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Menopause, Hormones, and the "Critical Therapeutic Window"

BY CHRISTINE M. DERZKO, MD, FRCSC

A decade ago, the prevailing opinion was that postmenopausal hormone therapy reduced coronary heart disease (CHD) by 30%-50%. This position was based on a vast body of evidence, including the results from several large, prospective, observational studies, epidemiological studies, and a variety of randomized controlled trials (RCTs) using surrogate markers. Further support came from the laboratory and from an improved understanding of vascular biology based on both human and animal data. All pointed to the conclusion that postmenopausal hormone therapy (HT), notably estrogen therapy (ET), was cardioprotective. However, two large RCTs – the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI), which were intended to definitively demonstrate that ET/EPT (estrogen + progestin therapy) was cardioprotective and generally safe – failed to do so. The medical world was stunned, clinicians and investigators were perplexed, and women stopped taking their hormones and sought alternative treatments for their symptoms. Scientists and investigators returned to their laboratories and their desks to seek explanations and, once again, the quest for "the truth" began. All of the factors leading the original conclusions were revisited. Finally, a plausible explanation for the incongruity of the findings from earlier observational studies and the more recent RCTs became clear. A "unified hypothesis" was proposed and the concept of a "critical therapeutic window" emerged, stating, "Reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications, and plaque vulnerability"¹. This issue of *Endocrinology Rounds* reviews relevant findings from the ongoing Nurses' Health Study (NHS), the largest and most comprehensive observational study, and the WHI which, to date, is the largest RCT examining postmenopausal hormone use. This issue will also show how the results of these studies differ or are similar, the reasons for these discrepancies and, finally, consider the vascular biological effects of estrogen since these data strongly support the proposed hypothesis.

The clinical trials

More than 20 early clinical observational studies and small RCTs have consistently demonstrated a reduction in CHD and deaths in postmenopausal women treated with hormones. In 1975, the NHS began by enrolling 121,00 female nurses, aged 20-50 years. In February 2006, Grodstein et al² reported on an impressive volume of data – 220,368 women-years (wy) of EPT, 124,391 wy of ET, and 313,661 wy of information on women who had never taken hormones. Their results continue to show a 30%-40% overall reduction in CHD in the ET/EPT treatment groups.

Two major RCTs, designed to provide definitive evidence for the cardioprotection of estrogen, while simultaneously assessing the risk of breast cancer, stroke, and thromboembolic complications, were started in the 1990s.

- The first was HERS, a secondary prevention trial examining postmenopausal hormone therapy in older women (study population: 2,763 women aged <80 years, mean age 67 years, average 18 years postmenopausal) with a history of significant CHD.
- The second, the WHI Trial, was intended as a primary prevention study in healthy, asymptomatic (women with hot flashes were actively discouraged from enrolling) postmenopausal women aged 50-79 years (16,608 women, mean age 63.3 years, more than two-thirds were aged 60 years at enrollment).

The study medication in both the HERS and WHI studies was continuous combined conjugated equine estrogen (CEE) 0.625 mg + medroxyprogesterone acetate (MPA) 2.5 mg. A second, parallel, estrogen-only arm of the WHI (10,739 women, aged 50-79 years, mean age 63.3 years), was designed to study hysterectomized women using continuous CEE 0.625 mg alone. At the conclusion of the HERS study in 1998, the results were analyzed and an overall null effect (HR 0.99; 95% CI, 0.80 -1.22) was reported (ie, there was neither an increase nor a decrease in cardiovascular [CV] events or death). Interestingly there was a significant increase in coronary events in the first year (HR 1.52; 95% CI, 1.01-2.29), with a trend towards benefit in the succeeding 4 years. There were similar findings on re-analysis of early vs late NHS and WHI results.³



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QINGHUA WANG, MD, PHD

TOM WOLEVER, MD, PHD

MINNA WOO, MD, PHD

St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

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Continuation of this trend towards a reduction in cardiac events in the treated vs the placebo-treated population was not seen in the 2-year observational HERS extension trial, which enrolled 95% of the year-5 HERS study patients, but since $\leq 44\%$ remained category and drug compliant, the validity of these results has been questioned.

