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THE WINDOW OF OPPORTUNITY FOR CORONARY HEART DISEASE PREVENTION WITH HORMONE THERAPY: PAST, PRESENT AND FUTURE IN PERSPECTIVE

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Abstract

Over the past decade two informative events in primary prevention of coronary heart disease (CHD) have occurred for women's health. The first concerns hormone therapy (HT) where data have come full circle from presumed harm to consistency with observational data that HT initiation in close proximity to menopause significantly reduces CHD and overall mortality. The other concerns sex-specific efficacy of CHD primary prevention therapies where lipid-lowering and aspirin therapy have not been conclusively shown to significantly reduce CHD and more importantly where there is lack of evidence that either therapy reduces overall mortality in women. Cumulated data supports a "window-of-opportunity" for maximal reduction of CHD and overall mortality and minimization of risks with HT initiation before 60 years of age and/or within 10 years of menopause and continued for 6 years or more. There is a substantial increase in quality-adjusted life-years over a 5–30 year period in women who initiate HT in close proximity to menopause supporting HT as a highly cost-effective strategy for improving quality-adjusted life. Although primary prevention therapies and HT contrast in their efficacy to significantly reduce

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CHD and especially overall mortality in postmenopausal women, the magnitude and types of risks associated with HT are similar to those associated with other medications commonly used in women's health. The cumulated data highlight the importance of studying the HT cardioprotective hypothesis in women representative of those from whom the hypothesis was generated.

Keywords

Hormone Therapy; Estrogen; Menopause; Women; Coronary Heart Disease; Randomized Controlled Trials; Mortality; Meta-Analysis

INTRODUCTION

In the public health arena, there are very few potential therapies with such consistent data for reducing CHD and overall mortality as postmenopausal hormone therapy (HT). The Women's Health Initiative (WHI) data over the past 10 years has spanned from presumed harm to consistency with observational data that postmenopausal HT reduces coronary heart disease (CHD) and more importantly overall mortality in recently menopausal women. Simultaneously, randomized controlled trials (RCTs) have failed to conclusively prove that lipid-lowering and aspirin therapy statistically significantly reduce CHD and overall mortality in women under primary prevention conditions. On the other hand, RCTs, observational studies and meta-analyses consistently support primary prevention of CHD and reduction of overall mortality in women who initiate HT in close proximity to menopause. Totality of data indicates that the "window-of-opportunity" for reducing CHD and overall mortality is initiation of HT before 60 years of age and/or within 10 years of menopause. HT use for 5–30 years in postmenopausal women who initiate HT in their 50s substantially increases quality-adjusted life-years (QALYs) by 1.5 QALYs and is highly cost-effective at $2,438 per QALY gained. Cumulated RCT results show a consistency with observational data that young postmenopausal women who use HT for long periods of time have lower rates of CHD and overall mortality than comparable postmenopausal women who do not use HT. The WHI has contributed to this knowledge base. Herein, we provide a historical perspective of the reporting of WHI results along with other studies and show the consistency of these data with observational data that show that CHD and overall mortality is reduced in young women who initiate HT in close proximity to menopause.

PRE-WHI

Over the past 5 decades, approximately 40 observational studies (including the WHI observational study) consistently show that HT is associated with a 30–50% reduction in CHD and overall mortality in postmenopausal women[1–10]. Results of the Heart and Estrogen-progestin Replacement Study (HERS), the first large RCT of HT and CHD (conducted in women with pre-existing CHD) were null for conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) taken daily versus placebo (hazard ratio (HR), 0.99; 95% confidence interval (CI), 0.80–1.22)[11]. Consistent with HERS were the Estrogen Replacement and Atherosclerosis (ERA) trial results that showed neither unopposed CEE nor CEE+MPA reduced coronary artery atherosclerosis progression[12]. On the other hand, the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) showed a reduction in subclinical atherosclerosis progression in healthy postmenopausal women who were randomized to unopposed oral estradiol versus placebo[13]. Since women randomized to EPAT were younger than those randomized to HERS and ERA, and the time from menopause to randomization was 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 HT initiation; particularly when initiated early in the intervention

of atherosclerosis progression at the start of menopause as the key to preventing CHD with HT[13]. This hypothesis, further supported by EPAT's sister study, the Women's Estrogen-progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) and animal studies later became known as the "timing hypothesis" or the "window-of-opportunity" for the reduction of CHD with HT in postmenopausal women[14]. Over the past 10 years a large accumulation of data strongly support the timing hypothesis, including WHI data[15].

