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The Timing Hypothesis: A Paradigm Shift in the Primary Prevention of Coronary Heart Disease in Women: Part 1, Comparison of Therapeutic Efficacy

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Abstract

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. However, over the past decade, data has 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/or 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 reduce CHD, and more importantly total mortality in women under primary prevention conditions. On the other hand, HRT significantly reduces both CHD and total mortality in primary prevention when HRT is initiated in women <60 years old and/or <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. In part 2 of this series the comparative risks of these therapies are discussed.

Keywords

hormone therapy in women; statins; timing hypothesis; women and CHD prevention; 31 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 both women and men. The prevailing belief is that statins reduce CHD events and total mortality under primary and secondary prevention conditions in both

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women and men. However, careful examination of the 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 (6 RCTs; n=11,435 women) and secondary (8 RCTs; n=8,272 women) CHD prevention trials were analyzed separately in women, the data support a significant reduction in CHD events (HR, 0.80; 95%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. However, neither CHD events (HR, 0.89; 95%CI, 0.69–1.09) nor total mortality (HR, 0.95; 95%CI, 0.62–1.46) is reduced in women under primary prevention conditions¹ (Table 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 whereas it did not in women under primary prevention conditions², 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 >5 years³. Statin therapy did not significantly reduce total mortality in either women or men under primary prevention conditions² (Table 1). These results were confirmed in another sex-specific meta-analysis of statins and CHD prevention⁴ (Table 1) that included RCTs conducted in patients with diabetes mellitus without a history of cardiovascular disease (CVD) as well as 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 women⁵. Even though this meta-analysis included a greater number of women at a greater risk for CHD than the previous meta-analyses, the risk reduction reported for CHD in women was statistically non-significant and total mortality was no different from the other meta-analyses (Table 1).

As shown by the consistency across individual primary CHD prevention trials as well as by sex-specific meta-analyses, there is no clear evidence that statins reduce CHD events or total mortality in women without pre-existing CVD. The one possible exception is JUPITER, a RCT stopped early after a median follow-up of 1.9 years where the CHD primary end point for women was reduced, HR=0.54 (95%CI, 0.37–0.80)⁵. However, it is unclear whether findings from JUPITER were due to the unique characteristics of the cohort (women 60 years of age with LDL-C <130 mg/dL and hsCRP ≥ 2 mg/dL)⁵, the controversial aspects of trial conduct^{6,7} or from the subjective nature of certain components of the primary end point⁵. The JUPITER primary cardiovascular end point was a composite comprised of “hard end points” (nonfatal myocardial infarction (MI), nonfatal stroke, or confirmed death resulting from cardiovascular causes) and “soft end points” whose occurrence rely on medical decisions (arterial revascularization or hospitalization for unstable angina). In men, all of the “hard” and “soft” components of the composite primary end point were significantly reduced in the rosuvastatin versus placebo arms. In women, only the “soft” end points (revascularizations and hospitalizations) were significantly reduced and clearly drove the primary end point to statistical significance since all of the “hard” end points in the women did not significantly differ (p>0.1) between the rosuvastatin and placebo arms⁵. Total mortality was not statistically different between the rosuvastatin and placebo arms in either women (p=0.12) or men (p=0.08)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 women⁴.

Aspirin

The sex-specific efficacy of primary prevention of CHD reported for statins is concordant with aspirin therapy⁸. 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 both 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 30–85 year old patients with type 2 diabetes mellitus (1,152 women), the effect of aspirin therapy on CHD was null relative to placebo (RR, 0.88; 95% CI, 0.53–1.44) after a median treatment of 4.37 years¹⁰. The consistency across individual primary CHD prevention trials as well as sex-specific meta-analyses show no evidence that aspirin therapy reduces CHD events or total mortality in women without pre-existing CVD including those at high risk with diabetes mellitus. Notably, sex-specific CVD benefits restricted to men under primary prevention conditions extend to other interventions such as angiotensin converting enzyme (ACE) inhibitor therapy^{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/or time-since-menopause¹³. Specifically, CHD events and total mortality benefits occur when HRT is initiated in younger women (<60 years of age) in close proximity to menopause (<10 years-since-menopause) and a null and possible adverse effect when initiated in older women (>60 years of age) remote from menopause (>20 years-since-menopause)¹³. The beneficial HRT effect 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-up¹⁴. When analyzed over all ages and in women who initiate HRT when >60 years of age and/or >10 years-since-menopause the HRT effect on CHD is null. In women who initiate HRT when <60 years of age and/or <10 years-since-menopause there is a statistically significant 32% reduction in CHD relative to placebo (Figure). The magnitude of CHD reduction for women <60 years of age or <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}.