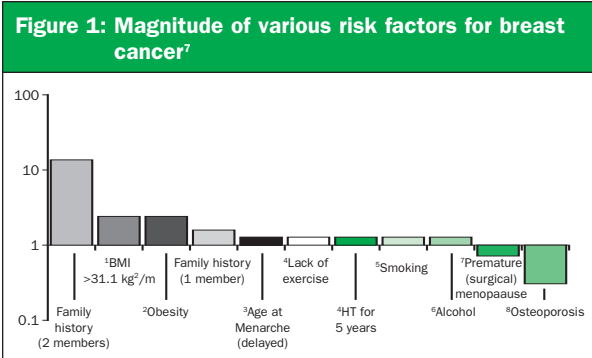
However, the once-held opinion that postmenopausal hormone therapy is cardioprotective was effectively reversed in 2002 when, as mandated by the Data Safety and Monitoring Board (DSMB), the EPT arm of the WHI was prematurely terminated after an average patient follow-up of only 5.2 of the planned 8.5 years.⁴ An excess in overall risks compared to overall benefits and, specifically, an increase in breast cancer incidence that had “crossed the pre-specified boundary,” was cited. Despite the fact that the absolute attributable risk (AR) over baseline of invasive breast cancer in EPT users amounted to an increase of $<1/1000/\text{year}$ (and all of the participants who developed breast cancer had taken EPT prior to enrolling in the WHI), the press headlined the following alarming percentage increases in adverse events in the study population: breast cancer 26%; CHD 29%; stroke 41%; and pulmonary emboli (PE) 113% in EPT users. The ARs of 8/10,000, 6/10,000, 7/10,000, and 8/10,000, per year, respectively, were not reported.

In addition, the subsequent publication of the corrected adjudicated results showing that the increase in CHD was not statistically significant (HR 1.24; 95% CI, 1.00-1.54) went relatively unnoticed. Nonetheless, the study had failed to validate the concept of cardioprotection in the hormone-treated (ie, the EPT-treated) group. The new conclusion was that HT, notably estrogen, increased breast cancer risk and was also harmful to the CV system, even in healthy menopausal women.

In 2004, the WHI estrogen-only arm was also stopped early (at 6.8 years),⁵ this time by the National Institutes of Health (NIH), rather than the DSMB. They cited a trend toward an increase in strokes in the treatment group without an improvement in the overall global score. Virtually unnoticed was the fact that, not only was there no increase in CHD (RR 0.91; 95% CI, 0.75-1.12), the risk of breast cancer in CEE-alone users (RR 0.77; 95% CI, 0.59-1.01) – when compared with the placebo group – was also lower than for the placebo group, and this number just missed being statistically significant. Furthermore, in the 50-59 year-old subgroup, there was no significant increase in strokes. That increase was limited to the 60-79 year-old group.⁶

Breast cancer: The WHI finding of reduced breast cancer in users of CEE alone was unexpected and requires confirmation. However, the breast cancer results in the EPT arm were entirely as expected (RR 1.24; 95% CI, 0.97-1.59). According to American Cancer Society statistics, a 50-year-old woman has a 2.8% chance of developing breast cancer before she turns 60 years of age. Thus, we would expect 2.8 cases per 100 women at age 60 years in the placebo group. This number increased to 3.5 cases/100 women in the EPT group, which translates into an attributable risk of 0.7/100 (ie, 0.7/2.6, a 26% increase as reported in the press). Figure 1 shows a composite of relative risk factors for breast cancer.

Cardiovascular disease: With respect to CHD, the WHI results in ET/EPT users initially were both unexpected and puzzling. The WHI was an RCT recognized as being the “gold standard” and, thus, its results were accepted over those of earlier observational trials that were generally considered to be less reliable and subject to a variety of known



RR of 1 = no risk; RR >1 = risk; RR <1 = benefit; Not head-to-head comparisons.

