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Review

Hormone replacement therapy and the association with coronary heart disease and overall mortality: Clinical application of the timing hypothesis☆

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ABSTRACT

Conclusions from randomized controlled trial (RCT) data over the past 10 years has spanned from presumed harm to consistency with observational data that hormone replacement therapy (HRT) decreases the risk for coronary heart disease (CHD) as well as overall mortality in women who are recently postmenopausal. Multiple clinical studies including randomized trials and observational studies converge with animal experimentation to show a consistency that HRT decreases CHD risk and overall mortality in primary prevention when HRT is started at the time of or soon after menopause. The totality of data supports the "timing" hypothesis that posits that HRT effects are dependent on when HRT is started in relation to age and/or time-since-menopause. The totality of data shows that HRT decreases CHD and overall morality when started in women who are less than 60 years old and/or less than 10 years postmenopausal, providing a "window-of-opportunity". Further evidence shows that women who start HRT when in their 50s and continued for 5–30 years that there is an increase of 1.5 quality-adjusted life-years (QALYs). Additionally, HRT is highly cost-effective at $2438 per QALY gained. The totality of data converges to show a consistency between randomized trials and observational studies that when started in women at or near menopause and continued long-term, HRT decreases CHD and overall mortality compared with women who do not use HRT.

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1. Early randomized controlled trials

Over the past 5 decades, 40–50 postmenopausal observational studies have shown that hormone replacement therapy (HRT) is consistently associated with a 30–50% decrease in coronary heart disease (CHD) risk and total mortality [1–10]. Consistent data from postmenopausal observational studies resulted in development of the hypothesis of "estrogen cardioprotection" [11]. Most recently, the observational study from the Women's Health Initiative (WHI) showed that users of HRT had a 50% reduction in CHD relative to women who did not use HRT [7].

The first large randomized controlled trial (RCT) of HRT and CHD outcomes was the Heart and Estrogen–progestin Replacement Study (HERS) [12]. HERS included women with established CHD and when randomized women had a mean age of 66.7 years and were 18 years postmenopausal. Relative to placebo, daily continuous combined conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) had a null effect on CHD outcomes in HERS (hazard ratio (HR), 0.99; 95% confidence interval (CI), 0.80–1.22) [12]. Consistent with HERS were the results from the Estrogen Replacement and Atherosclerosis (ERA) trial that included women with a mean age of 65.8 years and who were 23 years postmenopausal when randomized as ERA showed that neither unopposed CEE nor CEE + MPA reduced coronary artery atherosclerosis progression [13]. On the other hand, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed that in healthy postmenopausal women without established cardiovascular disease that oral 17β-estradiol alone reduced progression of subclinical atherosclerosis relative to placebo [14]. Since women randomized to EPAT were younger (mean age 62.2 years) than the HERS and ERA cohorts, and the years postmenopausal at the time of randomization was 5–10 years earlier in EPAT, the divergence in outcomes between EPAT and observational studies versus HERS and ERA was hypothesized to be dependent upon timing of HRT initiation. In particular, the key to preventing CHD appears to be starting HRT at an early stage in the process of atherosclerosis progression at the start of menopause [14]. This hypothesis, further

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supported by EPAT's sister study, the Women's Estrogen–progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) (mean time postmenopausal 18.2 years) and animal studies later became known as the "timing" hypothesis for the reduction of CHD with HRT in postmenopausal women [15]. Over the last decade, a large quantity of data strongly supporting the "timing" hypothesis, including WHI data has accumulated [11].

2. Studies supporting the timing hypothesis

Cumulated data from HRT RCTs demonstrate two populations of postmenopausal women who differ in their response to HRT; that is, modification of response based on when HRT is started in relation to age and/or years postmenopausal [11]. Specifically, CHD events and overall mortality are decreased when HRT is started in women less than 60 years old and/or less than 10 years postmenopausal whereas, there is a null effect on these outcomes (and possible adverse effect) when HRT is started in women greater than 60 years old and/or greater than 20 years postmenopausal [11].

The differential effect of HRT on CHD events in relation to age and/or years postmenopausal is summarized by a meta-analysis that included 23 RCTs comprising 191,340 women-years [16]. When analyzed across the entire age range of these randomized trials, CHD events were unaffected by HRT (HR, 0.99; 95% CI, 0.88–1.11) as was the effect of HRT when started in women greater than 60 years old and/or greater than 10 years postmenopausal (HR, 1.03; 95% CI, 0.91–1.16). On the other hand, when started in women who were less than 60 years old and/or less than 10 years postmenopausal, CHD is decreased 32% with HRT compared to placebo (relative risk (RR), 0.68; 95% CI, 0.48–0.96) [16]. The magnitude of CHD reduction for women less than 60 years old and/or less than 10 years postmenopausal at the time of randomization to HRT is comparable to the women in observational studies who started HRT at menopause [1–10].

It should be noted that other factors may be important in explaining the differences between observational studies and randomized trials of the effects of HRT on CHD. One prominent factor is body mass index (BMI). In general, women who used HRT in observational studies were relatively thin (BMI approximately 25 kg/m^2), whereas women randomized to clinical trials were primarily overweight to obese (BMI approximately 29 kg/m^2). For example, average BMI in the Women's Health Initiative (WHI) trials was 28.5 kg/m^2 in the CEE + MPA (WHI-E + P) trial and 30.1 kg/m^2 in the CEE alone (WHI-E) trial. In addition, 34% of the women in the WHI-E + P trial and 45% of the women in the WHI-E trial were obese with BMI > 30 kg/m^2 [17,18]. In HERS, 56% of the women had a BMI >27 kg/m^2 [12].