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-menopause¹⁷. Women randomized to conjugated equine estrogen (CEE) <10 years-since-menopause showed a 52% decreased risk of CHD relative to placebo (HR, 0.48; 95% CI, 0.20–1.17), whereas women randomized between 10–19 years-since-menopause and 20 years-since-menopause showed no benefit of CEE on CHD relative to placebo, 0.96 (95% CI, 0.64–1.44) and 1.12 (95% CI, 0.86–1.46), respectively. Women randomized to CEE + medroxyprogesterone acetate (MPA) within 10 years-since-menopause showed a 12% decreased risk of CHD relative to placebo (HR, 0.88; 95% CI, 0.54–1.43), whereas women randomized between 10–19 years-since-menopause and 20 years-since-menopause showed no benefit and possible elevated risk with CEE+MPA relative to placebo, 1.23 (95% CI, 0.85–1.77) and 1.66 (95% CI, 1.14–2.41), respectively. With both trials combined, women randomized to CEE and CEE+MPA within 10 years-since-menopause showed a 24% decreased risk of CHD relative to placebo (HR, 0.76; 95% CI, 0.50–1.16), whereas women

randomized between 10–19 years-since-menopause and 20 years-since-menopause showed no benefit and possible elevated risk of CEE and CEE+MPA on CHD relative to placebo, 1.10 (95% CI, 0.84–1.45) and 1.28 (95% CI, 1.03–1.58), respectively.

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 relative to placebo had 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 total 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 $p=0.04$, respectively¹⁸, indicating that the CEE effect on these outcomes differs by age. 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 randomization¹⁸.

Of immense importance to our understanding of early initiation and long-term HRT use and clinical outcomes in healthy young women is the Danish Osteoporosis Prevention Study (DOPS)¹⁹; the only prospective longitudinal randomized trial designed to examine clinical outcomes among women who were specifically a-priori randomized to HRT in the perimenopausal/early postmenopausal period. DOPS included 1,006 women who were on average 50 years old (age range, 45–58 years) and 7 months postmenopausal when randomized for 10 years to oral 17 β -estradiol plus sequential norethisterone acetate or to an untreated group. Hysterectomized women received oral 17 β -estradiol 2 mg daily. Subsequent to 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 end point of mortality or myocardial infarction (MI) or heart failure (HF) was significantly reduced by 52% (HR, 0.48; 95% CI, 0.27–0.89) and total mortality was reduced by 43% (HR, 0.57; 95% CI, 0.30–1.08) in the HRT group relative to the control group. After a total follow-up of 16 years, the composite primary trial end point remained significantly reduced by 49% (HR, 0.61; 95% CI, 0.39–0.94) and total mortality reduced by 34% (HR, 0.66; 95% CI, 0.41–1.08) in the women originally randomized to HRT relative to those women 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 who were 50–59 years old when randomized to CEE¹⁸ and to the 32% reduction in CHD¹⁴ and 39% reduction in total mortality²⁰ shown in meta-analyses of RCTs of women <60 years old and/or <10 years-since-menopause when randomized to HRT relative to placebo (Figure).

Total mortality

Although the risk:benefits of HRT continue to be debated, it is important to realize that postmenopausal HRT is the only primary prevention therapy in women that has been demonstrated to reduce total mortality and to extend life¹³. The beneficial HRT effect on total mortality according to age has been shown in a large meta-analysis of 30 RCTs with 119,118 women-years of follow-up²⁰. When analyzed across all ages and in women >60 years old when initiating HRT the effect on total mortality is null whereas there is a significant 39% reduction in total mortality in women <60 years old (mean age 54 years) when randomized to HRT relative to placebo (Figure); a reduction similar to observational studies. Age at HRT initiation among women in observational studies and age of younger women randomized to RCT's examined in the meta-analysis is similar^{15,16}.

