Review Article

Cardiovascular consequences of hormone therapy in postmenopausal women: Messages to clinicians

O. YLIKORKALA* and T. MIKKOLA

Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Finland

Results from the recent randomized clinical trials indicating that hormone therapy (HT) does not provide cardiovascular protection, but potentially harm are in profound disagreement with the sound evidence from numerous observational and experimental studies. While the observational studies have mainly assessed symptomatic recently menopausal women, the randomized trials have studied symptomless elderly postmenopausal women with established coronary heart disease or various risk factors for cardiovascular disease. Therefore, the recent trials have only revealed that HT does not provide secondary cardiovascular benefits. Since primary cardiovascular benefits of HT are

rational but not yet proven in clinical trials, new studies are in demand. Until more data from recently menopausal symptomatic women are available, we need to base our decisions on existing evidence and good clinical practice. Although the potential of HT to provide cardiovascular benefits is decreased by advancing age and time since menopause, this should not preclude the use of individualized HT in younger postmenopausal women. (Reprod Med Biol 2005; 4: 1–6)

Key words: atherosclerosis, hormones, hormone replacement therapy, Women's Health Initiative.

INTRODUCTION

THE WOMEN'S HEALTH Initiative (WHI) hormone therapy (HT) study came to a complete end when the National Institute of Health (NIH) announced, on 2 March 2004, that the estrogen-only arm of WHI had been terminated.¹ As already well known, the estrogen + progestin arm of the study was terminated 2002,² with a huge impact on postmenopausal women, physicians taking care of these women, and scientists devoted to the study of various health effects of HT. The WHI results, indicating that HT does not provide cardiovascular protection but potentially harm, are in profound disagreement with the sound evidence from numerous observational and experimental studies.^{3,4} In the aftermath of WHI, it is important to try to understand the likely explanations behind these confusing results.

OBSERVATIONAL STUDIES

THE MAJORITY OF observational studies assessing the effect of HT on coronary heart disease (CHD)

come from women who have chosen to initiate HT when entering menopause. The most comprehensive observational study is the Nurses' Health Study,⁵ where approximately 80% of the women included began to use hormones within 2 years after menopause. In the latest report, with 70 533 postmenopausal women followed for up to 20 years, current use of HT was associated with a relative risk for major coronary event of 0.61 (confidence interval [CI], 0.52–0.71) when adjusted for age and the common cardiovascular risk factors.⁶ Although the various observational studies differ considerably in their end-points and design, and in the methods used to eliminate the effects of confounding factors, the majority of the data suggest 30–50% reduction of CHD in HT users compared to non-users⁷ as seen in the Nurses' Health Study.⁵

INITIATION OF RANDOMIZED CLINICAL TRIALS

IN ORDER TO evaluate the possible confounding, selection or compliance bias in the observational studies, a large WHI study was originated in 1992. The aim of this study was in a randomized, placebo-controlled clinical trial (RCT) design to confirm the observational findings that HT (estrogen only or continuous combined estrogen-progestin) provides protection against

*Correspondence: Professor Olavi Ylikorkala, Department of Obstetrics and Gynecology, Helsinki University Central Hospital, P.O. BOX 140, FIN-00029 HUS, Helsinki, Finland. Email: olavi.ylikorkala@hus.fi
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CHD. It should be emphasized that in 1992, the dogma was that the benefits of long-term HT generally outweighed the slight increase in the risk of breast cancer, and therefore the WHI was designed to explore older postmenopausal women, based on the assumption that HT would be beneficial regardless of when it was started. For the WHI study, 373 092 postmenopausal women initiated screening, but less than 10% of the women provided consent for randomization for the HT trial. This reveals the difficulty to conduct a RCT with HT and questions how well this highly selected population represents women in clinical practice choosing to initiate HT. It should be also emphasized that although RCT design is considered the 'gold standard' in medical research, results from RCT can be generalized only to populations that represent the one in the trial. For the WHI, a total of 27 000 apparently healthy postmenopausal women were randomized to receive either conjugated equine estrogens (CEE) only (0.625 mg/day, hysterectomized women), CEE + medroxyprogesterone acetate (MPA) (0.625 mg + 2.5 mg/day), or placebo. The study was designed to last 8.5 years.