WHI DATA

WHI CHD data (including its interpretation) has changed no less than 3 times over the course of the past 10 years[16]. In July 2002, WHI investigators claimed[17] "the adverse effects of estrogen plus progestin applied to all women irrespective of age, ethnicity, or prior disease state". In 2007, WHI investigators reported[18] "women who initiated therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause". In the first WHI publication (July 2002), a significantly increased CHD risk was reported for CEE+MPA with the nominal statistic (HR, 1.29; 95% CI, 1.02–1.63) but not with the adjusted statistic (HR, 1.29; 95% CI, 0.85–1.97) that accounted for the multiple testing across time and across outcome categories that were conducted in this trial[19]. The authors reported "no noteworthy interaction with age for the effect of CEE+MPA on CHD." These initial results were published before all outcome data were collected and before final adjudication of the CHD outcome. In August 2003, the "final [adjudicated] results" of the WHI CEE+MPA trial were published; the HR decreased and the nominal CI now included 1.0 (HR, 1.24; 95% CI, 1.00–1.54) and after a significant increase in CHD events in the overall cohort within the first year of randomization (unknown whether this was related to age or pre-existing CVD), a trend for decreasing CHD risk with HT duration was statistically significant[20]. Although the data showed an 11% reduction in CHD risk among women randomized within 10 years of menopause and a trend toward increasing risk with greater time from menopause when randomized, the categorical interaction between treatment and years-since-menopause on CHD was not statistically significant[20]. However, in a re-analysis of the data using a p-for-trend analysis, a statistically significant trend of an HT effect on CHD according to time-since-menopause was subsequently reported[21]. In April 2004, WHI CEE trial results showed a non-significant CHD reduction among women who received CEE relative to placebo (HR, 0.91; 95% CI, 0.75–1.12) and a 44% CHD reduction (HR, 0.56; 95% CI, 0.30–1.03) in women who were 50–59 years of age when randomized[22]. These results were published before collection of all outcome data and before final adjudication of the CHD outcome; the "final [adjudicated] results" of the WHI CEE trial were published in February 2006[23]. Among women aged 50–59 years when randomized, several categories of CHD composite outcomes of nonfatal myocardial infarction (MI), coronary death, confirmed angina and coronary artery revascularization were significantly reduced 34–45% in the CEE-treated group relative to placebo[23].

Addressing accumulating data supportive of the timing hypothesis from both within WHI as well as from independent research (see below), WHI data supportive of the timing hypothesis were published in April 2007[18]. The HRs and CIs for CHD in this publication were different from the "final" results reported previously for CEE (HR, 0.95; 95% CI, 0.78–1.16) and for CEE+MPA (HR, 1.23; 95% CI, 0.99–1.53) especially for the latter in which the CEE+MPA effect on CHD over all ages was clearly nonsignificant. Significant trends of an HT effect on CHD according to years-since-menopause was reported; women randomized to HT within 10 years of menopause showed a nonsignificant decreased risk relative to placebo (Table 1).

Similar to CHD trends, overall mortality was reduced 30% with both CEE+MPA and CEE relative to placebo among women who were aged 50–59 years when randomized[18] (Table 2). With both WHI trials combined (effectively increasing the total sample size), overall mortality was statistically significantly reduced 30% in those women aged 50–59 years when randomized to HT relative to placebo (Table 2).

The 11-year WHI CEE trial follow-up (7 years of randomized treatment and 4 years of post-intervention follow-up) showed that women aged 50–59 years when randomized to CEE versus placebo had statistically significant reductions in CHD (HR, 0.59; 95% CI, 0.38–0.90), total MI (HR, 0.54; 95% CI, 0.34–0.86) and overall mortality (HR, 0.73; 95% CI, 0.53–1.00); compared with women aged 60–69 and 70–79 years the p-for-interaction was statistically significant for each outcome, p=0.05, p=0.007 and p=0.04, respectively[24]. Importantly, invasive breast cancer was statistically significantly reduced 23% (HR, 0.77; 95% CI, 0.62–0.95) in women who received CEE relative to placebo regardless of age at randomization[24].

Although only one-third of the women randomized to the WHI trials were younger than 60 years of age and less than 5% were within a few years of menopause, the subgroup of women randomized to these trials who are more representative of women using HT in observational studies had reduced CHD and overall mortality with HT. On the other hand, women older than 60 years of age who were randomized to HT many years beyond menopause (>10 years) who are not representative of women in HT observational studies showed no reduction in CHD or overall mortality with HT[15].

STUDIES SUPPORTING THE TIMING HYPOTHESIS

Although the HT effect on CHD over all ages is null in RCTs, these trials indicate that there are distinct populations of women who are HT responsive. Specifically, beneficial HT effects on CHD and overall mortality occurs when HT is initiated in younger women in close proximity to menopause and a null effect and possible adverse effect (in women >20 years-since-menopause) when initiated in older women remote from menopause[15]. The beneficial HT effect on CHD according to timing of HT initiation has been shown in a large meta-analysis of 23 RCTs (191,340 patient-years of follow-up)[25]. Over all ages, the HT effect on CHD was null whereas a statistically significant 32% reduction in CHD was found for women younger than 60 years of age or within 10 years-since-menopause when randomized to HT relative to placebo (Table 1). Magnitude of CHD reduction for women younger than 60 years of age or within 10 years-since-menopause when randomized to HT was similar to observational studies[1–10]. This large meta-analysis of cumulated RCTs of HT clearly demonstrates two distinct populations of women who respond differently to HT according to timing of HT initiation relative to age and/or time-since-menopause. Another line of evidence that HT initiation in young postmenopausal women in close proximity to menopause may reduce CHD derives from 1,064 women who participated in the WHI Coronary Artery Calcium Study in which 50–59 year old women who were randomized to CEE had significantly less coronary artery calcium at year 7 of the trial compared with those women randomized to placebo[26].

Most recently, the cardiovascular outcome from the Danish Osteoporosis Prevention Study (DOPS) was presented (by LLS) at the American Heart Association Scientific Meeting 2011. These results included >1,000 postmenopausal women who were on average 50 years old and on average 7 months postmenopausal when randomized for 11 years to oral 17β-estradiol daily plus sequential norethisterone acetate 10 days each month or to control in an open-label parallel design. Hysterectomized women received oral 17β-estradiol daily. The overall cardiovascular results of this study are remarkably similar to the 11-year WHI CEE

trial follow-up data of the women who were 50–59 years of age when randomized to WHI CEE[24] and to the HT meta-analyses of RCTs and CHD[25] and mortality[27] outcomes in women <60 years old or <10 years-since-menopause when randomized. No significant difference in breast cancer, stroke or venous thromboembolism (VTE) was found between treatment groups.