Similar to CHD trends, total mortality in WHI was reduced 30% with both CEE+MPA and CEE therapies relative to placebo among women aged 50–59 years when randomized¹⁷.

Women randomized to CEE when <60 years old showed a 29% decreased risk of total mortality relative to placebo (HR,0.71; 95%CI, 0.46–1.11), whereas women randomized between 60–69 years old and between 70–79 years old showed no benefit of CEE on total mortality relative to placebo, 1.02 (95%CI, 0.64–1.44) and 1.20 (95%CI, 0.93–1.56), respectively. Women randomized to CEE+MPA when <60 years old showed a 31% decreased risk of total mortality relative to placebo (HR,0.69; 95%CI, 0.44–1.07), whereas women randomized between 60–69 years old and between 70–79 years old showed no benefit of CEE+MPA on total mortality relative to placebo, 1.09 (95%CI, 0.83–1.44) and 1.06 (95%CI, 0.80–1.41), respectively. In both trials combined, women randomized to CEE +MPA or CEE when <60 years old showed a statistically significant 30% decreased risk of total mortality relative to placebo (HR,0.70; 95%CI, 0.51–0.96), whereas women randomized between 60–69 years old and between 70–79 years old showed no benefit of CEE and CEE+MPA on total mortality relative to placebo, 1.05 (95%CI, 0.87–1.26) and 1.14 (95%CI, 0.94–1.37), respectively.

To address risk:benefits of HRT, a Bayesian meta-analysis was conducted using RCTs and observational studies to evaluate the HRT effect on total mortality in young postmenopausal women <60 years old who initiated HRT in close proximity to menopause²¹. Results from this meta-analysis using 19 RCTs with 16,283 women (mean age 54.5 years) followed for 83,043 women-years over 5.1 years (range, 1–6.8 years) showed a total mortality reduction of 27% (RR,0.73; 95% Credible Interval (CrI), 0.52–0.96) among women randomized to HRT relative to placebo. 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), total mortality was reduced 22% (RR,0.78; 95%CrI, 0.69–0.90) in HRT users relative to non-users²¹. Total 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 HRT effect on total mortality in women who initiate HRT in close proximity to menopause. Further, results from this meta-analysis indicate that RCTs and observational studies are similar, each with a total mortality reduction of approximately 25%, results similar to the 10-year randomized trial follow-up of DOPS (43% reduction in total mortality) and to the 16-year total follow-up of DOPS (34% reduction in total mortality)¹⁹, similar to the 11-year follow-up of WHI CEE (27% reduction in total mortality)¹⁸ and similar to the significant 30% reduction (HR,0.70; 95%CI, 0.51–0.96) in total mortality shown in postmenopausal women <60 years of age when randomized to HRT relative to placebo in the WHI trials¹⁷.

HRT Cost Effectively Extends Life

A cost-effectiveness analysis indicates that compared with no therapy, HRT given to postmenopausal women in their 50s for 5–30 years results in a substantial increase of 1.5 quality-adjusted life years (QALY) at a cost of \$2,438 per QALY gained²². Net gains gradually increase with treatment durations of 5–30 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. On the other hand, for 65-year old postmenopausal women initiating HRT there is a smaller net gain of 0.11 QALYs at a cost of \$27,953 per QALY gained²². Cost effectiveness ratios <\$50,000 per QALY are considered worthwhile and those <\$5,000 per QALY gained are considered highly cost effective while a cost effectiveness ratio > \$100,000 per QALY is considered unattractive²³.

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.

On the other hand, data are consistent in showing that when initiated in women <60 years of age and/or <10 years-since-menopause, HRT reduces CHD events and total mortality, is associated with rare risk (See Part 2), extends life and is highly cost-effective. The evidence-based data are large and consistent across approximately 40 observational studies and meta-analyses encompassing 20–30 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 data are clear in showing sex-specific benefits restricted to men under primary prevention conditions with statin and aspirin therapy^{2–5}, 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 of CHD events and total mortality under primary prevention conditions for women are lacking (Table 2). On the other hand, data consistently support that when initiated in women <60 years of age and/or <10 years-since-menopause, HRT reduces CHD and total mortality (Table 2). The statistically significant increased risk of diabetes mellitus, similar breast cancer risk to that of CEE+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 as well as meta-analyses show no benefit in reducing CHD events or total mortality in women (See Part 2). In relation to the accumulating data and safety label changes required by the FDA (2012)²⁵ to include incident diabetes mellitus and cognitive impairment, the use of statin therapy for the primary prevention of CHD in men has also been questioned²⁶.