Shortly after the WHI was initiated, another RCT, the Heart and Estrogen/Progestin Replacement Study (HERS) was started.⁸ Between 1993 and 1994, the HERS investigators enrolled 2763 postmenopausal women that had established CHD; 1380 women were assigned for CEE + MPA treatment and 1383 for placebo. The primary outcome of this 4.1-year secondary prevention trial was the occurrence of non-fatal myocardial infarction or CHD death. In addition to the HERS, other similar secondary prevention trials were conducted,^{9,10} reflecting the opinion in the mid 1990s that HT had the potential to become even a 'cardiovascular drug' for the treatment of CHD.

FALL OF THE HORMONE THERAPY DOGMA

THE HERS WAS the first RCT on hormone therapy, and showed no protective effect of HT in the CHD secondary prevention.⁸ A total of 179 women in the HT group and 182 women in the placebo group experienced CHD events (CI, 0.81–1.22). Within this overall null effect, a pattern of CHD risk reduction in years 3–5 was offset by a 50% increase in risk during the first year. Difficulty to accept and understand these results raised enormous criticism toward the HERS trial, including limited statistical power, short duration, impact of high dose estrogen, impact of harmful MPA, low compliance, etc. In light of results from similar studies following HERS and considering biological explanations from

various experimental studies, we now admit that HT does not cure established CHD, but may rather cause vulnerable plaque destabilization and rupture, especially if HT is introduced several years after menopause.¹¹ However, rapidly after the HERS results, increasing expectations were set toward the WHI study that was supposed to reveal the final truth of HT and CHD risk. More importantly, it was now emphasized that the WHI was a primary prevention trial with healthy postmenopausal women.

In April 2000, the WHI Data and Safety Monitoring Board informed the participants that 'during the first 2 years, there was a small increase in the number of heart attacks, strokes, and blood clots in women taking active study pills compared to inactive placebo pills', but recommended that the study continue. Furthermore, in Spring 2000 and 2001, all WHI study participants received a warning letter from the investigators that informed them about a slight increase in risk of cardiovascular events in HT users during the first study year. Obviously, these letters must have caused uncertainty among the study subjects, especially since approximately 40% of the participants on the HT treatment were unblinded. These women, knowing that they were receiving active treatment, may have more frequently requested additional electrocardiograms that could detect 'silent' myocardial infarctions (approximately 40% of all infarctions in elderly populations) that could have remained undiagnosed in the placebo group.¹² Therefore, in addition to observational studies, RCT are subject to bias.

On 9 July 2002, the news heard around the world was that the WHI Data and Safety Monitoring Board had decided to cancel the CEE + MPA arm of the study, after an average of 5.2 years of follow up, because breast cancer exceeded the stopping boundaries.² However, the major focus was on the cardiovascular aspects, since WHI showed HT to be associated with more CHD (37 vs 30 per 10 000 patient years) and strokes (29 vs 21 per 10 000 patient years). The excess in CHD risk was borderline significant, but the message in the lay press was loud and clear; hormones are harmful for the heart. Little attention was paid to the following 'final' report of the WHI cardiovascular end-points where the increased CHD risk in the HT group was no longer statistically significant.¹³ After the initial report from the WHI, the overall attitude towards HT rapidly shifted and these RCT results were considered 'solid, definitive, and final'. This new position even originated new terminology, where the 'replacement' was excluded from HT.¹⁴ Thus, it was no surprise that recently the NIH decided to discontinue the estrogen-only arm of the

WHI, although no safety boundaries were exceeded.¹ Furthermore, the main message from this study arm was that estrogen increased the risk of stroke, whereas no news was the fact that estrogen alone did not increase breast cancer risk but showed a trend toward protection (hazard ratio 0.77, CI 0.59–1.01).

