studies and the clinical trials that may have modified the effect of HT on CHD. An examination of the Nurses' Health Study (NHS) and WHI cohorts indicates some differences in risk factors: NHS women had slightly higher rates of ever smoking (60% vs. 50%), but lower rates of hypertension (18% vs. 28%), being overweight (38% vs. 70%), having diabetes mellitus (3% vs. 4%), or a history of coronary disease (0% vs. 4%).³¹ However, with the exception of the small proportion of women with existing disease admitted to the trials, the existence of risk factors does not imply that the trials were not primary prevention. Primary prevention is defined as an intervention in persons without diagnosed clinical disease. Preclinical disease may exist, but such persons are included in the concept of primary prevention. On the other hand, primordial prevention intervenes on risk factors at an earlier stage before preclinical disease. Because hormone treatment was typically started in adulthood, neither observational studies of HT use nor clinical trials can qualify as being primordial prevention, but both can represent primary prevention. Nonetheless, primary prevention encompasses such a wide spectrum of health status that it remains possible that there were substantive differences between the primary prevention observational studies and the primary prevention clinical trials. This is not true for the secondary prevention observational studies and the clinical trials, where by definition established disease is present at baseline.

Possibly the most informative differences in respect of primary prevention are that the age range in NHS was lower (30–63 years compared to 50–79 years in WHI) and most of the women started HT at menopause and (presumably) had vasomotor symptoms, while most women in WHI commenced study HT many years subsequent to the menopause and did not have vasomotor symptoms. However, it should be noted that with 8,832 women aged 50–59 years the WHI trials constitute the largest randomized trial experience of HT in younger women, that 26% of women in the CEE + MPA trial and 48% in the CEE trial had used HT in the past or were using them at baseline, and 12% and

17%, respectively, reported having moderate/severe vasomotor symptoms at baseline.^{20,21} The existence of subgroups that overlap with those in the NHS and other observational studies provides an opportunity to try to reconcile the divergent findings between clinical trials and observational studies, by examining whether characteristics such as age, years since menopause, prior use of hormone therapy, or presence of vasomotor symptoms modify the effects of HT. Baseline CHD risk factors are unlikely to explain the more adverse findings for CHD in WHI, because subgroup analyses did not suggest that women with these factors (including prior CVD) had a greater increase in risk of CHD on hormone therapy than women without the factors. However, other subgroup analyses have suggested a possible role for years since menopause (in the CEE + MPA trial) or age (in the CEE trial).^{32,33} Prior use of HT did not appear to influence the results. Further, more detailed analyses of the possible interactions of age, years since menopause, and presence of vasomotor symptoms on HT effect on CHD are under way.

The theoretical model for a role of age (or years since menopause) in modifying the effect of HT can be conceptualized as three different effects of estrogen depending on the underlying state of the arteries: retardation of the initiation of the earliest stages of atherosclerosis (impaired endothelial function, fatty streaks) in young adults, no effect on progression of existing raised lesions in middle age, and triggering of clinical events in complicated lesions (erosion or rupture of unstable plaque, with subsequent thrombosis and occlusion).³¹ Mechanistic studies in animals and in the laboratory support estrogen effects in the first, angiographic trials in the second, and large clinical outcome trials plus limited mechanistic studies in the third stage. Unfortunately, by the time most women reach the age of menopause, they are likely to have raised lesions and a small proportion will also have complicated lesions. Hence, it is not at all clear whether there is a potential for clinical benefit in preventing CHD at middle age, though there may be for women who start HT at a younger age (e.g., women who undergo premature surgical menopause). At best, it may turn out that women undergoing a natural menopause at the average age of 50–59 years are not at any substantially increased risk from HT for several years, in part because they are at very low absolute risk whether or not they take HT. What is very clear is that initiation of HT does not protect against CHD in women older than 60 years, and that HT increases the risk in the first year or two after therapy is begun. Even if there is a “window of opportunity” at middle age where there is no harm, one cannot assume that the lack of harm will continue with prolonged therapy as women and their arteries age. A further caveat against thinking that the age of initiation explains the different results of observational studies and clinical trials is that the observational studies predicted equal or even greater benefit in women with existing heart disease or atherosclerosis. We know that this cannot be true, given the results of the angiographic trials and the clinical outcome trials. Hence, at a minimum, the observational studies overestimate any potential benefit.