OTHER ESTROGEN RECEPTOR-BINDING AGENTS THAT SUPPORT THE TIMING HYPOTHESIS

Broadening support for the timing hypothesis are accumulating data that show products other than mammalian hormones that bind to the estrogen receptor exert similar CHD beneficial effects as HT in young postmenopausal women. In the Raloxifene Use for the Heart (RUTH) trial (10,101 postmenopausal women), raloxifene, a selective estrogen receptor modulator had no effect on CHD incidence over all ages after a median treatment of 5.6 years. However, among women younger than 60 years of age when randomized to raloxifene, CHD was statistically significantly reduced 41% relative to placebo[28] (Table 1), a finding similar to WHI in which CHD was reduced 52% in women who were <10 years-since-menopause when randomized to CEE relative to placebo[18] (Table 1).

Although an age or time-since-menopause analysis is not presented, randomized treatment for 5 years of lasofoxifene 0.5 mg daily versus placebo in a cohort of 8,556 women between the ages of 59 and 80 years, statistically significantly reduced: CHD by 32% (HR, 0.68; 95% CI, 0.50–0.93), stroke by 36% (HR, 0.64; 95% CI, 0.41–0.99); vertebral fractures by 42% (HR, 0.58; 95% CI, 0.47–0.70), nonvertebral fractures by 24% (HR, 0.76; 95% CI, 0.64–0.91), ER-positive breast cancer by 81% (HR, 0.19; 95% CI, 0.07–0.56) and invasive breast cancer by 85% (HR, 0.15; 95% CI, 0.04–0.50); VTE was statistically significantly increased two-fold (HR, 2.06; 95% CI, 1.17–3.61) indicating 15 additional VTE events per 10,000 women per year of lasofoxifene therapy[29].

In the Women's Isoflavone Soy Health (WISH) study, a RCT examining the effects of high-dose isoflavone soy protein supplementation on the progression of subclinical atherosclerosis, women who were randomized within 5 years of menopause to isoflavone soy protein supplementation had a significant reduction in progression of subclinical atherosclerosis relative to placebo whereas women more than 5 years beyond menopause when randomized had no significant effect[30]. Isoflavones are plant estrogens that preferentially bind to estrogen receptor-beta.

OVERALL MORTALITY AND BENEFIT-RISK OF HT

The beneficial HT effect on overall mortality according to age has also been demonstrated in a large meta-analysis of 30 RCTs (119,118 patient-years)[27]. Over all ages, the HT effect on overall mortality was null whereas a statistically significant 39% reduction in overall mortality was found for subjects younger than 60 years of age (mean age 54 years) when randomized to HT relative to placebo (Table 2); a reduction similar to observational studies[1–10]. Age at HT initiation among women in observational studies and age of younger women randomized to RCT's examined in the meta-analysis is similar. On the other hand, in this meta-analysis the HT effect on overall mortality in women who were older than 60 years of age (mean age 66 years) when randomized was null as reported over all ages in RCTs.

To address benefit-risk of HT, a Bayesian meta-analysis was conducted using RCTs and observational studies to evaluate the HT effect on overall mortality in young postmenopausal women who initiated HT in close proximity to menopause[31]. Results from

this meta-analysis using 19 RCTs with 16,283 women (mean age 54.5 years) followed for 83,043 patient-years over 5.1 years (range, 1–6.8 years) showed an overall mortality reduction of 27% (RR, 0.73; 95% credible interval (CrI), 0.52–0.96) among women randomized to HT relative to placebo. The 95% CrI used in the Bayesian analysis is comparable to the 95% CI used in traditional meta-analyses. Using pooled data from 8 prospective observational studies in which a total of 212,717 women were followed for 2,935,495 patient-years over a mean of 13.8 years (range, 6–22 years), overall mortality was reduced 22% (RR, 0.78; 95% CrI, 0.69–0.90) in HT users relative to non-users. Overall mortality was reduced 28% (RR, 0.72; 95% CrI, 0.62–0.82) with the RCT and prospective observational data combined. Results from this study indicate a convergence of evidence from several sources that support a beneficial HT effect on overall mortality in women who initiate HT in close proximity to menopause. Further, results from this meta-analysis indicate that RCTs and observational studies are similar, each with an overall mortality reduction of approximately 25%, results similar to the 30% reduction in overall mortality shown in postmenopausal women who were younger than 60 years of age when randomized to HT in the WHI trials (Table 2).

HT COST EFFECTIVELY EXTENDS LIFE WHEN INITIATED AT YOUNGER AGE

A cost-effectiveness analysis indicates that compared with no therapy, HT given to postmenopausal women in their 50s for 5–30 years results in a substantial increase of 1.5 QALYs at a cost of $2,438 per QALY gained[32]. Net gains gradually increase with treatment durations of 5–30 years and results for younger women are robust to all sensitivity analyses with HT remaining highly cost effective (defined as <$10,000 per QALY gained). At $2,438 per QALY gained, these data indicate that HT is a highly cost-effective strategy for improving quality-adjusted life. The substantial increase in QALYs in younger women is due to a net benefit in quality of life and reduced overall mortality compared with no therapy. On the other hand, for 65-year old postmenopausal women initiating HT there is a smaller net gain of 0.11 QALYs at a cost of $27,953 per QALY gained[32].