WHAT THE WOMEN'S HEALTH INITIATIVE REVEALED

WHEN INTERPRETING THE WHI data, the key question is whether the study was a truly primary prevention trial, or had these women in fact had a greater risk for cardiovascular events before HT initiation than did women in the observational studies. Although the women in WHI were apparently healthy, the population had a mean age of 63 years (two-thirds were over 60 years), the women were obese (mean body mass index 28.5; 34% had a body mass index over 30), and almost 50% of the subjects were past or current smokers. Furthermore, the WHI population was on average 12 years past menopause and only 4 years younger than the HERS population with established CHD.⁸ Since we know that in women the most active progression in atherosclerotic lesions is after entering the menopause, probably the majority of the 'healthy' but elderly WHI women had subclinical atherosclerosis and even complicated plaques¹⁵ (Fig. 1). This may have a major impact on the effect of HT when introduced to the vascular wall years after menopause, when the potentially beneficial direct effects of HT on healthy vascular wall are lost or become even adverse due to the advanced atherosclerosis.^{4,11} The loss of estrogen effect after further atherosclerosis progression is convincingly shown in studies with non-human primate model¹⁶ (Fig. 2). Furthermore, oral estrogen treatment is shown

Figure 1 Age and progression of coronary artery plaque complication (calcification). Data adapted from Raggi *et al.*¹⁵

Figure 2 Pre-existing atherosclerosis and effectiveness of estrogen treatment. Modified from Karas and Clarkson.¹⁶

to increase matrix metalloproteinases¹⁷ and C-reactive protein,¹⁸ which both may destabilize and promote rupture of vulnerable atherosclerotic plaques. Interestingly, statins that are well known to stabilize atherosclerotic plaques, concomitantly used with HT, resulted to a lower CHD event rate in both HERS¹⁹ and WHI¹³ populations. Thus, even if WHI was intended to be a primary prevention trial, the results may only indicate again that HT does not work in secondary prevention.

The fact that the WHI population does not represent the women starting HT during the menopausal transition has encouraged the investigators to carry out subgroup analyses in younger women. These analyses were claimed to show the same lack of cardioprotection with HT in the 50- to 59-year-old WHI women as in the overall population.²⁰ However, no further information was provided on the composition of this 50- to 59-year-old group; whether the group had homogenous age distribution and perhaps most importantly, what was the 'menopausal age' (i.e. years since menopause at initiation of the treatment). Naftolin *et al.*,²¹ using these parameters, had re-evaluated the WHI estrogen + progestin 50–59-year-old group and compellingly showed that the WHI population was 10-fold underpowered to show cardioprotection of women starting HT during the menopausal transition. Although there were over 5000 women in the 50–59-year-old group, less than half of these had <5 years since menopause, and most importantly, only 574 women were 50–54 years of age and moderately or severely symptomatic, thus representing the women starting HT in clinical practice (Fig. 3). Using age-specific data from the Nurses' Health Study,⁶ the incidence of cardiac events in the 50–54-year-old population translates to approximately 1.5 events in these 574 women over a 5-year period.

Figure 3 Subjects in The Women's Health Initiative representing women who initiate hormone therapy in clinical practice. Modified from Naftolin *et al.*²¹

STILL MUCH TO BE LEARNT

THE CONSIDERABLE BODY of observational and experimental data support the likelihood that HT provides primary cardiovascular benefits if initiated soon after the onset of estrogen deficiency. To prove this in a RCT setting is exceptionally challenging due to the fact that women normally initiate HT when entering menopause with troublesome menopausal symptoms. Since HT very effectively alleviates vasomotor symptoms, blinding is difficult in these typical candidates.²² The fact that women with severe menopausal symptoms did not participate in the recent RCT could be a major bias if vasomotor symptoms would be a marker for vascular response to the ovarian hormones. Although it has been shown that there are differential vascular responses in flushers and non-flushers, only few studies have investigated in which way absence or presence of menopausal symptoms influences treatment effects.²³ Studies indicate that women with vasomotor symptoms have a higher basal forearm vascular flow and greater dilation responsiveness to vasoactive amines, norepinephrine and epinephrine. Therefore, these results support the possibility that there are biologic differences between symptomatic and asymptomatic women that might also affect the individual benefit-risk profile for HT.

