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Lessons Learned From the Women's Health Initiative Trials of Menopausal Hormone Therapy

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Abstract

We re-evaluate the Women's Health Initiative (WHI) findings and their implications for clinical practice. Menopausal hormone therapy (HT) was effective for relief of vasomotor symptoms, and the risk of coronary heart disease (CHD) tended to be reduced in women close to menopause compared to the increased risk in women more distant from menopause. In recently menopausal women, short-term absolute risks of stroke and venous thromboembolism were small. Estrogen plus progestin therapy, but not estrogen therapy (ET), increased the risk of breast cancer, with a suggestion of greater risk when initiated close to the menopause. Menopausal HT increased the risk of CHD in women more than 20 years distant from menopause, particularly in women with vasomotor symptoms. It remains unknown whether the suggestive benefit for CHD in younger women will translate into benefits or harms if menopausal HT is continued into older ages. Based on WHI data, the use of menopausal HT for fewer than 5 years is a reasonable option for the relief of moderate to severe vasomotor symptoms. The risks seen with EPT suggest careful periodic re-assessment of the ongoing therapy needs for women taking estrogen plus progestin therapy. The more favorable profile of ET allows for individualized management with respect to duration of use when symptoms persist. For both ET and estrogen plus progestin therapy the baseline risk profile of the individual woman needs to be taken into account. Menopausal HT is not suitable for long-term prevention of CHD given risks of stroke, venous thromboembolism, and breast cancer (for estrogen plus progestin therapy) found in both clinical trials and in observational studies.

Prior to 2002, prescriptions for menopausal hormone therapy (HT) were climbing, professional organizations were recommending menopausal HT for prevention of osteoporosis and coronary heart disease (CHD), and one third of prescriptions were for women aged older than 60 years. Against this background, the National Institutes of Health launched the Women's Health Initiative (WHI) randomized trials of menopausal HT to test whether the association with reduced risk for CHD found in observational studies was real, and to obtain reliable information on the overall risks and benefits for chronic disease prevention in postmenopausal women aged 50–79 years. The WHI trials tested standard-dose oral conjugated equine estrogens with and without standard-dose continuous medroxyprogesterone acetate. In 2002, the trial of estrogen plus progestin (EPT) in women with an intact uterus was stopped early because of increased risks of breast cancer, CHD, stroke, and pulmonary embolism.[1] Risks exceeded the benefits from reductions in hip

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fractures and colorectal cancer. In 2004 the companion trial of estrogen alone (ET) in hysterectomized women was also stopped prematurely, this time because of an increased risk of stroke and because it was unlikely that a significant benefit for CHD would emerge.[2] The findings from the trial of ET were less adverse than those from EPT in showing no effect on CHD, a non-significant reduction in risk of breast cancer, and a more favorable benefit–risk profile for younger than older women.

The WHI findings received wide attention and prescriptions for menopausal HT dropped precipitously after 2002, and have continued to decline in subsequent years.[3] Declines were most marked for standard-dose EPT and in older women. Prescriptions for lower-dose, transdermal, and vaginal menopausal HT increased but still lagged behind those of standard-dose menopausal HT. The large majority of prescriptions were written by obstetricians and gynecologists, who were also more likely to prescribe transdermal therapy than other providers. In parallel with the decline in hormone prescriptions national rates of breast cancer have declined, but rates of hip fracture increased in women who stopped therapy compared to those who continued.

A decade later, it has become widely accepted that menopausal HT should not be used for the prevention of chronic disease in older women; however, short-term use for treatment of vasomotor symptoms remains an accepted indication. The debate has shifted to whether the risks and benefits found in the entire postmenopausal age range apply also to women who are close to the menopause, in particular women who are treated for vasomotor symptoms. Proponents of the timing hypothesis point to findings from earlier observational studies (which were thought to assess effects of menopausal HT initiated in closer proximity to menopause onset than for women in the trials) and also to subgroup analyses within the trials. Both strands of evidence build on biologic findings supporting the concept that healthy arteries respond more favorably to estrogen than atherosclerotic arteries. The goal of this commentary is to shed further light on the WHI findings and their implications for clinical practice, with a particular focus on treatment of vasomotor symptoms and effects on CHD.