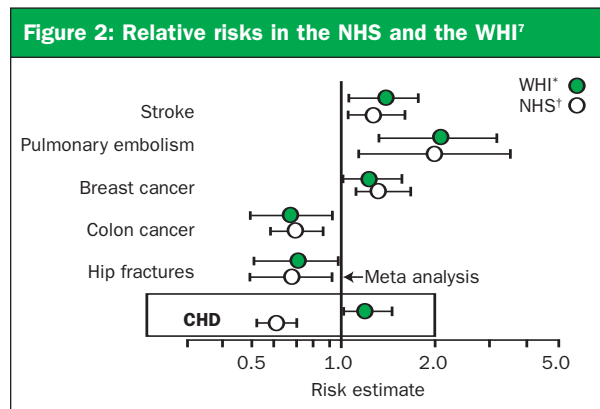
¹Morimoto LM, et al. *Cancer Causes Control* 2002;13:741-51; ²Huang Z, et al. *JAMA* 1997;278:1407-11; ³Thune I, et al. *N Engl J Med* 1997;336:1269-75; ⁴McTiernan A, et al. *JAMA* 2003;290:1331-6; ⁵Reynolds P, et al. *J Natl Cancer Inst* 2004;96:29-37; ⁶Li Ci, et al. *Cancer Epidemiol Biomark Prev* 2003;12:1061-6; ⁷Society of Obstetricians and Gynaecologists of Canada. Available at: <http://sogc.medical.org/>; ⁸Kuller LH, et al. *Environ Health Perspect* 1997;105(Supple 3):593-9.

and unknown biases. Surprisingly, however, when comparing the findings from the WHI and the NHS, there was remarkable homology, except for the number of CHD events (Figures 2 and 3). The reduction in osteoporotic fractures, endometrial and colorectal cancer, diabetes mellitus, and the increase in deep vein thrombosis (DVT), PE, and stroke were quite similar, but the difference in coronary heart disease events was striking!

Why are the findings from the HERS and WHI different from the NHS and earlier studies? Is it a problem with the study?

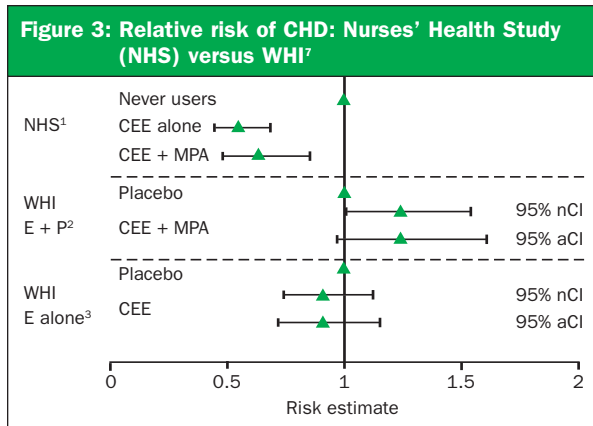
RCTs and observational studies each have their strengths and weaknesses. Karas provides the following comparison, “Observational studies, despite their potential for uncontrolled confounding, have the distinct advantage of being able to study large populations of individuals followed over extended periods of time and whose treatment, by definition, reflects common clinical practice.”⁸

RCTs, on the other hand, are powerful investigative tools and “generally considered” to be the gold standard for evaluating drug effects. However, RCT study results are applicable only to the specific populations studied in the trial. When divergent results are obtained from these



*HT vs placebo; †Current use vs never use.

Manson JE, et al. *N Engl J Med* 2003;349:523-34; Grodstein F, et al. *Ann Intern Med* 2000;133:933-41; Colditz GA, et al. *N Engl J Med* 1995;332:1589-93; Kiel DP, et al. *N Engl J Med* 1987;317:1169-74; Grodstein F, et al. *Ann Intern Med* 1998; 128:705-12; Torgerson DJ, Bell-Syer SE. *JAMA* 2001;285:2891-7; Grodstein F, et al. *N Engl J Med* 1997;336:1769-75; Writing Group for the Women’s Health Initiative Investigators. *JAMA* 2002;288:321-33.



CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; nCI = nominal confidence interval; aCI = adjusted confidence interval
¹Manson JE, et al. *N Engl J Med* 2003;349:523-34; ²Grodstein F, et al. *Ann Intern Med* 2000;133:933-41; ³Women's Health Initiative Steering Committee. *JAMA* 2004; 291:1701-12.

two sources, it is prudent to look at "if" and "how" the evidence can be reconciled.

WHI – methodologic issues

A number of peer-reviewed critiques of the WHI and its published results have recently appeared in the literature,⁹⁻¹⁵ pointing out statistical shortcomings, epidemiological issues, methodological problems, and the prematurity of the conclusions. Unquestionably, the WHI results are of major importance to our understanding the benefits and risks of HT use in postmenopausal women. However, the fact that eminent scholars, academicians, scientists, and clinicians are questioning the validity of the conclusions gives us reason to question them as well. We will address a few of the many questions:

Does the WHI qualify as an RCT? Many would answer "no." Despite the initial study design, the trial had a number of shortcomings, including the fact that, after randomization, women were free to decide whether to continue their assigned treatment or undergo additional diagnostic procedures; 45% were unblinded as to their treatment; and warnings were sent out to study patients advising them of an increase in myocardial infarctions (MIs), cerebrovascular accidents (CVAs), and PEs in HT-users. Therefore, some epidemiologists and statisticians assert that this makes the "WHI no better than any observational study with the same limitations."¹²

Was the WHI truly a primary prevention trial? Clearly, the answer to this question is of major importance and determines the applicability of the results to healthy perimenopausal or symptomatic early menopausal women presenting for care.

Was this a healthy population? Of the women recruited into the WHI study, 69.25% were overweight, (more than half were obese, ie, body mass index [BMI] ≥ 30), 37.2% were hypertensive, 18.0% were hyperlipidemic, 4.4% had diabetic risk factors for CHD, and 19% had been prescribed acetylsalicylic acid (ASA) for MI or CVA prevention. An additional 7.19% reported angina, a history of an MI, angioplasty, DVT, PE, or stroke. The placebo group had a similar distribution of illness.^{10,14} Critics have pointed out that, in all, 78.12% of the recruited subjects had a pre-existing condition or illness that would clearly disqualify them from being categorized as "healthy," and disqualify the trial from being a primary prevention trial.

Figure 4: NHS vs WHI: differences between trial participants^{7**}**

	NHS	WHI
Age @ enrolment (in years)	30-55 (range)	63 (mean)
Years since menopause	< 5 years	~15-18 years
Began ET/EPT	@ Menopause	Years or decades after menopause
Mean BMI % overweight/obese	25.1 38%	28.5* (34% >30 kg.m ²) 70%
Menopausal symptoms (hot flashes)	Predominant	Uncommon (excl. from study)
Prevalent MI or angina (self reported)	None	4%
HT (self reported)	18%	28%
Diabetes (self reported)	3%	4%
HT regimen	Unopposed or SQ	Continuous combined

**** Grodstein F, et al. *Ann Intern Med* 2000;133:933-41; Grodstein F, et al. *N Engl J Med* 1996;335:453-61; Writing Group for the Women's Health Initiative Investigators. *JAMA* 2002;288:321-33; The Women's Health Initiative Steering Committee. *JAMA* 2004;291:1701-12.

Practice related questions regarding the WHI

- Are the WHI conclusions applicable to *healthy* menopausal women who do not present with the same "unhealthy" profile, particularly those who are symptomatic, in early menopause, who seek and need menopausal hormone therapy?
- Was the appropriate age group studied?
- Are these women typical of those who come to us requesting EPT/ET?