The Cancer Prevention Study II, a 12-year observational study of 290,823 women who were free from cancer and cardiovascular disease at enrollment best demonstrates the effect of HRT on CHD according to BMI [19]. Among HRT users, all cause mortality was reduced relative to never-users (RR, 0.82; 95% CI, 0.78–0.87). Specifically, CHD death was lowest for women using HRT with BMI <22 kg/m^2 while there was no association between HRT use and CHD in women with BMI >30 kg/m^2, p-for-interaction = 0.02. For women who used HRT, CHD mortality was reduced 51% (RR, 0.49; 95% CI, 0.37–0.65) among those with BMI <22 kg/m^2, reduced 28% (RR, 0.72; 95% CI, 0.57–0.91) among women with BMI 22 kg/m^2 to <25 kg/m^2 and reduced 23% (RR, 0.77; 95% CI, 0.59–1.01) among women with BMI 25 kg/m^2 to <30 kg/m^2. On the other hand, CHD mortality was increased 45% (RR, 1.45; 95% CI, 1.00–2.11) among women who used HRT with BMI of >30 kg/m^2.

Assuming that the Cancer Prevention Study II results extend to both fatal and nonfatal myocardial events, the Cancer Prevention Study II results predict based on the average BMI of women randomized to clinical trials, no overall significant HT effect on CHD outcome relative to placebo (with the exception of the Danish Osteoporosis Study (DOPS) in which average BMI was 25.2 kg/m^2) [20]. Specifically, the Cancer Prevention Study II results predict no HRT effect on CHD in women with BMI >25 kg/m^2 and a potential increased CHD risk with HRT among women with BMI >30 kg/m^2 [19]. In contrast to the clinical trials, women enrolled in observational studies were much leaner (average BMI of approximately 25 kg/m^2) and those who used HRT had reductions in CHD risk [1–10]. In terms of BMI, women randomized to clinical trials were similar to HRT nonusers in observational studies [1–10]. The CHD outcome according to BMI from the WHI-E trial showed a similar pattern as to the results from the Cancer Prevention Study II as described above [21]. Women with BMI <25 kg/m^2, 25 kg/m^2 to <30 kg/m^2 and >30 kg/m^2 and randomized to CEE therapy relative to placebo in the WHI-E trial showed respectively, a 24% reduction, 13% reduction and 11% increase in CHD events [21].

As reviewed above, comparisons across the cumulative studies clearly show that the women randomized to clinical trials were very different across several parameters from the women studied in observational studies. As such, the hormone cardioprotective hypothesis has yet to be appropriately tested since the population of women studied in observational studies from which the hypothesis was derived has not been studied in randomized trials; the one exception is DOPS in which time from menopause when HT was initiated and BMI of the cohort were similar to women studied in observational studies [20].

3. WHI data supporting the timing hypothesis

In response to the growing accumulation of data supportive of the timing hypothesis, WHI post hoc analyses were conducted that are also supportive of the "timing" hypothesis by showing significant trends of an HRT effect on CHD relative to years postmenopausal when HRT is initiated [22].

Compared with placebo, there was a 52% (HR, 0.48; 95% CI, 0.20–1.17) reduced CHD risk in the women who were randomized to CEE and less than 10 years postmenopausal in the WHI-E trial [22]. On the other hand, compared with placebo there was no CHD benefit (HR, 0.96; 95% CI, 0.64–1.44) in the women who were randomized to CEE and 10–19 years postmenopausal or when randomized to CEE and more than 20 years postmenopausal (HR, 1.12; 95% CI, 0.86–1.46) [22]. Compared with placebo, there was a 12% (HR, 0.88; 95% CI, 0.54–1.43) reduced CHD risk in the women who were randomized to CEE + MPA and less than 10 years postmenopausal in the WHI-E + P trial [21]. On the other hand, compared with placebo there was a 23% (HR, 1.23; 95% CI, 0.85–1.77) elevated CHD risk in the women who were randomized to CEE + MPA and 10–19 years postmenopausal and a 66% (HR, 1.66; 95% CI, 1.14–2.41) increased risk in the women who were randomized to CEE + MPA and more than 20 years postmenopausal [22]. In both WHI trials combined, the women randomized to CEE and CEE + MPA and 10 years postmenopausal had a 24% (HR, 0.76; 95% CI, 0.50–1.16) reduced CHD risk compared with placebo [22]. On the other hand, compared with placebo there was no CHD benefit (HR, 1.10; 95% CI, 0.84–1.45) in the women who were randomized to CEE and to CEE + MPA and 10–19 years postmenopausal and a 28% (HR, 1.28; 95% CI, 1.03–1.58) increased risk in the women who were randomized to CEE and CEE + MPA and more than 20 years postmenopausal [22].

Women who were 50–59 years old when randomized to CEE showed significant 34–45% reductions in several categories comprising the CHD composite outcomes of CHD death, myocardial infarction (MI), confirmed angina pectoris and coronary artery revascularization compared with placebo [21]. The 11-year WHI