Treatment of vasomotor symptoms in relation to time since menopause onset

The majority of menopausal women experience vasomotor symptoms ranging from mild to severe, with the most severe symptoms usually occurring close to the menopause. However, bothersome symptoms may persist for a decade or longer. The WHI trials were not designed to address the risks and benefits of hormones given for relief of vasomotor symptoms; rather, they focused on the issue of whether postmenopausal women over a wide age range should consider HT to prevent chronic disease.[1,2] Nonetheless, the trials included substantial numbers of younger women (ages 50–59 years=8,832, 60–69 years=12,362 and 70–79 years=6,153), and women closer to the menopause (<10 years=7,137, 10–19 years=8,988, >20 years=8,203).[4] Subgroup analyses must be interpreted very cautiously because of limited power (thus a real subgroup effect may be missed); on the other hand, they may spuriously identify effects (because of unstable point estimates and chance findings due to multiple testing). With those caveats, as noted in the original WHI EPT trial publication, the increased risks of cardiovascular disease and invasive breast cancer were present across all age strata.[1] More detailed subsequent analyses of the EPT trial confirmed that treatment effects were not modified by age, and suggested the possibility that CHD risk due to EPT may be reduced in women close to the menopause at the time of initiation compared to women distant from the menopause.[4] However, similar analyses revealed that risk of breast cancer due to EPT was somewhat greater when initiated close to the menopause.[5] In the ET trial effects on the major clinical outcomes were not significantly modified by age or years

since menopause. However, CHD, all-cause mortality, and global index (a summary of disease risks and benefits) tended to be in the direction of benefit in women aged 50–59 years.[2,4] In women closer to menopause onset, ET was associated with an elevated point estimate for stroke and a neutral estimate for breast cancer.[4,5] Where present, the absolute excess risks (and benefits) associated with hormone therapy were low, and were even lower in women close to the menopause because of their low baseline risk.[4]

A substantial proportion of women enrolled in the trials had vasomotor symptoms at baseline (in the ET trial the prevalence of self-reported moderate/severe symptoms in women <10 years, 10–19, and >20 years since menopause was 21%, 14%, and 12% respectively; in the EPT trial the corresponding proportions were 21%, 9%, and 5%).[4] In younger women aged 50–54 with moderate/severe vasomotor symptoms at baseline, the symptoms were no longer present one year later in about three-quarters of women on menopausal HT (compared to about half on placebo). Despite some relief of vasomotor symptoms, other domains of health-related quality of life (including mood and depression) in younger women were not markedly improved by hormone therapy. However, hormone therapy (ET or EPT) in older women (>70 years of age, or >20 years since menopause) with moderate or severe vasomotor symptoms was associated with a particularly high risk of CHD, which was not seen in younger women.[4]

Overall, in women <10 years of menopause onset, the benefit from relief of vasomotor symptoms and the small absolute risks support the position that ET represents appropriate treatment for healthy symptomatic women with prior hysterectomy and that decisions regarding duration of therapy can be individualized.[8] Greater caution is needed for women with an intact uterus considering EPT, since use in the early menopausal interval is associated with greater breast cancer risk. Similarly, caution would be appropriate in considering ET or EPT for women at higher risk of cardiovascular disease (CVD) such as women with a history of CVD, metabolic syndrome, or multiple risk factors. A lower dose, minimizing duration, and use of other regimens (including transdermal estradiol and intravaginal or intrauterine progestational agents) may help to mitigate these risks, although these options have not been adequately evaluated. The high rate of symptom improvement on placebo suggests that lifestyle approaches, if not already explored, can be tried first in many women.

An unresolved question is what is meant by “short-term.” The most robust data from WHI relates to fewer than 5 years of treatment and this can be used to anchor thinking about duration, since data from the later years in the trials reflect increasing non-adherence with less reliable estimates of effect. For women with persistent bothersome symptoms or women with elevated risk of osteoporosis, some authorities support somewhat longer use in the case of ET because of its more favorable risk profile.[8] Treatment durations in excess of 5 years are more problematic for EPT because of continuing increase in breast cancer risk during treatment and later increase in breast cancer mortality. Longer durations of treatment may also be problematic for either ET or EPT in women at higher risk of CVD. It is the clinician’s obligation to inform women regarding risks as well as benefits of menopausal HT as they help their patients make individualized decisions regarding dose, duration, and route of menopausal HT.