In sum, the totality of RCT data indicate that young postmenopausal women who initiate HT in close proximity to menopause have a reduced incidence of CHD and overall mortality[15]. These results parallel the consistent reduction in CHD and overall mortality in observational studies where the majority of women initiated HT within 6 years of menopause[1–10]. Focused in young healthy postmenopausal women (average age 50 years) randomized early after menopause (average of 7 months), DOPS provides strong evidence for the long-term efficacy and safety of HT for reducing CHD and overall mortality when initiated in young postmenopausal women in close proximity to menopause. Additionally, the timing hypothesis appears to extend to other agents that bind to the estrogen receptor.

CLINICAL PERSPECTIVE OF HT RELATIVE TO OTHER PRIMARY PREVENTIVE THERAPIES

A detailed discussion of current primary prevention therapies for women is beyond the scope of this review. However, it is important to appreciate that meta-analyses of cumulated RCT data show a sex-specific efficacy for the major therapies used for CHD primary prevention. Relative to placebo, lipid-lowering[33–35] and aspirin[36,37] therapy have a null effect on CHD primary prevention in women including aspirin use in women with diabetes mellitus[38]. There is no evidence that either therapy reduces overall mortality in women[33–37].

Although the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is the only primary prevention trial to show a possible

reduction in CHD in women, this result deserves special attention since it is unclear whether this finding resulted from the unique characteristics of the cohort (women ≥60 years of age with LDL-C <130 mg/dL and hsCRP ≥2 mg/dL)[39], the controversial aspects of trial conduct[40,41] or from the subjective nature of certain components of the primary end point[39]. The primary cardiovascular end point of JUPITER was a composite end point comprised of "hard end points" (nonfatal MI; any MI; nonfatal stroke; any stroke; MI, stroke, or confirmed death resulting from cardiovascular causes) and "soft end points" whose occurrence rely on medical decisions (arterial revascularization; arterial revascularization or hospitalization for unstable angina). In men, all of the "hard" and "soft" components of the composite primary end point were statistically significantly reduced in the rosuvastatin arm versus placebo arm[39]. In women, only the "soft" end points were statistically significantly reduced in the rosuvastatin arm versus placebo arm. These "soft" composite end points (revascularizations and hospitalizations) clearly drove the primary end point to statistical significance in the women since all of the "hard" end points in the women were firmly nonsignificantly different (p>0.1) between the rosuvastatin arm and placebo arm[39]. Overall mortality was not statistically different between the rosuvastatin arm versus the placebo arm in women (p=0.12) or in men (p=0.08)[39]. Including JUPITER in a meta-analysis with other primary prevention trials does not alter the conclusion that statin therapy has a null effect on CHD and overall mortality in primary prevention in women[35].

Aspirin therapy is interesting in that in men, aspirin statistically significantly reduces MI by 32% with a null effect on stroke whereas in women, aspirin has a null effect on MI but statistically significantly reduces ischemic stroke by 17%[37]. With aspirin therapy there is a nonsignificant increase in odds of hemorrhagic stroke in women (Odds Ratio (OR), 1.07; 95% CI, 0.42–2.69) and a significant 69% increase in the odds of hemorrhagic stroke in men (OR, 1.69; 95% CI, 1.04–2.73)[37]. Although the Women's Health Study showed a null effect of aspirin therapy versus placebo with the a-priori defined statistical analysis of the primary cardiovascular end point amongst all women (≥45 years of age) randomized to this trial, a statistically significant reduction in the subgroup of women ≥65 years of age was found amongst multiple subgroup comparisons that requires cautious interpretation[36].

Recommendations for lipid-lowering and aspirin therapy for CHD primary prevention in women are extrapolated from data derived from men and secondary prevention trials in women[42,43]. In contrast to the lack of demonstrated efficacy of lipid-lowering and aspirin therapy on CHD and mortality in primary prevention for women, cumulated data across more than two dozen RCTs (including the recently completed DOPS) demonstrate a significant reduction in CHD and overall mortality in women who initiate HT before 60 years of age and/or within 10 years of menopause[25,27,31,32] (Tables 1 and 2).

WEIGHING THE RISKS OF HT RELATIVE TO OTHER MEDICATIONS

Although the benefits and risks of postmenopausal HT are known, over the past decade their magnitude and perspective to other therapies have become more fully defined. Review of RCTs indicates that the risks of postmenopausal HT including breast cancer, stroke and VTE are similar to other agents commonly used in women's health. The majority of these risks are rare (<1 event per 1,000 treated women) and even rarer when HT is initiated in women less than 60 years of age and/or within 10 years of menopause. These data have been extensively reviewed previously[15,16,44–47] and are only summarized here.

Breast Cancer

In the WHI CEE+MPA trial, breast cancer risk was originally reported to "almost reach nominal statistical significance" in the CEE+MPA arm versus the placebo arm (HR, 1.26; 95% CI, 1.00–1.59) and was clearly nonsignificant with adjustment for multiple testing

across time and across outcome categories (HR, 1.26; 95% CI, 0.83–1.92)[19]. This 26% increased risk accounted for 8 additional breast cancer cases per 10,000 women treated with CEE+MPA per year, a rare event (<1 event per 1,000 treated women). A subsequent analysis in the same cohort of subjects that adjusted for baseline risk factors for breast cancer (i.e., age, body mass index, alcohol intake, physical activity, parity, family history, etc.) resulted in a slightly reduced relative risk with a nominal nonsignificant statistical difference in breast cancer risk in the CEE+MPA arm relative to the placebo arm (HR, 1.20; 95% CI, 0.94–1.53)[48]. Additionally, there was no increased risk of breast cancer over an average 5.6 years amongst those women who were randomized to CEE+MPA therapy and previously never used HT that is, for those women who were HT naive (HR, 1.02; 95% CI, 0.77–1.36) [48]. In the 3-year open-label follow-up in which women were no longer on their randomized regimens (CEE+MPA versus placebo), the HR over time from the randomized phase to the open-label phase was unchanged[49].

