The Timing Hypothesis and Hormone Replacement Therapy: A Paradigm Shift in the Primary Prevention of Coronary Heart Disease in Women. Part 1: Comparison of Therapeutic Efficacy

Howard N. Hodis, MD,*†‡ and Wendy J. Mack, PhD*‡

The long-held belief that outcome data from intervention trials in men are generalizable to women has created the framework in which the primary prevention of coronary heart disease (CHD) in women is viewed, but over the past decade, data have accumulated to refute such a supposition of generalizability. These lines of evidence concern the sex-specific efficacy of CHD primary prevention therapies and timing of postmenopausal hormone replacement therapy (HRT) initiation according to age and time since menopause as modifiers of efficacy and risk. Although the standard primary prevention therapies of statins and aspirin reduce CHD in men, neither therapy reduces CHD and, more importantly, mortality in women under primary prevention conditions. Nonetheless, HRT significantly reduces CHD and mortality in primary prevention when it is initiated in women who are younger than 60 or are less than 10 years since menopause. Herein, the efficacy of the commonly used therapies for the primary prevention of CHD in women, statins, aspirin, and postmenopausal HRT is discussed. The comparative risks of these therapies will be discussed in Part 2 of this series.


Key words: hormone therapy in women; statins; timing hypothesis; women and CHD prevention; meta-analyses

Sex-Specific Primary Prevention Therapy: Statins and Aspirin

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins)

Statins are the most commonly used medications for lipid lowering and for the primary prevention of CHD in women and men. The prevailing belief is that statins reduce CHD events and mortality under primary and secondary prevention conditions in women and men. However, careful examination of randomized control trial (RCT) data does not provide clear evidence that statins reduce CHD events or total mortality in women under primary prevention conditions.

In the first large meta-analysis of RCTs of statin therapy in which primary (six RCTs; n = 11,435 women) and secondary (eight RCTs; n = 8,272 women) CHD prevention trials were analyzed separately in women, the data support a significant reduction in CHD events (hazard ratio (HR) = 0.80; 95% confidence interval (CI) = 0.71–0.91) but not in total mortality (HR = 1.00, 95% CI = 0.77–1.29) in women under secondary prevention conditions, although neither CHD events (HR = 0.89, 95% CI = 0.69–1.09) nor total mortality (HR = 0.95, 95% CI = 0.62–1.46) was reduced in women under primary prevention conditions (Table 1).1

In the first sex-specific meta-analysis to analyze primary CHD prevention trials independently from secondary prevention trials, statin therapy reduced CHD in men but not in women under primary prevention conditions,2 even with inclusion of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trial in which 5,356 women were enrolled and followed for more than 5 years.3 Statin therapy did not significantly reduce total mortality in women or men under primary prevention conditions (Table 1).2 These results were confirmed in another sex-specific meta-analysis of statins and CHD prevention4 (Table 1) that included RCTs conducted in individuals with diabetes mellitus without a history of cardiovascular disease (CVD), as well as in MEGA and the Justification for the Use of Statins in
Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), another primary CHD prevention RCT with a large cohort of 6,801 women.5 Even though this meta-analysis included a greater number of women at greater risk for CHD than the previous meta-analyses, the risk reduction reported for CHD in women was statistically nonsignificant, and total mortality was no different than in the other meta-analyses (Table 1).

As the consistency across individual primary CHD prevention trials and sex-specific meta-analyses shows, there is no clear evidence that statins reduce CHD events or total mortality in women without preexisting CVD. The one possible exception is JUPITER in which the primary trial endpoint for CHD was lower (HR = 0.54, 95% CI = 0.37–0.80)5 in women but JUPITER was stopped early, after a median follow-up of 1.9 years, and it is unclear whether findings from JUPITER were due to the unique characteristics of the cohort (women aged ≥60 with low-density lipoprotein cholesterol <130 mg/dL and high-sensitivity C-reactive protein ≥2 mg/dL),5 the trial biases and flaws6–7 or to the subjective nature of certain components of the primary endpoint.5 The JUPITER primary cardiovascular endpoint was a composite comprising “hard endpoints” (nonfatal myocardial infarction (MI), nonfatal stroke, or confirmed death resulting from cardiovascular causes) and “soft endpoints,” whose occurrence rely on medical decisions (arterial revascularization or hospitalization for unstable angina pectoris). In men, all of the hard and soft components of the composite primary endpoint were significantly lower in the rosuvastatin than in the placebo arm. In women, only the soft endpoints (revascularizations and hospitalizations) were significantly lower and clearly drove the primary endpoint to statistical significance because none of the hard endpoints in the women differed significantly (P > .10) between the rosuvastatin and placebo arms.5 Total mortality was not statistically different between the rosuvastatin and placebo arms in women (P = .12) or men (P = .08).5 Including JUPITER in meta-analyses along with other primary prevention trials does not alter the conclusion that statin therapy has a null effect on CHD events and total mortality in primary CHD prevention in women.4