Unlike CHD, the risk of stroke on HT does not appear to be modified by age or years since menopause.^{34,35} This is consistent with the observational studies which suggest an increased risk of stroke in the same populations, with the same drugs, and the same dosages at which the studies suggested benefit for CHD. It is unclear why stroke and CHD should react differently to HT, but one possibility is that stroke is less dependent on the favorable lipid changes on HT, and is affected more adversely by the prothrombotic effects of HT.

RESEARCH QUESTIONS

Some of the research questions that remain are whether lower doses of estrogen, or different routes of administration, different types and regimens of progestin, or selective estrogen receptor modulators (SERMs) may have different effects on CHD risk. Trials of SERMs have thus far yielded results similar to those of HT: increased risk of stroke and no effect on CHD risk.³⁶ If the gender difference in CHD by age is informative at all in relation to estrogen and progestin, then nonoral estradiol and progesterone starting at a younger age would be the most likely candidates for offering protection against CHD. Transdermal estradiol avoids the first-pass hepatic circulation, and thus has much less effect on coagulation factors and on CRP. Use of transdermal estradiol appears to be associated with less risk of venous thromboembolism than do oral estrogens, but whether this has any clinical implication for CHD or stroke has not been adequately tested.³⁷ Similarly, the effects of lower doses of estrogen and of progesterone (either orally or intravaginally) have not been adequately tested. Surrogate outcome trials using carotid intima-media thickness or coronary artery calcification as indicators of effect on atherosclerosis are testing lower doses of oral CEE, transdermal estradiol, and oral or vaginal progesterone in younger women.^{38,39} Favorable results from these surrogate trials will be somewhat reassuring for younger women considering the use of HT in the shorter term for the relief of symptoms, or even for women with osteoporosis as an initial therapy before switching to bisphosphonates, raloxifene, or other therapies at an older age.

While it is possible that these trials will demonstrate a slowing of the onset of early lesions, such findings would be unlikely to change the current paradigm that HT should not be used for the prevention of CHD. HT has other effects beyond any effect on atherosclerosis, and in particular the prothrombotic and proinflammatory effects may be important for the triggering of clinical events. The short-term trials cannot answer the question of whether continued estrogen use over many decades will overcome the inevitable age-related degeneration of arterial health. In addition, long-term HT is associated with increasing risk of breast cancer. Given the availability of other well-proven, effective, and safe strategies for preventing CHD, there will be no need to rely on HT for this indication. Favorable results from the surrogate outcome trials are also unlikely

to lead to a definitive trial with clinical outcomes, given the very large number or younger women that would need to be enrolled, and the very long-term follow-up that would be needed. Such large and long-duration trials are at this point the sole strategy that might change the current paradigm. The history of estrogen and heart disease has been permeated with “magical thinking” ever since the days of Robert Wilson. A recent commentary points out that the observational epidemiology that provided respectability to the idea of cardio-protection ignored some hard realities; the contradiction with the trials in men and the adverse effects of oral contraceptives in women; that mechanism does not prove causality; and that it is not possible to adjust for all confounders.⁴⁰ Without proof that initiating estrogen at an earlier age, or that transdermal estrogen or newer SERMs have a different effect, any assumption that they do could well be another exercise in “magical thinking” that ignores contrary evidence. There are no other examples of cardio-protective drugs that work in women but not in men, and there are no examples of drugs that work in primary (or primordial) prevention, but not in secondary prevention.⁴⁰

CLINICAL IMPLICATIONS

The implications of what we have learned thus far from the clinical trials vary by specialty. Cardiologists, who have a vast armamentarium of strategies to choose from, no longer see any role for HT in prevention of CHD. Endocrinologists and internists focusing on prevention of osteoporosis face a more limited role for HT at lower dose and for shorter periods than used in the past. Other effective and safe drugs are preferred as first line for the prevention of osteoporosis. Gynecologists who are looking to treat menopausal vasomotor symptoms have been advised to reconsider the need for women with less severe symptoms, and to exhaust other options first. If HT is used, it should be used at the lowest dose and the shortest duration needed, with periodic evaluation of whether there is a continuing need.