To date, only a few studies have assessed HT and atherosclerosis progression among women in menopausal transition without cardiovascular disease or major risk factors. In a study by de Kleijn *et al.*,²⁴ 121 perimenopausal women between the ages 40–60 years were randomized to receive either estrogen or placebo, and carotid intima media thickness was measured before and after 2-year treatment. Estrogen treatment

showed a trend toward reduced progression of intima media thickness, but a high 48% drop-out rate prevented reliable conclusions, once again demonstrating the difficulty to carry out a RCT in women entering menopause. In a more recent study, HT and coronary artery atherosclerosis was evaluated by measuring coronary artery calcium score in 2213 women.²⁵ Noteworthy in this study is that the average age of the HT users was 59 years and the duration of use was 9 years, thus the HT was started close to menopause. The duration of HT was significantly associated with a reduction in coronary artery calcification, suggesting coronary artery atherosclerosis protection by HT in these women. In October 2003, the Kronos Longevity Research Institute in Phoenix, AZ, USA, announced funding for a 5-year study (KEEPS-trial), assessing HT and atherosclerosis progression in women between ages 45–54 years: 'This RCT will evaluate both oral and transdermal estrogen treatment compared to placebo and thus, will hopefully shed light on the effect of age/stage of atherosclerosis at the time treatment is initiated and the significance of different routes of administration.' (Wall Street Journal, October 8, 2003).

When individualizing HT treatment, an important question is whether genetic factors can substantially modify individual women's responses to HT. Recently, new studies have examined the effects estrogen receptor polymorphisms on the response to HT. Women from the Estrogen Replacement and Atherosclerosis Trial were genotyped, and estrogen receptor alpha gene polymorphisms were strongly related to high-density-lipoprotein-cholesterol (HDL-C) response, that is, HDL-C increased by 26% with estrogen treatment in women with minor C/C allele, compared with only 10% in women who were carriers of the major T/C or T/T alleles.²⁶ Furthermore, a different estrogen receptor alpha polymorphism is associated with atherosclerosis in patients with hyperlipidemia.²⁷ If we could in the future determine women with a greater or lesser response to HT, the treatment could be directed to women most able to benefit from it. Knowledge of genetic factors will also contribute to the understanding of the biological variability in many other physiological processes influenced by both endogenous and exogenous estrogen.

WHERE DO WE STAND NOW

IT IS CLEAR that HT is not a 'cardiovascular drug', and asymptomatic women several years past menopause should not be treated with HT. Although RCT of older postmenopausal women have not supported the

observational and experimental data indicating a cardiovascular benefit of HT, the crucial question is whether HT for the treatment of postmenopausal symptoms provides cardiovascular benefits that offset its risks. Before more data from these recently menopausal symptomatic women are available, we need to base our decisions on existing evidence and good clinical practice. Studies suggesting that symptomatic women should use behavioral measures, such as lowering ambient temperature, drinking cold liquids, and deep abdominal breathing²⁸ are inappropriate since it is contrary to the accumulated literature and, most importantly to clinical experience. Although the potential of HT to provide cardiovascular benefit is decreased by advancing age and time since menopause, this should not preclude the use of individualized HT in younger postmenopausal women.