Aspirin

The sex-specific efficacy of primary prevention of CHD reported for aspirin is concordant with that of statin therapy.8 In meta-analyses of primary CHD prevention trials, aspirin significantly reduced MI by approximately 32% with a null effect on stroke in men, whereas in women, aspirin had a null effect on MI but significantly reduced ischemic stroke by approximately 17%.8,9 In women and men, aspirin therapy has a null effect on total mortality under primary CHD prevention conditions. Consistent with statin therapy, the null effect of aspirin therapy on CHD extends to high-risk women with diabetes mellitus without a history of CVD. In the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial, the largest RCT of aspirin therapy and primary CHD prevention in individuals aged 30 to 85 with type 2 diabetes mellitus (1,152 women), the effect of aspirin therapy on CHD was null relative to placebo (relative risk (RR) = 0.88, 95% CI = 0.53–1.44) after a median treatment of 4.4 years.10 The consistency across individual primary CHD prevention trials and sex-specific meta-analyses show no evidence that aspirin therapy reduces CHD events or total mortality in women without preexisting CVD, including those with diabetes mellitus who are at high risk of CHD. The sex-specific nature of CVD benefits restricted to men under primary prevention conditions is seen with other interventions such as angiotensin-converting enzyme inhibitor therapy, with men having less CVD and mortality, whereas women do not.11,12

Timing of Initiation of Postmenopausal HRT

Coronary heart disease

Over the last decade, cumulated data from RCTs of HRT clearly demonstrate two distinct populations of women who respond differentially to HRT according to timing of HRT initiation relative to age and time since menopause.13 Specifically, CHD events and total mortality benefits occur when HRT is initiated in younger women (<60) in close proximity to menopause (<10 years since menopause) and a null and possible adverse effect when initiated in older women (≥60) remote from menopause (>20 years since menopause).13 The beneficial effect of HRT on CHD according to timing of HRT initiation has been shown in a large meta-analysis of 23 RCTs with 191,340 women-years of follow-up.14 When analyzed over all ages and in women who initiate HRT when aged 60 and older or more than 10 years after menopause, the effect of HRT on CHD is null. In women who initiate HRT when younger than 60 or less than 10 years since menopause, the risk of CHD is statistically significantly 32% less than with placebo (Figure 1). The magnitude of CHD reduction for women younger than 60 or less than 10 years since menopause when randomized to HRT is similar to observational studies of populations of women who initiated HRT at the time of menopause.15,16

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<tr>
<th>Outcome</th>
<th>Women</th>
<th>Men</th>
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<td></td>
<td>HR (95% CI)</td>
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<td>Coronary heart disease</td>
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<td>Walsh and Pignone1</td>
<td>0.89 (0.69–1.09)</td>
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<td>13,346</td>
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<td>Brugs et al.4</td>
<td>0.79 (0.56–1.13)</td>
<td>20,817</td>
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<td>Total mortality</td>
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<td>Brugs et al.4</td>
<td>0.91 (0.76–1.08)</td>
<td>20,817</td>
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HR = hazard ratio; CI = confidence interval.
The Women’s Health Initiative (WHI) trial data also support the “timing” hypothesis, showing significant trends of an HRT effect on CHD according to time since menopause. Women randomized to conjugated equine estrogen (CEE) less than 10 years after menopause had a 52% lower risk of CHD than with placebo ($HR = 0.48, 95\% \text{ CI} = 0.20–1.17$), whereas women who were 10 to 19 years since menopause ($HR = 0.96, 95\% \text{ CI} = 0.64–1.44$) and 20 or more years since menopause ($HR = 1.12, 95\% \text{ CI} = 0.86–1.46$) showed no benefit of CEE on CHD. Women randomized to CEE plus medroxyprogesterone acetate (MPA) within 10 years after menopause had a 12% lower risk of CHD than with placebo ($HR = 0.88, 95\% \text{ CI} = 0.54–1.43$), whereas women 10 to 19 years after menopause ($HR = 1.23, 95\% \text{ CI} = 0.85–1.77$) and 20 or more years after menopause ($HR = 1.66, 95\% \text{ CI} = 1.14–2.41$) showed no benefit and possibly a greater risk with CEE plus MPA than with placebo. With both trials combined, women randomized to CEE and CEE plus MPA within 10 years of menopause had a 24% lower risk of CHD than with placebo ($HR = 0.76, 95\% \text{ CI} = 0.50–1.16$), whereas women 10 to 19 years since menopause ($HR = 1.10, 95\% \text{ CI} = 0.84–1.45$) and 20 or more years since menopause ($HR = 1.28, 95\% \text{ CI} = 1.03–1.58$) showed no benefit and possibly a greater risk of CEE and CEE plus MPA on CHD than with placebo.