CONCLUSIONS

Postmenopausal HT has come full circle. It started as a therapy to treat vasomotor symptoms and vaginal dryness, and it has returned to that status. It is no longer recommended for the prevention of chronic disease, and even its use for osteoporosis prevention is now more limited. Increasing attention is being paid to the issue of whether the short-term use of HT in more recently menopausal women for the relief of symptoms has been discouraged to a greater extent than needs be, given the very low absolute risks of major disease and the possibility that HT may retard atherosclerosis if initiated early. However, the return of HT for the prevention of CHD appears unlikely (even if initiated early), because of the trial findings and unresolvable uncertainties surrounding long-term use.

REFERENCES

1. WILSON, R.A. 1966. *Feminine Forever*. Evans. New York, NY.
2. ANON. 1970. The Coronary Drug Project. Initial findings leading to modifications of its research protocol. *JAMA* **214**: 1303–1313.
3. ORY, H.W. 1977. Association between oral contraceptives and myocardial infarction. *JAMA* **237**: 2619–2622.
4. SMITH, D.C., R. PRENTICE, D.J. THOMPSON, *et al.* 1975. Association of exogenous estrogen and endometrial carcinoma. *N. Engl. J. Med.* **293**: 1164–1167.
5. ZIEL, H.K. & W.D. FINKLE. 1975. Increased risk of endometrial carcinoma among users of conjugated estrogens. *N. Engl. J. Med.* **293**: 1167–1170.
6. STAMPFER, M.J. & G.A. COLDITZ. 1990. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev. Med.* **20**: 47–63.
7. LOBO, R.A. 1990. Estrogen and cardiovascular disease. *Ann. N. Y. Acad. Sci.* **592**: 286–294.
8. ANON. 1992. Hormone replacement therapy. ACOG Technical Bulletin Number 166–April 1992 (replaces No. 93, June 1986). *Int. J. Gynaecol. Obstet.* **41**: 194–202.
9. ANON. 1992. Guidelines for counseling postmenopausal women about preventive hormone therapy. American College of Physicians. *Ann. Intern. Med.* **117**: 1038–1041.
10. ANON. 1993. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* **269**: 3015–3023.
11. MOSCA, L., J.E. MANSON S.E. SUTHERLAND, *et al.* 1997. Cardiovascular disease in women. A statement for healthcare professionals from the American Heart Association. *Circulation* **96**: 2468–2482.
12. GRADY, D., S.M. RUBIN, D.B. PETITTI, *et al.* 1992. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann. Intern. Med.* **117**: 1016–1037.
13. ROSSOUW, J.E. 1996. Estrogens for prevention of coronary heart disease. Putting the brakes on the bandwagon. *Circulation*. **94**: 2982–2985.
14. SOTELO, M.M. & S.R. JOHNSON. 1997. The effects of hormone replacement therapy on coronary heart disease. *Endocrinol. Metab. Clin. North Am.* **26**: 313–328.
15. HULLEY, S., D. GRADY, T. BUSH, *et al.* 1998. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* **280**: 605–613.
16. GRADY, D., D. HERRINGTON, V. BITTNER, *et al.* 2002. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* **288**: 49–57.
17. HERRINGTON, D.M., D.M. REBOUSSIN, K.B. BROSNIHAN, *et al.* 2000. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N. Engl. J. Med.* **343**: 522–529.
18. WATERS, D.D., E.L. ALDERMAN, J. HSIA, *et al.* 2002. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* **288**: 2432–2440.
19. HODIS, H.N., W.J. MACK, S.P. AZEN, *et al.* 2003. Hormone therapy and the progression of coronary-artery atherosclerosis in postmenopausal women. *N. Engl. J. Med.* **349**: 535–545.