The mean age of the women recruited into the WHI was 63.3 yrs (± 7.1 years) and, on average, they were 18 years postmenopausal. Thus, by calculation, women aged <56.1 yrs were >2 standard deviations (SDs) outside of the mean age group studied. Furthermore, there was a 12-year difference between the mean age of menopausal women (51.3 yrs) and those studied in the WHI trial. It is doubtful then that the results are applicable to younger menopausal women, given that 70% of women in the study were aged 60-79 years and, most certainly, the results are not relevant to women aged <50 years with premature menopause, since these women were not even represented in the WHI population.

Subjects in the NHS were, for the most part, younger, slimmer, symptomatic for menopause, more likely to have started HT at menopause, and more likely to be using a cyclic, sequential, or unopposed estrogen routine (Figure 4). They were also less likely to have advanced pre-existing coronary artery disease (CAD) and more likely to be taking ASA at baseline. The results of treatment were also different. While in the WHI, CEE alone increased the risk of stroke (HR 1.39; 95% CI, 1.10-1.77) and PE (HR 1.34; 95% CI, 0.87-2.06), and did not affect the incidence of CAD (HR 0.91; 95% CI, 0.75-1.12); CEE + MPA led to a nonstatistically significant excess of CHD with 7/10,000 more events (HR 1.29; 95% CI, 1.02-1.68), PE (HR 2.13; 95% CI, 1.39-3.25), and stroke (HR 1.41; 95% CI, 1.07-1.85).¹⁶ In contrast, the NHS showed a reduction in CHD events (RR in current E users of 0.61 (95% CI, 0.52-0.71) with similar results for CEE \pm MPA at doses of 0.3-0.625 mg but, interestingly, stroke risk RR of 0.58 (95% CI, 0.3-0.92) with 0.3 mg, but RR 1.35 (95% CI, 1.08-1.68) with 0.625 mg and RR 1.63 (95% CI, 1.18-2.26) for 1.25 mg CEE and 1.45 (95% CI, 1.10-1.92) for CEE + MPA.¹⁷

Years since menopause vs age as a factor (in the NHS, WHI clinical trial, and the WHI observational study)¹⁶⁻²¹

Most women in the WHI clinical trial began ET/EPT upon entry into the study (mean age 63.3 years, approximately 18 years postmenopausal). In contrast, most women in observational trials, including the NHS and the Observational arm of the WHI, began ET/EPT in the perimenopause, ie, at a younger age and “healthier stage” than the WHI clinical trial group. Nonetheless, the results are remarkably uniform. The RR for women on HT developing CAD by subgroup:

- WHI 50-59 years old, HR 0.56; NHS ET/EPT started within 4 years of menopause, HR 0.48 and HR 0.45
- WHI 60-69 years old, HR 0.92; NHS ET/EPT started 10 years postmenopausally, HR 0.60 and 0.70
- WHI Observational Study: if HT at 50-59 years old, RR in CAD approaching 50%.¹⁸

Summary

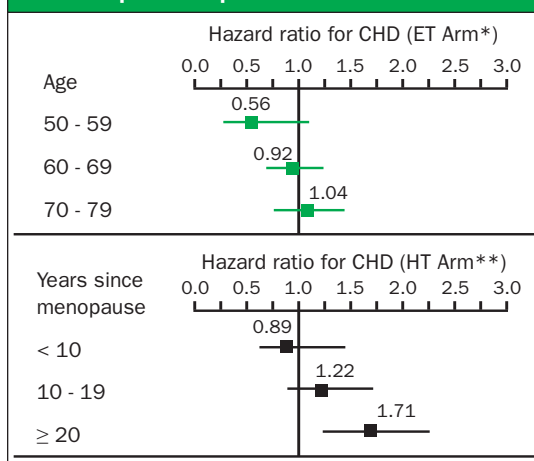
Compared to the NHS study population, women in the WHI Trial – on average – were older, thus they started their HT at an older age and had more CV risk factors than did women in the NHS and in most other observational studies. Compared to the WHI, the NHS study population is more representative of women in our clinical practice who start ET/EPT.