Figure 1. (A) Relative risks (RRs) and 95% confidence intervals (CIs) for coronary heart disease events associated with hormone replacement therapy (HRT) from a meta-analysis of 23 randomized controlled trials (RCTs) in 39,049 women (followed for 191,340 women-years). Results are shown for all ages and for women aged 60 and older or more than 10 years after menopause or younger than 60 years old or less than 10 years after menopause when randomized and HRT initiated. (B) RRs and 95% CIs for total mortality associated with HRT from a meta-analysis of 30 RCTs in 26,708 women (followed for 119,118 women-years). Results are shown for all ages and for women aged 60 and older or more than 10 years after menopause or younger than 60 years old or less than 10 years after menopause when randomized and HRT initiated.

The 11-year WHI CEE trial follow-up (7 years of randomized treatment and 4 years of postintervention follow-up) showed that women aged 50 to 59 given CEE had a significantly lower risk of CHD ($HR = 0.59, 95\% \text{ CI} = 0.38–0.90$), total MI ($HR = 0.54, 95\% \text{ CI} = 0.34–0.86$), and total mortality ($HR = 0.73, 95\% \text{ CI} = 0.53–1.00$) than with placebo. Compared with women aged 60 to 69 and 70 to 79, the $P$-value for interaction was statistically significant for each outcome ($P = .05, P = .007$, and $P = .04$, respectively), indicating that the CEE effect on these outcomes differs according to age. Invasive breast cancer was statistically significantly 23% lower ($HR = 0.77, 95\% \text{ CI} = 0.62–0.95$) in women who received CEE than with placebo regardless of age at randomization.

Of immense importance to understanding early initiation of HRT, long-term use, and clinical outcomes in healthy young women is the Danish Osteoporosis Prevention Study (DOPS), the only prospective longitudinal randomized trial designed to examine clinical outcomes in women who were specifically a priori randomized to HRT in the perimenopausal or early postmenopausal period. DOPS included 1,006 women who were on average 50 years old (range 45–58) and 7 months postmenopausal when randomized for 10 years to oral 17β-estradiol plus sequential norethisterone acetate or to an untreated group. Hysterectomized women received oral 17β-estradiol 2 mg daily. After randomized treatment, the women were followed for another 6 years for a total follow-up of 16 years. After 10 years of randomized treatment, the composite primary trial endpoint of mortality, MI, or heart failure (HF) was significantly 52% lower ($HR = 0.48, 95\% \text{ CI} = 0.27–0.89$), and total mortality was 43% ($HR = 0.57, 95\% \text{ CI} = 0.30–1.08$) lower in the HRT group than in the control group. After a total follow-up of 16 years, the composite primary trial endpoint remained significantly 49% lower ($HR = 0.61, 95\% \text{ CI} = 0.39–0.94$) and total mortality was 34% ($HR = 0.66, 95\% \text{ CI} = 0.41–1.08$) lower in the women originally randomized to HRT than in those randomized to the control group. There were no statistically significant differences in incident breast cancer, stroke, or venous thromboembolism between treatment groups in DOPS. DOPS results are similar to the 11-year WHI CEE trial follow-up data of the women aged 50 to 59 when randomized to CEE and to the 32% lower CHD and 39% lower total mortality shown in meta-analyses of RCTs of women younger than 60 or less than 10 years since menopause with HRT than with placebo (Figure 1).