REFERENCES

- 1 The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA* 2004; **291**: 1701–1712.
- 2 Writing Group for the Women's Health Initiative Investigators. 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**: 321–333.
- 3 Genazzani AR, Gambacciani M. A personal initiative for women's health: to challenge the Women's Health Initiative. *Gynecol Endocrinol* 2002; **16**: 255–257.
- 4 Mikkola TS, Clarkson TB. Estrogen replacement therapy, atherosclerosis, and vascular function. *Cardiovasc Res* 2002; **53**: 605–619.
- 5 Stampfer MJ, Willett WC, Colditz GA *et al.* A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med* 1985; **313**: 1044–1049.
- 6 Grodstein F, Manson JE, Colditz GA *et al.* A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133**: 933–941.
- 7 Grady D, Rubin SM, Petitti DB *et al.* Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; **117**: 1016–1037.
- 8 Hulley S, Grady D, Bush T *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.
- 9 Herrington DM, Reboussin DM, Brosnihan KB *et al.* Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000; **343**: 522–529.
- 10 Viscoli CM, Brass LM, Kernan WN *et al.* A clinical trial of estrogen-replacement therapy after ischemic stroke. *N Engl J Med* 2001; **345**: 1243–1249.
- 11 Mikkola TS, Clarkson TB, Notelovitz M. Postmenopausal hormone therapy before and after the women's health initiative: what consequences? *Ann Med* 2004; **36**: 1–12.
- 12 Garbe E, Suissa S. Issues to debate on the Women's Health Initiative (WHI) study. Hormone replacement therapy and acute coronary outcomes. Methodological issues between randomized and observational studies. *Hum Reprod* 2004; **19**: 8–13.
- 13 Manson JE, Hsia J, Johnson KC *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; **349**: 523–534.
- 14 Gambacciani M, Genazzani AR. The missing R. *Gynecol Endocrinol* 2003; **17**: 91–94.
- 15 Raggi P, Callister TQ, Coil B *et al.* Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. *Circulation* 2000; **101**: 850–855.
- 16 Karas RH, Clarkson TB. Considerations in interpreting the cardiovascular effects of hormone replacement therapy observed in the WHI: timing is everything. *Menopausal Med* 2003; **10**: 8–12.
- 17 Zanger D, Yang BK, Ardans J *et al.* Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management. *J Am Coll Cardiol* 2000; **36**: 1797–1802.
- 18 Kah KK, Ahn JY, Kang MH *et al.* Effects of hormone replacement therapy on plaque stability, inflammation, and fibrinolysis in hypertensive or overweight postmenopausal women. *Am J Cardiol* 2001; **88**: 1423–1426.
- 19 Herrington DM, Vittinghoff E, Lin F *et al.* Statin therapy, cardiovascular events, and total mortality in the heart and estrogen/progestin replacement study (HERS). *Circulation* 2002; **105**: 2962–2967.
- 20 Langer RD. Legend meets reality: estrogen plus progestin and coronary heart disease in the Women's Health Initiative. *Menopausal Med* 2003; **10**: 5–7.
- 21 Naftolin F, Taylor HS, Karas R *et al.* The Women's Health Initiative could not have detected cardioprotective effects of starting hormone therapy during the menopausal transition. *Fertil Steril* 2004; **81**: 1498–1501.
- 22 Ylikorkala O. Balancing between observational studies and randomized trials in prevention of coronary heart disease by estrogen replacement: HERS study was no revolution. *Acta Obstet Gynecol Scand* 2000; **79**: 1029–1036.
- 23 Beljic T, Babic D, Marinkovic J *et al.* Effect of estrogen replacement therapy on cardiac function in postmenopausal women with and without flushes. *Gynecol Endocrinol* 1999; **13**: 104–112.
- 24 De Kleijn MJJ, Bots ML, Bak AAA *et al.* Hormone replacement therapy in perimenopausal women and 2-year change of carotid intima-media thickness. *Maturitas* 1999; **32**: 195–204.
- 25 Akhrass F, Evans AT, Wang Y *et al.* Hormone replacement therapy is associated with less coronary atherosclerosis in

- postmenopausal women. *J Clin Endocrinol Metab* 2003; **88**: 5611–5614.
- ²⁶ Herrington DM, Howard TD, Hawkins GA *et al.* Estrogen-receptor polymorphism and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. *N Engl J Med* 2002; **346**: 967–974.
- ²⁷ Lu H, Higashikata T, Inazu A *et al.* Association of estrogen receptor- α gene polymorphisms with coronary artery disease in patients with familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 2002; **22**: 817–823.
- ²⁸ Grady D. Postmenopausal hormones – therapy for symptoms only. *N Engl J Med* 2003; **348**: 1–3.