Women who begin ET/EPT close to menopause, notably symptomatic women, may experience significant reductions in CHD risk. This was seen in the NHS women, in women in the Observational Arm of the WHI, and also in the small subgroup of younger women in the WHI ET/EPT Study. Older women are likely to have more advanced pre-existing atherosclerosis. For this reason, initiation of ET/EPT in older women may be ineffective or potentially harmful.

A unifying theory – The “critical window” hypothesis^{19,20}

The “critical window hypothesis” is a unifying theory that aims to explain the animal data, as well as the seemingly divergent results from both observational studies (eg, NHS) and RCTs (eg, WHI and HERS). In fact, both are correct when applied to the appropriate population. The “timing is everything” hypothesis states that if ET/EPT is begun in early menopause when pre-existing arteriosclerotic heart disease (ASHD) (“vulnerable plaque”) is minimal, the effect is cardioprotective, as seen in observational and animal studies and in the small WHI cohort of 547 symptomatic women aged ≤56 years. However, once significant CAD exists, the addition of estrogen is no longer beneficial and may result in the progression of atherosclerosis, plaque destabilization, or plaque rupture. The hypothesis predicts “early harm/late benefit” in this population as well. With ET/EPT, there will be a sharp increase in CHD events in the first 1 to 2 years when vulnerable plaques rupture, followed by decreased plaque formation and, eventually, by fewer CAD events than in the untreated population, the net benefit being apparent after 5 to 6 years. Thus, the “reproductive stage,” which determines the estrogen status at onset of treatment, is the crucial factor in predicting the effect of ET/EPT on the CV system (Figure 5).

Figure 5: Effect of ET and HT on CHD in postmenopausal women²⁶



*The Women's Health Initiative Steering Committee. *JAMA*. 2004;291:1701-11.
 **Manson et al. *N Engl J Med* 2003;394:523-34. Used with permission.

Supporting evidence for this hypothesis

Clinical trials:^{22,11} Data from the NHS and WHI (EPT and ET trials) and the WHI observational study clearly support this concept, as do results from other RCTs (ie, ERA, WAVE, ESPIRIT, PHASE, WELL-HART, and EPAT). Different doses, different preparations, and different regimens were studied and various endpoints used. EPAT was the only primary prevention study and the only trial showing a positive outcome with estrogen therapy. In the other studies, all of which were secondary prevention trials, no demonstrable benefit of hormone therapy was seen.

Vascular biology: laboratory and animal studies

Mechanisms of estrogen action^{10,23,24} A review of data from laboratory and animal studies offers insight into the pathophysiology of this vascular process. The CV effects of estrogen are complex and may be *indirect* or *direct*. The indirect effects can be *positive* (lipids - ↑HDL, ↓LDL, ↑NO-mediated vasodilation, ↓vascular response to injury, ↓atherosclerosis development), or *negative* (↑triglycerides, ↑inflammatory markers (C-reactive protein, IL-6) ↑prothrombotic markers (↑prothrombin time [PT], ↓antithrombin III) predisposing to venous thromboembolism (VTE). Estrogen also has *direct* effects on the heart and the blood vessels mediated through estrogen receptors (ER α and ER β). For example, circulating lipids and coagulation factors exert their effects through ERs that reside in the cell nucleus and regulate gene expression in response to hormone binding. This “*genomic pathway*” is slower and the result longer lasting. From animal data, we know that this includes a reduction in atherosclerosis and a less florid response to vascular injury (ie, decreased migration and proliferation of both endothelial cells and vascular smooth muscle cells at sites of vascular injury). However, there is also a faster, short-acting, “*non-genomic pathway*” (that responds in minutes), mediated through ERs in the cell membrane. The most important of these effects is the rapid release of nitric oxide, resulting in vasodilation in response to acute estrogen stimulation. Other effects include decreased production

of endothelin-1 (a vasoconstrictor), downregulation of angiotensin-converting enzyme, and low-density lipoprotein (LDL) oxidation. As well, hormones may exert their effects indirectly on the CV system through their effects on carbohydrate (CHO) cell metabolism (reduced glucose intolerance and diabetes mellitus), on coagulation factors (both positive and negative), as well as on inflammatory markers and homocysteine.