**Total mortality**

Although the risks and benefits of HRT continue to be debated, postmenopausal HRT is the only primary prevention therapy in women that has been demonstrated to reduce total mortality and extend life. The beneficial effect of HRT on total mortality according to age was shown in a large meta-analysis of 30 RCTs with 119,118 women-years of follow-up. When analyzed across all ages and in women aged 60 and older when initiating HRT, the effect on total mortality was null, whereas there was significant 39% lower total mortality in women younger than 60 (mean age 54) when with HRT than with placebo.
(Figure 1), a difference similar to that found in observational studies. Age at HRT initiation in women in observational studies and age of younger women randomized to RCTs examined in the meta-analysis was similar.15,16

Similar to CHD trends, total mortality in WHI was 30% lower with CEE plus MPA and CEE therapies than with placebo in women aged 50 to 59 when randomized.17 Women randomized to CEE when younger than 60 had a 29% lower risk of total mortality than with placebo (HR = 0.71, 95% CI = 0.46–1.11), whereas women aged 60 to 69 (HR = 1.02, 95% CI = 0.64–1.44) and 70 to 79 (HR = 1.20, 95% CI = 0.93–1.56) showed no effect of CEE on total mortality. Women randomized to CEE plus MPA when younger than 60 had a 31% lower risk of total mortality than with placebo (HR = 0.69, 95% CI = 0.44–1.07), whereas women aged 60 to 69 (HR = 1.09, 95% CI = 0.83–1.44) and 70 to 79 (HR = 1.06, 95% CI = 0.80–1.41) showed no benefit of CEE plus MPA on total mortality. In both trials combined, women randomized to CEE plus MPA or CEE when younger than 60 had a statistically significant 30% lower risk of total mortality than with placebo (HR = 0.70, 95% CI = 0.51–0.96), whereas women aged 60 to 69 (HR = 1.05, 95% CI = 0.87–1.26) and 70 to 79 (HR = 1.14, 95% CI = 0.94–1.37) showed no benefit of CEE and CEE plus MPA on total mortality.

To address the risks and benefits of HRT, a Bayesian meta-analysis was conducted using RCTs and observational studies to evaluate the effect of HRT on total mortality in postmenopausal women younger than 60 who initiated HRT in close proximity to menopause.21 Results from this meta-analysis using 19 RCTs with 16,283 women (mean age 54.5) followed for 83,043 women-years over 5.1 years (range 1–6.8 years) showed total mortality of 27% less (RR = 0.73, 95% credible interval (CrI) = 0.52–0.96) in women randomized to HRT than in those who received placebo. Using pooled data from eight prospective observational studies in which 212,717 women were followed for 2,935,495 patient-years over a mean of 13.8 years (range 6–22 years), total mortality was 22% (RR = 0.78, 95% CrI = 0.69–0.90) lower in HRT users than in nonusers.21 Total mortality was 28% (RR = 0.72, 95% CrI = 0.62–0.82) lower with the RCT and prospective observational data combined. Results from this study indicate a convergence of evidence from several sources that support a beneficial effect of HRT on total mortality in women who initiate HRT in close proximity to menopause. Results from this meta-analysis also indicate that RCTs and observational studies are similar, each with a total mortality reduction of approximately 25%, similar to the 10-year randomized trial follow-up (43% lower total mortality) and 16-year total follow-up (34% lower total mortality) of DOPS,19 the 11-year follow-up of WHI CEE (27% lower total mortality),18 and the significant 30% lower (HR = 0.70, 95% CI = 0.51–0.96) total mortality shown in postmenopausal women younger than 60 with HRT than with placebo in the WHI trials.17

HRT Cost-Effectively Extends Life

A cost-effectiveness analysis indicates that, compared with no therapy, HRT given to postmenopausal women in their 50s for 5 to 30 years results in a substantial increase of 1.5 quality-adjusted life years (QALYs) at a cost of $2,438 per QALY gained.22 Net gains gradually increase with treatment durations of 5 to 30 years, and results for younger women are robust to all sensitivity analyses, with HRT remaining highly cost effective. At $2,438 per QALY gained, these data indicate that HRT is a highly cost-effective strategy for improving quality-adjusted life. Alternatively, there is a smaller net gain of 0.11 QALYs at a cost of $27,953 per QALY gained for 65-year-old postmenopausal women initiating HRT.22 Cost effectiveness ratios of less than $50,000 per QALY are considered worthwhile, those less than $5,000 per QALY gained are considered highly cost effective, and a cost-effectiveness ratio greater than $100,000 per QALY is considered unattractive.

CONCLUSION

The cumulated data and their implication for women’s health in the primary prevention of CHD have become clearer over the past decade as the sex-specificity of statins and aspirin and timing of initiation of HRT as modifiers of efficacy and risk in women have become more fully elucidated. The data clearly show that standard primary CHD prevention therapies that are presumably efficacious in men (statins and aspirin) do not statistically significantly reduce CHD events or total mortality in women.