In contrast, the initial results for the WHI CEE trial showed a nonsignificant trend toward a reduction in breast cancer (HR, 0.77; 95% CI, 0.59–1.01) in the CEE arm relative to the placebo arm, indicating 8 fewer breast cancer cases per 10,000 women treated with CEE per year[22]. Ductal carcinoma was statistically significantly reduced 29% in the CEE arm versus placebo arm (HR, 0.71; 95% CI, 0.52–0.99) in the WHI CEE trial[50]. Regardless of age at randomization, women in the WHI CEE trial had a reduction in breast cancer with CEE therapy, including those in the highest age group (70–79 years old) with the greatest expected risk of breast cancer[50]. In a compliance analysis among women who were actually adherent to their study regimen consuming ≥80% of their study medication, there was a statistically significant 33% reduction in breast cancer with CEE therapy relative to placebo (HR, 0.67; 95% CI, 0.47–0.97) after a mean randomized follow-up of 7.1 years[50]. The decreasing trend in breast cancer was confirmed in the WHI CEE follow-up study of 11 years; over the entire follow-up period the lower incidence of breast cancer amongst the CEE treated group persisted and was statistically significantly 23% lower relative to the placebo group (HR, 0.77; 95% CI, 0.62–0.95)[24]. Although the CI is wide, data from the Women's Estrogen for Stroke Trial (WEST) showed that 17β-estradiol had a null effect on breast cancer risk relative to placebo (HR, 1.00; 95% CI, 0.30–3.50)[51]. DOPS confirms these results as HT did not increase the risk of breast cancer after 11 years of randomized follow-up.

Stroke

Although WEST has been the only randomized controlled trial of HT designed with stroke as the primary trial outcome[51], HERS and WHI have also provided information concerning HT and stroke as an additional secondary trial outcome. In WEST, including 664 postmenopausal women who were on average 71 years old and approximately 20 years postmenopausal at randomization, 17β-estradiol 1 mg daily had a null effect on the combined outcome of nonfatal stroke or all-cause mortality (RR, 1.1; 95% CI, 0.8–1.4) relative to placebo[51]. Although the women had a documented non-disabling stroke or transient ischemic attack within 90 days of randomization into the trial, the effect of HT on nonfatal and fatal stroke and both strokes combined was nonsignificant in this trial of secondary prevention of stroke in women at high risk for recurrent stroke. HERS showed that continuous combined CEE+MPA had a null effect on the primary prevention of nonfatal and fatal stroke in postmenopausal women with established CHD[52]. In the WHI CEE+MPA trial, there was nominal statistical significance of 8 additional strokes per 10,000 women treated with CEE+MPA per year in the CEE+MPA arm versus the placebo arm (HR, 1.31; 95% CI, 1.03–1.68)[18], but this difference was nonsignificant in the a-priori defined outcome adjusting for multiple testing across time and across outcome categories (HR, 1.31; 95% CI, 0.93–1.84)[53]. In the WHI CEE trial, there was nominal statistical significance of 11

additional strokes per 10,000 women treated with CEE per year in the CEE arm versus the placebo arm (HR, 1.33; 95% CI, 1.05–1.68)[18], but this difference was nonsignificant in the a-priori defined outcome adjusting for multiple testing across time and across outcome categories (HR, 1.39; 95% CI, 0.97–1.99)[22]. Importantly, the risk of stroke is statistically nonsignificant and rare in women who initiate HT when <60 years of age. WHI showed that there are 5 additional strokes per 10,000 women per year of CEE+MPA therapy when initiated in women <60 years of age and even lower for CEE therapy, 2 fewer strokes per 10,000 women per year of CEE therapy[18]. DOPS results are consistent with these findings as HT did not increase the risk of stroke after 11 years of randomized follow-up.

Venous Thromboembolism

Although CEE+MPA therapy was associated with a doubling of VTE risk compared with placebo in the WHI CEE+MPA trial, the increase in absolute risk was small, 18 additional VTE events per 10,000 women treated with CEE+MPA per year[19]. This risk of VTE was statistically significant with both the nominal statistic and with adjustment for multiple testing across time and across outcome categories[19,54]. The absolute risk of VTE was lowest for women <60 years old when randomized. The additional absolute risk for VTE events per 10,000 women treated with CEE+MPA per year was 11 events for women 50–59 years old at randomization, 16 events for women 60–69 years old at randomization, and 35 events for women 70–79 years old at randomization[54]. Although there were 7 additional VTE events per 10,000 women treated with CEE per year in the WHI CEE trial, the risk of VTE was not statistically significant with either the nominal statistic (HR, 1.33; 95% CI, 0.99–1.79) or with adjustment for multiple testing across time and across outcome categories (HR, 1.33; 95% CI, 0.86–2.08)[22,55]. The additional absolute risk for VTE events per 10,000 women treated with CEE per year was 5 events for women 50–59 years old at randomization, 6 events for women 60–69 years old at randomization, and 12 events for women 70–79 years old at randomization[55]. In WEST, there was a 20% nonsignificant decrease in VTE events (HR, 0.80; 95% CI, 0.20–3.40) accounting for 12 fewer VTE events per 10,000 women treated with 17β-estradiol per year[51]. Over 11 years of randomized follow-up VTE events were not different between treatment groups in DOPS.