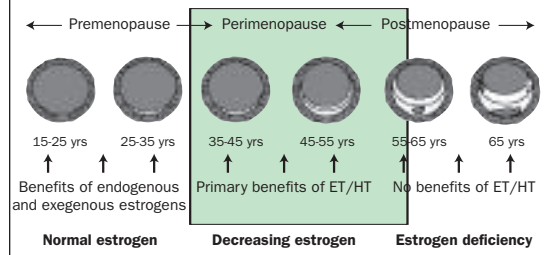
The altered response of diseased arteries¹¹

Estrogen prevents plaque formation and progression in undiseased or minimally-diseased arteries, an effect lost once atherosclerosis is established. Endothelial damage results in reduced ER expression, with consequent endothelial dysfunction, loss of vasodilation, and increased inflammation in proportion to the degree of existing damage. Exposure of established plaques to estrogen may result in plaque destabilization and acute rupture. Plaque rupture occurs because of a resulting imbalance between the estrogen-induced upregulation of matrix metalloproteinases (MMPs), without a proportional increase in the release of their balancing inhibitors, tissue inhibitors of metalloproteinases (TIMPs). In this unbalanced state, the MMPs proceed to degrade the extracellular matrix of the arterial wall and, if this occurs in the shoulder region of an established plaque, rupture of plaque stroma may occur and estrogen-induced neo-vascularization may lead to plaque hemorrhage.

Many elegant experiments from Dr. Thomas Clarkson's primate laboratory using a well-established monkey model of atherosclerosis directly support this theory; ie, that the effect of estrogen on CV risk depends on whether treatment is initiated before or after significant atherosclerosis has developed. Similar to results observed in the NHS, where ET/EPT was initiated in perimenopausal women who were free of CHD, treatment of ovariectomized monkeys with CEE or 17 β estradiol (E2) resulted in a 50%-72% ($p \leq 0.04-0.05$) reduction in CAD compared with placebo-treated monkeys. This is in contrast to results seen when monkeys with established atherosclerosis were treated (similar to the HERS study) or when there was a delay in the initiation of treatment following oophorectomy (ie, similar to the WHI population). The atheroinhibitory effect of CEE treatment was only seen in the monkeys with the lowest plaque burden, which is considered similar to women at the end of the perimenopausal transition and in the early postmenopausal years. There is a total loss of effects if treatment is delayed for a period calculated to be the equivalent of 6 postmenopausal years for women. The best results were seen in monkeys treated with an estrogen-containing oral contraceptive (OC) during the menopausal transition, followed immediately by postmenopausal HT.²⁷

Clarkson has also shown in the primate model that statins inhibit the production and release of MMPs from vascular smooth muscle cells and control the estradiol-induced upregulation of MMP enzymatic activity in plaque-derived macrophages. These findings provide us with a probable explanation as to why adverse cardiac events may have been reduced in both the HERS and WHI study patients who were taking statins, a point to remember for patient management. (Figures 6 and 7)

Figure 6: There is increasing evidence that ET/HT initiated during the perimenopausal/early postmenopausal period, but NOT late menopause, inhibits the progression of atherosclerosis



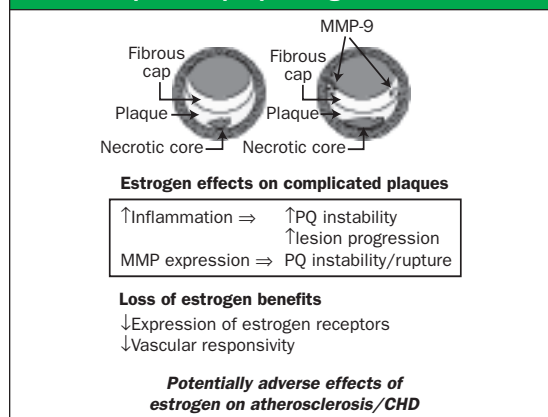
Used with permission: Mikkola TS, et al. *Ann Med* 2004;36:402-13.