Data are consistent in showing that, when initiated in women younger than 60 or less than 10 years after menopause, HRT reduces CHD events and total mortality, extends life, and is highly cost effective. The risks associated with HRT, such as breast cancer, are considered rare (<1 event per 10,000 women treated per year) (see Part 2). The evidence-based data are large and consistent across approximately 40 observational studies and meta-analyses encompassing 20 to 30 RCTs. In addition, the type and magnitude of risks associated with the standard primary CHD prevention therapies are similar to those associated with HRT (see Part 2).

Although the data are clear in showing sex-specific benefits restricted to men under primary prevention conditions with statin and aspirin therapy,23,24 the old paradigm that “what works in men must work in women” continues to be promulgated as evidence-based data indicating the fallacy of this paradigm are ignored. Data supporting the use of statin and aspirin therapy for a significant reduction in CHD events and total mortality under primary prevention conditions for women are lacking (Table 2). The data consistently support that, when initiated in women younger than 60 or less than 10 years after menopause, HRT reduces CHD and total mortality (Table 2). The statistically significantly greater risk of diabetes mellitus, risk of breast cancer similar to that with CEE plus MPA therapy, and potential for the increase in new cancer cases in older persons24 associated with statin therapy have important implications for the balance of benefit and risk of statin therapy under primary prevention conditions in which individual RCTs and meta-analyses show no benefit in reducing CHD events or total mortality in women (see Part 2). In light of the accumulating data and safety label changes to include warnings of diabetes and cognitive impairment that the Food and Drug Administration...
requires the use of statin therapy for the primary prevention of CHD in men has also been questioned.6,26

DOPS, the only prospective longitudinal randomized trial conducted specifically in women younger than 60 (average age 50) and less than 10 years after menopause (average 7 months), provides direct and compelling evidence for up to 16 years that the benefits of prevention of chronic diseases outweigh the risks.19 Women included in DOPS specifically represent women studied in previous observational studies, and hence, DOPS is the only randomized trial to appropriately test the “estrogen cardioprotective” hypothesis in the same population of women in which this hypothesis was generated. In addition, few prevention therapies other than HRT have been studied under randomized conditions for 10 years.

Timing of initiation of primary prevention therapy appears to have significant biological and clinical consequences for women. The timing of initiation of primary prevention therapies provides opportunity for reduction of CHD events and total mortality throughout the postmenopausal period and forges a new paradigm in the primary prevention of CHD in women. It is important to rethink the appropriate clinical application of the evidence-based data: reduction of CHD events and total mortality in women who initiate HRT when younger than 60 or less than 10 years after menopause versus no reduction of CHD events or total mortality with statin and aspirin therapy (Table 2). Women aged 60 and older or more than 10 years after menopause have likely missed the window of opportunity for benefit from HRT and should probably not initiate HRT for the primary prevention of CHD.

In conclusion, a large body of RCT data converges with results from observational studies, animal studies, and basic science supporting that HRT health outcomes vary according to age or time since menopause. Focused in young healthy postmenopausal women with an average age of 50 and an average of 7 months after menopause, DOPS provides strong evidence of the long-term efficacy and safety of HRT for reducing CHD and total mortality. Inconsistencies in presentation and interpretation of HRT data has created great confusion for healthcare providers and patients alike, culminating in the call for an independent commission to evaluate the interpretation and dissemination of the evidence-based data in relation to public health recommendations.27

The totality of evidence indicates that the benefits of the initiation of HRT at or near menopause outweigh the risks, with the weight of evidence supporting downstream prevention of morbidity and mortality. Healthcare providers and patients can be confident in applying the cumulative data in making clinical decisions concerning chronic disease prevention, keeping in mind that any prevention strategy must be personalized. Cumulative data provide not only strong evidence of the beneficial effects of HRT when initiated in women in close proximity to menopause, but also reassurance of their safety.

**ACKNOWLEDGMENTS**

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**Author Contributions:** Both authors took part in all aspects of this paper.

**Sponsor’s Role:** None.

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**Table 2. Comparison of the Effect of Initiation of Hormone Replacement Therapy in Young Postmenopausal Women with that of Statin and Aspirin Therapy on Coronary Heart Disease and Total Mortality in Primary Prevention**

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<th>Outcome</th>
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<th>Aspirin Therapy</th>
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<sup>a</sup>Initiation in women younger than 60 or less than 10 years after menopause.


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