Comparing HT risks with risks of other medications

Although recommended primary prevention therapies and HT contrast in their efficacy to reduce CHD and overall mortality in women, the magnitude and types of risk associated with HT are similar to those associated with other common therapies used in women's health such as lipid-lowering including statins and fibrates, aspirin, oral antidiabetic medications, bisphosphonates, calcium supplements and vitamin supplements (Table 3).

In RCTs of statins published to date, the risk of breast cancer in the women randomized to a statin relative to placebo ranges from a reduction of 25% to a 12-fold increase indicating an absolute risk of 10 fewer to 77 additional breast cancer cases per 10,000 women per year of statin therapy[44–47]. In three meta-analyses of statins and cancer risk[56–58], statin therapy was associated with a nonsignificant increase in breast cancer risk relative to placebo (HRs ranging from 1.04 to 1.33), accounting for 2 to 7 additional breast cancer cases per 10,000 women per year of statin therapy. These data suggest similar magnitudes of risk for breast cancer diagnosis for continuous combined CEE+MPA and statin therapy[44–47]. On the other hand, the 23–33% reduced breast cancer risk indicating 8 fewer breast cancer cases per 10,000 women treated with CEE per year contrasts with the 4–33% increased risk of 2 to 7 additional breast cancer cases per 10,000 women per year of statin therapy[44–47].

Other medications used in women's health are associated with the same magnitude of risk for stroke and VTE and also exhibit other types of risk equal to or greater than those of HT

seen over all ages (Table 3). One risk of particular importance is mortality which is decreased with HT while it is increased with certain medications commonly used in women's health (Table 3). Certain risks appear to be greater in women than men, such as the association of bone fracture risk with thiazolidinedione use and new onset diabetes mellitus with statin use (Table 3). Although aspirin significantly reduces ischemic stroke by 24% in women without pre-existing CVD, the risk of hemorrhagic stroke is nonsignificantly increased by 24% with aspirin vs. placebo[36]. In addition, bleeding diatheses are significantly increased with aspirin use. Any gastrointestinal bleeding is statistically significantly increased 22% with aspirin versus placebo, and gastrointestinal bleeding requiring blood transfusion is statistically significantly increased 40% with aspirin versus placebo (Table 3). RCTs have also shown increased hemorrhagic stroke with statins vs. placebo in secondary prevention (Table 3).

Another important consideration for the use of primary prevention therapy for CHD is the risk of new onset diabetes mellitus. Analysis of both WHI and HERS indicates that CEE +MPA therapy significantly reduces the incidence of diabetes mellitus. In WHI, CEE+MPA statistically significantly reduced new onset diabetes mellitus by 21% (HR, 0.79; 95% CI, 0.67–0.93) relative to placebo, accounting for 15 fewer cases of new onset diabetes mellitus per 10,000 women treated with CEE+MPA per year[59]. In HERS, CEE+MPA statistically significantly reduced new onset diabetes mellitus by 35% (HR, 0.65; 95% CI, 0.48–0.89) relative to placebo, accounting for 81 fewer cases of new onset diabetes mellitus per 10,000 women treated with CEE+MPA per year[60]. In WHI, CEE alone reduced new onset diabetes mellitus by 12% (HR, 0.88; 95% CI, 0.77–1.01) relative to placebo, accounting for 14 fewer cases of new onset diabetes mellitus per 10,000 women treated with CEE per year[61]. In contrast, statin therapy is associated with an increased risk of new onset diabetes mellitus[39,62,63]. In a meta-analysis of 13 RCTs with 91,140 participants, statin therapy was associated with a statistically significant 9% increased risk of incident diabetes mellitus (HR, 1.09; 95% CI, 1.02–1.17) accounting for 10 additional cases of new onset diabetes mellitus per 10,000 individuals treated with statin therapy per year[62]. Female sex is significantly associated with an increased risk of statin-induced new onset diabetes mellitus[63] and in JUPITER new onset diabetes mellitus was statistically significantly increased 49% in women in the rosuvastatin arm versus placebo arm (HR, 1.49; 95% CI, 1.11–2.01) while nonsignificantly increased 14% in men (HR, 1.14; 95% CI, 0.91–1.43)[39]. In women, the JUPITER results indicate 50 additional incident diabetes mellitus cases per 10,000 women treated with rosuvastatin per year while in men it indicates 16 additional incident diabetes mellitus cases per 10,000 men treated with rosuvastatin per year[39]. Higher versus lower dosages of statin therapy also is associated with increased risk for new onset diabetes mellitus. In a meta-analysis of 5 RCTs with 32,752 participants, intensive-dose statin therapy versus moderate-dose statin therapy was associated with a statistically significant 12% increased risk of incident diabetes mellitus (HR, 1.12; 95% CI, 1.04–1.22) accounting for 20 additional cases of new onset diabetes mellitus per 10,000 individuals treated with intensive-dose statin therapy per year[64]. These findings are especially important in the absence of convincing evidence that statins significantly reduce CHD or overall mortality when used for primary prevention in women.