20. WRITING GROUP FOR THE WOMEN'S HEALTH INITIATIVE INVESTIGATORS. 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* **288**: 321–333.
21. WOMEN'S HEALTH INITIATIVE STEERING COMMITTEE. 2004. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative Randomized Controlled Trial. *JAMA* **291**: 1701–1712.
22. SHUMAKER, S., C. LEGAULT, L. KULLER, *et al.* 2004. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. *JAMA* **291**: 2947–2958.
23. CIRILLO, D., R. WALLACE, R. RODABOUGH, *et al.* 2005. Effect of estrogen therapy on gallbladder disease. *JAMA* **293**: 330–339.
24. HENDRIX, S.L., B.B. COCHRANE, I.E. NYGAARD, *et al.* 2005. Effects of estrogen with and without progestin on urinary incontinence. *JAMA* **293**: 935–948.
25. HAYS, J., J. OCKENE, R. BRUNNER, *et al.* 2003. Effects of estrogen plus progestin on health-related quality of life. *N. Engl. J. Med.* **348**: 1839–1854.
26. BRUNNER, R.L., M. GASS, A. ARAGAKI, *et al.* 2005. Effects of conjugated equine estrogen on health-related quality of life in postmenopausal women with hysterectomy: results from the Women's Health Initiative Randomized Clinical Trial. *Arch. Intern. Med.* **165**: 1976–1986.
27. HERSH, A.L., M.L. STEFANICK & R.S. STAFFORD. 2004. National use of postmenopausal hormone therapy. *JAMA* **291**: 47–53.
28. SPEROFF, L. 2005. Clinical appraisal of the Women's Health Initiative. *J. Obstet. Gynaecol. Res.* **31**: 80–93.
29. NAFTOLIN, F., H.S. TAYLOR, R. KARAS, *et al.* 2004. The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil. Steril.* **81**: 1498–1501.
30. MANSON, J.E., S. BASSUK & S. HARMAN. 2006. Postmenopausal hormone therapy: new questions and the case for new clinical trials. *Menopause* **13**: 139–147.
31. ROSSOUW, J.E. 2005. Coronary heart disease in menopausal women: implications of primary and secondary prevention trials of hormones. *Maturitas* **51**: 51–63.
32. MANSON, J.E., J. HSIA, K.C. JOHNSON, *et al.* 2003. Estrogen plus progestin and the risk of coronary heart disease. *N. Engl. J. Med.* **349**: 523–534.
33. HSIA, J., R.D. LANGER, J.E. MANSON, *et al.* 2006. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch. Intern. Med.* **166**: 357–365. Erratum in *Arch. Intern. Med.* **166**: 759.
34. HENDRIX, S.L., S. WASSERTHEIL-SMOLLER, K.C. JOHNSON, *et al.* 2006. Effects of conjugated equine estrogen on stroke in the Women's Health Initiative. *Circulation* **113**: 2425–2434.
35. WASSERTHEIL-SMOLLER, S., S.L. HENDRIX, M. LIMACHER, *et al.* 2003. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA* **289**: 2673–2684.
36. STEFANICK, M.L. 2006. Risk-benefit profiles of raloxifene for women. *N. Engl. J. Med.* **355**: 190–192.
37. LOWE, G.D.O. 2004. Hormone replacement therapy and cardiovascular disease: increased risks of venous thromboembolism and stroke, and no protection from coronary heart disease. *J. Intern. Med.* **256**: 361–374.
38. HARMAN, S.M., E.A. BRINTON, M. CEDARS, *et al.* 2005. KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* **8**: 3–12.
39. NCT00114517 available at www.clinicaltrials.gov (accessed August 14, 2006)
40. PETITTI, D. 2004. Commentary: hormone replacement therapy and coronary heart disease: four lessons. *Int. J. Epidemiol.* **33**: 461–463.