Prevention of Coronary Heart Disease

WHI has provided clear data indicating that menopausal HT is not suitable for prevention of CHD in women who initiate treatment distant from menopause onset. A question still remains as to whether menopausal HT, and particularly ET, initiated close to the menopause onset may reduce CHD risk. Subgroup findings based on joint analyses of the two WHI

trials suggested a tendency towards decreased risk of CHD (and reduced coronary artery calcium in the case of younger women on ET) in women closer to menopause onset when they initiate menopausal HT. However, WHI findings relate to relatively short-term use and do not address how continued long term use into later decades of life will affect cardiovascular health. Most CHD prevention strategies are aimed at slowing the age-related atherosclerotic process and thereby reducing the rate of acute CHD events. The ideal of maintaining healthy arteries over decades and eliminating acute events entirely has not been achieved by any prevention strategy, including statin therapy. However, unlike statin therapy, which will slow progression and prevent CHD at any age and any stage of disease, menopausal HT does not prevent progression of established atherosclerosis and precipitates acute CHD events in older women. Therefore, it would be unwise to assume that the usual prevention paradigm holds, i.e. that slowing disease progression will result in lower CHD rates into older age. Absent the remote possibility that menopausal HT can completely abolish age-related initiation and progression of atherosclerosis, at some unknown point sufficient plaques will have developed that menopausal HT may promote rather than prevent acute coronary events.

It is often stated that protective associations between menopausal HT use and CHD risk are seen in observational studies because such studies represent healthy women who started menopausal HT closer to the menopause, in contrast to participants in trials who were often older or who had pre-existing vascular disease. However, recent analyses have questioned this assumption. Secular trends in prescribing hormones to older women and for indications other than vasomotor symptoms led to a substantial proportion of new prescriptions being written for women distant from the menopause. For example, in the Nurses' Health Study (NHS) as the cohort aged the proportion of women who initiated EPT >10 years after menopause rose dramatically between 1984 and 1998, leading to an overall hormone user population that did not differ substantially from that in the WHI trial population in terms of years since menopause.[9,10]

The time-dependent effect of menopausal HT on CHD may be one of the keys to resolving the discrepancy between clinical trials and observational study findings. As shown in the primary prevention WHI trial and the secondary prevention Heart and Estrogen/Progestin Study (HERS), EPT increases CHD risk in the first year or two, after which the risk attenuates towards neutral and even reverses towards a non-significant benefit.[11,12] The WHI trial of ET showed a less pronounced pattern of early increase followed by a decrease in risk. Since the trials were of relatively short durations compared to observational studies, their overall risk estimates are dominated by the early increases in risk. By way of contrast, observational studies of current users miss most of the early increase in CHD risk and the data mainly reflect the reduced risk seen in longer-term adherent survivors. Women classified as current users in most observational studies may have been using menopausal HT for years before the baseline examination, and therefore any early events after initiation would not have been counted as being associated with hormone use. For example, in the WHI observational study only 15% of current users at baseline had used EPT for less than 2 years. Without consideration of time since initiation the WHI observational data indicated benefit of both EPT and ET for CHD; however after accounting for time since initiation the clinical trial and observational risk estimates for both ET and EPT agreed closely and showed no CHD benefit.[12] Similarly, novel re-analyses of the NHS data for EPT use, which for the first time attributed CHD events in between 2-yearly updates to hormone initiators during that interval, yielded results similar to those of the WHI trial of EPT.[9,10] It would be of interest to examine NHS data for ET using this analytic approach.

Twenty years ago the "secondary prevention" and "primary prevention" observational studies were frequently cited to support the potential cardioprotective effect of menopausal

HT, and these study findings were the major rationale for the HERS and WHI trials. In retrospect, it appears that this rationale was based on methodologically limited studies that did not adequately account for the early increase in CHD risk, and therefore overestimated benefit. Indeed, after the publication of the HERS trial findings several investigators re-analyzed their secondary prevention observational study data and were able to identify an early increase in risk. It is also noteworthy that there is substantial agreement between observational studies and clinical trials for stroke, venous thromboembolism, and breast cancer (for EPT) where the harmful effects are not limited to the first few years, as well as for reductions in fracture and colorectal cancer.