Conclusion

Studies have yielded diametrically opposite results vis-a-vis CAD when postmenopausal women were treated with estrogen and estrogen/progestin. Though initially confusing to patients and perplexing to clinicians, we are now able to better understand these results, based on a proposed "unifying hypothesis" that explains these seemingly diametrically opposite conclusions and, in fact, reveal that both may be correct. Whether or not estrogen is cardioprotective is dependent on the underlying status of the CV system. This finding, which was evident in both observational studies and clinical trials, has been elegantly reproduced in animal studies, particularly in the primate model.

The cardioprotective effects of estrogen, including the prevention and progression of plaque development, are lost once atherosclerosis is established. The biologic effects of estrogen that have been demonstrated in animal studies is markedly altered in disease states. Estrogen receptor function is reduced, resulting in endothelial dysfunction, loss of vasodilation, increased inflammatory activation and destabilization, and possible acute rupture of established plaques. Thus, the diverse results from the treatment of younger, healthier, menopausal women in the NHS, the Observational Arm of the WHI, as well as the younger group of the WHI ET/EPT trial group, with poorer results in the older HERS study population, support the hypothesis that "timing is every-

Figure 7: Effects of initiating estrogen treatment at the complicated plaque stage of atherosclerosis



Used with permission from Dr. Thomas B. Clarkson, Winston-Salem, NC.

thing!” and that, “reproductive stage is a major determinant of the effect of estrogens on atherosclerosis progression, complications, and plaque vulnerability.”

Using different estrogen/progesterone preparations and alternative regimens and delivery systems, the “timing is everything” hypothesis is currently being tested in two ongoing clinical trials, the Kronos Early Estrogen Protection Study (KEEPS) and the Early vs Late Intervention Trial with Estradiol (ELITE) trial.²² Results are expected in 2009.

The unifying hypothesis proposes that to enjoy the beneficial effects of estrogen on the CV system, therapy must be initiated in early menopause, when estrogen deficiency begins to appear. Treatment begun outside this “critical window,” rather than being beneficial, may have undesirable and, indeed, even harmful effects. Emerging early data suggest that the same “window of opportunity” may also exist for the beneficial effects of estrogen on the brain,²⁷ colon, bone and, possibly, the breast.

We should remain cautiously optimistic that future clinical trials will provide supportive evidence for this concept. More information is needed on the effect of lower doses, alternate routes of therapy, different regimens, and other progestins. For this we await the results of the KEEPS and ELITE studies. The ongoing observational arm of the WHI and the results from the NHS regarding the long-term use of ET/EPT will be helpful for those “hardy” women who continued their HT even after the results of HERS and both arms of the WHI were announced. With older women for whom we consider prescribing HT, we await further information about the benefits of treatment with a statin prior to their starting HT.

While it is clear that we need to exercise care and prudence as we move ahead and use HT in the clinical management of our patients, move ahead we must, lest the women we serve miss the chance to take advantage of the benefits of ET/EPT offered by initiating treatment during this critical window of opportunity. At the very least, we should not hesitate to prescribe HT for symptomatic women in early menopause, whose risks of treatment are minimal and the potential benefits large. Official opinion²⁸⁻³¹ is changing and new, more positive guidelines and position papers are emerging from various official bodies, including a “white paper” from the American Society of Reproductive Medicine, an updated statement from the North American Menopause Society, and new treatment guidelines from the International Menopause Society after their annual winter meeting. Updates from other organizations are also anticipated. Perimenopausal and recently menopausal women will be the beneficiaries.

Christine M. Derzko MD, FRCSC, is an Associate Professor in Obstetrics and Gynecology and Internal Medicine (Endocrinology) at St. Michael's Hospital, University of Toronto.

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