In summary, all medications present benefits and risks that can only be placed into perspective when viewed in relation to other commonly used medications. HT benefits and risks vary by dosage, regimen and timing of initiation. As such, broad sweeping conclusions concerning HT risks are not possible and attempts to generalize risk as comparable to continuous combined CEE+MPA results in misleading and inaccurate information concerning HT. Regardless, a few overall consistencies concerning HT risks are apparent, even when considering continuous combined CEE+MPA as the "worse case scenario" for risk: 1) HT risks are predominantly rare and even rarer when initiated in women before 60

years of age and/or within 10 years of menopause (<1 event per 1,000 treated women); 2) overall benefit-risk of HT favors reduced overall mortality (see previous sections, Overall Mortality…and, HT Cost Effectively…); and, 3) HT risks are of similar type and magnitude as other medications commonly used in women's health and for the primary prevention of CHD in women. Placing medications into clinical perspective is perhaps the most common approach to understanding overall utility and reasonable acceptance of benefits and risks.

TEST OF THE ESTROGEN CARDIOPROTECTIVE TIMING HYPOTHESIS

In the wake of early trial results showing discordance between RCTs and observational studies, the Early versus Late Intervention Trial with Estradiol (ELITE; clinicaltrials.gov NCT00114517) was funded by the National Institutes of Health; enrollment initiated in 2004. Designed to specifically test the timing hypothesis, 643 postmenopausal women have been randomized to a 2×2, double-blind, placebo-controlled, single-center trial according to time-since-menopause. Women without pre-existing clinical cardiovascular disease <6 years- and >10 years-since-menopause were randomized to oral estradiol (1 mg/d) or placebo (with vaginal progesterone gel or placebo for 10 days each month) in each stratum. The primary trial end point is CIMT progression measured every 6 months. The secondary trial end point is rate of cognitive decline. Based on the wealth of evidence that accumulated since 2003 in support of the initial ELITE proposal to the NIH of the timing hypothesis[13–15,44–47], a 3-year extension of the trial was awarded. The three specific aims of the ELITE extension include: 1) increased randomized treatment for an average of 5 years; 2) addition of a secondary vascular end point using non-contrast and contrast cardiac computed tomography to non-invasively measure coronary artery calcium and coronary artery lesions; and, 3) addition of a third cognitive assessment to extend measurement of cognitive decline over an average of 5 years. Primary trial results from ELITE are expected in 2013. In the Kronos Early Estrogen Prevention Study (KEEPS; clinicaltrials.gov NCT00154180), 720 women within 6–36 months of menopause were randomized across 9 sites to oral CEE 0.45 mg/d, transdermal estradiol 50 ug/d or to placebo with oral micronized progesterone 200 mg/d or placebo for 12 days each month. The primary trial end point is progression of CIMT measured every year by the same methodology and technology as used in ELITE. Although women were screened for coronary artery calcium at baseline and excluded if their Agatston score was >50 U, repeat coronary artery calcium measurements will be determined at end of study and progression and incident coronary artery calcium determined as a secondary end point. Cognition will also be assessed in KEEPS. Primary trial results from KEEPS are expected in 2012.

CONCLUSION

Ten years after WHI the data have come full circle and we are left with the task of more appropriately studying the estrogen cardioprotective hypothesis in a cohort of women from whom the hypothesis was derived namely, young postmenopausal women in close proximity to menopause. The totality of data shows that the postmenopausal HT effect on CHD and overall mortality is modified by duration of therapy and by age and/or time-since-menopause when initiated. HT appears to exert its greatest benefit when initiated in women before 60 years of age and/or within 10 years of menopause. It is this latter group of women who are in most need for symptomatic relief from menopausal symptoms such as flushing for which estrogen remains the most effective therapy[65]. RCTs are supported by approximately 40 observational studies that also indicate that HT initiation early in the postmenopausal period and continued for a prolonged period of time results in a significant reduction of CHD and overall mortality. Initiation of HT before tissue damage due to aging becomes too extensive appears to be key for successful amelioration of further damage. Comparison of RCT and observational data indicates that selection bias does not explain the

consistent evidence that HT is associated with a duration- and time-dependent lowering of CHD and overall mortality; DOPS results directly confirm this evidence. Analyses of the subgroups of women within RCTs that resemble women from observational studies indicate a consistency between the two study designs with similar HT benefit on the reduction of CHD and overall mortality. The “window-of-opportunity” for maximal expression of HT beneficial effects on CHD and overall mortality while minimizing the risks appears to occur with HT initiation before 60 years of age and/or within 10 years of menopause and continued for 6 years or more[15]. HT risks, especially in this subgroup of women appear comparable to medications commonly used in women’s health. Due to reduced overall mortality there is a substantial increase in QALYs in younger postmenopausal women who initiate HT in close proximity to menopause supporting HT as a highly-cost effective strategy for improving quality-adjusted life[31,32].

In the final analysis, discordance in the association of HT with CHD and overall mortality between RCTs and observational studies is a function of differences in study design and characteristics of the populations studied. As such, the cardioprotective hypothesis is only beginning to be appropriately tested with RCTs like DOPS in a cohort of women with characteristics like those women from whom the hypothesis was generated. ELITE is a 2×2 factorial RCT designed specifically to study the estrogen cardioprotective hypothesis through the timing hypothesis. KEEPS will extend the findings from EPAT[13] to women <3 years-since-menopause and provide a comparison between low-dose oral and transdermal HT. As data from RCTs accumulate it has become clearly evident that there is concordance with observational studies that indicate that young postmenopausal women who use HT for long periods of time have lower rates of CHD and overall mortality than comparable postmenopausal women who do not use HT.