Current short-term trials test the timing hypothesis in women close to menopause onset using surrogate outcomes such as carotid intima-media thickness (CIMT) and coronary artery calcium (CAC). Preliminary findings from the Kronos Early Estrogen Prevention Study (KEEPS) indicate that 4 years of low dose oral conjugated equine estrogen or standard dose transdermal estradiol (both with oral progesterone) did not affect CIMT or CAC but had benefits for quality of life.[13] The results of the Early Versus Late Intervention Trial With Estrogen (ELITE) testing low-dose oral estradiol (with vaginal progesterone in women with a uterus) are not yet known.[14] These small trials are not powered to answer the question of whether menopausal HT will reduce risk of clinical disease nor address breast cancer safety. Menopausal HT could reduce progression of early atherosclerosis but still increase the risk of CHD events, for example, through effects on thrombosis and plaque rupture. Recently published findings from the Danish Osteoporosis Prevention Study are not persuasive because of its open label design with no placebo control, and it recorded only 5 cases of myocardial infarction over 10 years.[15] Definitive testing of the timing hypothesis would involve a randomized placebo-controlled trial with clinical outcomes of women enrolled close to the menopause. However, low event rates and the need to examine long-term effects translate into a very large trial (N~30,000) lasting 10–15 years. It is questionable whether such a trial is feasible in the light of the costs and likely low adherence over time. In addition, there would be ethical issues with a trial of standard-dose oral menopausal HT, given what we now know about increased risk of stroke and venous thrombo-embolism, and longer term risk of breast cancer (with EPT). Lower doses, transdermal estradiol, and intravaginal or intrauterine progestational agents may help to avoid some of the adverse effects of standard-dose oral menopausal HT.

In conclusion detailed examination of existing data support the current recommendations that short term menopausal HT can be used for treatment of moderate to severe vasomotor symptoms in healthy women soon after menopause onset; it is not suitable for long term prevention of CHD. It seems unlikely that new data will emerge anytime soon to change this recommendation.

References

1. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin for healthy postmenopausal women. JAMA. 2002; 288:321–333. [PubMed: 12117397]
2. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SAA, Black H, et al. Women's Health Initiative Steering Committee(2004) Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. JAMA. 2004; 291:1701–1712. [PubMed: 15082697]
3. Ettinger B, Wang SM, Leslie RS, Patel BV, Boulware MJ, Mann ME, et al. Evolution of postmenopausal hormone therapy between 2002 and 2009. Menopause. 2012; 19:610–615. [PubMed: 22207318]
4. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465–1477. [PubMed: 17405972]

5. Chlebowski RT, Anderson GL. The influence of time from menopause and mammography on hormone therapy-related breast cancer risk assessment. JNCI. 2011; 103:284–285. [PubMed: 21278357]

6. Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, et al. Effects of estrogen plus progestin on health-related quality of life. N Engl J Med. 2003; 348:1839–1854. [PubMed: 12642637]

7. Brunner RL, Gass M, Aragaki A, Hays J, Granek I, Woods N, et al. 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. 2005; 165:1976–1986. [PubMed: 16186467]

8. The North American Menopause Society. The 2012 hormone therapy position statement of the North American Menopause Society. Menopause. 2012; 19:257–271. [PubMed: 22367731]

9. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008; 19:766–779. [PubMed: 18854702]

10. Toh S, Hernández-Díaz S, Logan R, Rossouw JE, Hernán MA. Coronary heart disease in postmenopausal recipients of estrogen plus progestin therapy: does the increased risk ever disappear? A randomized trial. Ann Intern Med. 2010; 152:211–217. [PubMed: 20157135]

11. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280:605–613. [PubMed: 9718051]

12. Prentice RL, Manson JE, Langer RL, Anderson GL, Pettinger M, Jackson RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol. 2009; 170:12–23. [PubMed: 19468079]

13. The Kronos Early Estrogen Prevention Study. Available at: http://keepstudy.org/news/index.cfm. Retrieved October 16, 2012.

14. ClincalTrials.gov. ELITE: Early Versus Late Intervention Trial With Estradiol. Available at: http://clinicaltrials.gov/ct2/show/NCT00114517. Retrieved October 16, 2012.

15. Schierbeck LL, Reynmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently menopausal women: randomized trial. BMJ. 2012; 345:e6409. [PubMed: 23048011]