DOPS, the only prospective longitudinal randomized trial conducted specifically in women <60 years of age (average age=50 years) and <10 years-since-menopause (average=7 months), provides direct and compelling evidence for up to 16 years that the benefits of prevention of chronic diseases outweigh the risks¹⁹. Importantly, women randomized to DOPS specifically represent the women studied in previous observational studies and hence, DOPS is the only randomized trial to date to appropriately test the “estrogen cardioprotective” hypothesis in the very same population of women from which this hypothesis was generated. It should also be noted that other than HRT, no other prevention therapy has 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 <60 years of age and/or <10 years-since-menopause versus no reduction of CHD events or total mortality with statin and aspirin therapy (Table 2). Women >60 years of age and/or >10

years-since-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 by age and/or time-since-menopause. Focused in young healthy postmenopausal women on average 50 years old soon after menopause on average 7 months, DOPS provides strong evidence for 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 health-care 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 recommendations²⁷.

The totality of evidence supports benefits over risks with the initiation of HRT at or near menopause with the weight of evidence supporting downstream prevention of morbidity and mortality. Health-care 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 not only provide strong evidence for the beneficial effects of HRT when initiated in women in close proximity to menopause but also reassurance of their safety.

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A. Coronary Heart Disease **B. Total Mortality** **Figure 1.**

A. Relative risks (and 95% confidence intervals) for coronary heart disease events associated with hormone replacement therapy from meta-analysis of 23 randomized controlled trials in 39,049 women (followed for 191,340 women-years). Results are shown across all ages and for women >60 years old and/or >10 years-since-menopause or <60 years old and/or <10 years-since-menopause when randomized and initiated on hormone replacement therapy.

B. Relative risks (and 95% confidence intervals) for total mortality associated with hormone replacement therapy from meta-analysis of 30 randomized controlled trials in 26,708 women (followed for 119,118 women-years). Results are shown across all ages and for women >60 years old (mean age = 66 years) and <60 years old (mean age = 54 years) when randomized and initiated on hormone replacement therapy.

Table 1

Comparison of Statin Therapy on Coronary Heart Disease and Total Mortality in Primary Prevention in Women and Men

Outcome	Women HR (95% CI)*	N	Men HR (95% CI)	N
Coronary Heart Disease	0.89 (0.69–1.09) ¹	11435		
	0.95 (0.78–1.16) ²	13346	0.55 (0.41–0.75) ²	28346
	0.79 (0.56–1.13) ⁴	20817	0.72 (0.61–0.86) ⁴	26921
Total Mortality	0.95 (0.62–1.46) ¹	11435		
	0.96 (0.81–1.13) ²	11849	0.93 (0.83–1.04) ²	20426
	0.91 (0.76–1.08) ⁴	20817	0.95 (0.86–1.06) ⁴	26921

* Hazard Ratio (95% Confidence Interval)

Table 2

Comparison of Postmenopausal Hormone Replacement Therapy to Statin and Aspirin Therapy on Coronary Heart Disease and Total Mortality in Primary Prevention^{*}

Outcome	Hormone Replacement Therapy [#]	Statin Therapy	Aspirin Therapy
Coronary Heart Disease	0.68 (0.48–0.96) ¹⁴	0.89 (0.69–1.09) ¹	1.01 (0.84–1.21) ⁸
	0.48 (0.26–0.87) ¹⁹	0.95 (0.78–1.16) ²	0.91 (0.80–1.03) ⁹
		0.79 (0.56–1.13) ⁴	
Total Mortality	0.61 (0.39–0.95) ²⁰	0.95 (0.62–1.46) ¹	0.94 (0.74–1.19) ⁸
	0.72 (0.62–0.82) ²¹	0.96 (0.81–1.13) ²	0.95 (0.85–1.06) ⁹
	0.57 (0.30–1.08) ¹⁹	0.91 (0.76–1.08) ⁴	

^{*} Hazard Ratio (95% Confidence Interval)

[#] Initiation in women <60 years old and/or <10 years-since-menopause