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Table 1

Number of Participants and Relative Risks of Coronary Heart Disease for Hormone Therapy and Raloxifene Compared to Placebo by Age and Years-Since-Menopause at Randomization

Study	Relative Risk	Number of Participants	P-Value for Trend
HT Meta-analysis[25]	OR (95% CI)		
All ages	0.99 (0.88–1.11)	39,049	
<60 years old or <10 YSM	0.68 (0.48–0.96)	not given	
≥60 years old or ≥10 YSM	1.03 (0.91–1.16)	not given	
WHI[18] (years-since-menopause)	HR (95% CI)		
CEE+MPA Trial			0.05
<10	0.88 (0.54–1.43)	5,494	
10–19	1.23 (0.85–1.77)	6,041	
≥20	1.66 (1.14–2.41)	3,653	
CEE Trial			0.15
<10	0.48 (0.20–1.17)	1,643	
10–19	0.96 (0.64–1.44)	2,936	
≥20	1.12 (0.86–1.46)	4,550	
Combined CEE+MPA and CEE Trials			0.02
<10	0.76 (0.50–1.16)	7,137	
10–19	1.10 (0.84–1.45)	8,977	
≥20	1.28 (1.03–1.58)	8,203	
RUTH[28] (age, years)			0.01
<60	0.59 (0.41–0.83)	1,670	
60–69	1.06 (0.88–1.28)	4,534	
≥70	0.98 (0.82–1.17)	3,897	

HT = hormone therapy

YSM = Years-since-menopause

OR (95% CI) = Odds ratio (95% Confidence Interval)

HR (95% CI) = Hazard ratio (95% Confidence Interval)

WHI = Women's Health Initiative

CEE = conjugated equine estrogen

MPA = medroxyprogesterone acetate

RUTH = Raloxifene Use for the Heart

Table 2

Number of Participants and Relative Risks of Overall Mortality for Hormone Therapy Compared to Placebo by Age at Randomization

Study	Relative Risk	Number of Participants	P-Value for Trend
HT Meta-analysis[27] (age, years)	OR (95% CI)		
All ages	0.98 (0.87–1.18)	26,708	
<60	0.61 (0.39–0.95)	not given	
≥60	1.03 (0.90–1.18)	not given	
WHI[18] (age, years)	HR (95% CI)		
CEE+MPA Trial			0.19
50–59	0.69 (0.44–1.07)	5,494	
60–69	1.09 (0.83–1.44)	6,041	
70–79	1.06 (0.80–1.41)	3,653	
CEE Trial			0.18
50–59	0.71 (0.46–1.11)	1,643	
60–69	1.02 (0.80–1.30)	2,936	
70–79	1.20 (0.93–1.55)	4,550	
Combined CEE+MPA and CEE Trials			0.06
50–59	0.70 (0.51–0.96)	7,137	
60–69	1.05 (0.87–1.26)	8,977	
70–79	1.14 (0.94–1.37)	8,203	

HT = hormone therapy

OR (95% CI) = Odds ratio (95% Confidence Interval)

HR (95% CI) = Hazard ratio (95% Confidence Interval)

WHI = Women's Health Initiative

CEE = conjugated equine estrogen

MPA = medroxyprogesterone acetate

Table 3

Relative and Absolute Risks of Commonly used Agents

Therapy	Event	Risk ratio (95% CI)	Additional cases per 10,000 persons/year
Atorvastatin[66]	Hemorrhagic stroke	1.66 (1.08–2.55)	19
Simvastatin[67]	Hemorrhagic stroke	1.86 (not reported)	2
Pravastatin[68]	New cancer diagnosis	1.25 (1.04–1.51)	52
Rosuvastatin[39]	New onset diabetes mellitus	1.49 (1.11–2.01)	50
Fenofibrate[69]	Deep vein thrombosis	not reported	7
Fenofibrate[69]	Pulmonary embolus	not reported	9
Aspirin[36]	GI bleeding requiring blood transfusion	1.40 (1.07–1.83)	2
Aspirin[36]	GI bleeding	1.22 (1.10–1.34)	8
Rosiglitazone[70]	Myocardial infarction	1.66 (0.73–3.80)	8
Rosiglitazone[71]	Bone fracture	1.82 (1.37–2.41)	94
Pioglitazone[72,73]	Bone fracture	2.04 (1.22–3.41)	88
Alendronate[74]	Atrial fibrillation	1.86 (1.09–3.15)	not reported
Zolendronate[75]	Serious atrial fibrillation	~2.5 ($p<0.001$)	26
Bisphosphonates[76]	Atypical spiral fracture of the femoral shaft	47.3 (25.6–87.3)	5
Calcium supplements[77]	CHD (MI, stroke, sudden death)	1.43 (1.01–2.04)	70
Calcium supplements[77]	Stroke	1.45 (0.88–2.49)	36
Calcium supplements[77]	Myocardial infarction	1.67 (0.98–2.87)	45
Beta-carotene[78]	Lung cancer	1.28 (1.04–1.57)	13
	Relative and absolute risks of mortality with commonly used agents		
Fenofibrate[69]	Total mortality	1.11 (0.95–1.29)	13
Aspirin[79]	Sudden death	1.96 (0.91–4.23)	5
Rosiglitazone[80]	Total mortality	1.14 (1.05–1.24)	45
Calcium supplements[81]	Total mortality	1.09 (0.96–1.23)	8
Beta-carotene[78]	Total mortality	1.17 (1.03–1.33)	25

CHD = coronary heart disease; MI = myocardial infarction; GI = gastrointestinal