

# Postmenopausal hormones and coronary artery disease: potential benefits and risks

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## ABSTRACT

Various secondary prevention trials, including the Women's Health Initiative (WHI), assessing the effects of hormone therapy (HT) on coronary artery disease (CAD) showed no benefit, and a trend towards early harm. However, in the WHI trial, there was a significant trend for decreasing CAD with time. The observational arms of WHI for both estrogen and estrogen/progestin suggested results which were similar to the cardioprotective effects reported in earlier observational studies. Women in these observational trials initiated hormones at a younger age and were generally healthier than women in the randomized trials. Hypotheses have been generated to explain the phenomenon of early harm, based on the induction of plaque instability in the older woman with existent significant atherosclerosis. A report of over 7000 early postmenopausal women initiating prospective trials on hormonal use did not find any evidence suggesting early harm. In the estrogen-only arm of the WHI trial, an analysis of the 50–59-year-old age group showed a near statistical decrease in coronary events: 63 (0.36–1.08), and a statistically significant reduction in a global coronary score, 0.66 (0.45–0.96). In a pooled analysis of 23 randomized clinical trials of hormonal therapy, those women within 10 years of menopause had a significant reduction in coronary events, 0.68 (0.48–0.96). Recent publications from WHI have shown a significant trend for reduced CAD and total mortality in younger women, as well as a reduced coronary calcium score when estrogen alone was given. In that neither aspirin nor statins have been shown to afford a statistical primary benefit for reducing CAD, the benefit of estrogen remains an attractive yet unproven possibility for younger women. In conclusion, while it is clear that HT has no place in the treatment of older women with CAD, emerging evidence strongly suggests a possible coronary benefit in younger healthy women.

## POSTMENOPAUSAL HORMONE THERAPY

It was the expectation that postmenopausal hormonal therapy (HT) could significantly reduce coronary artery disease (CAD) that led to the design and execution of several prospective clinical trials. Earlier observational data had been

remarkably consistent in showing a reduction in CAD risk with HT<sup>1</sup>. The majority of the randomized clinical trials were secondary prevention trials, i.e. in older women with established coronary disease<sup>2–6</sup>. Although the Women's

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Health Initiative (WHI) trials were thought to be primary prevention trials, in that the age range was 50–79 years, only a small proportion of women were under age 55. It has been estimated that no more than 17% of the entire study population were within 5 years of menopause. The trial, therefore, included many older women who were expected to have coronary atherosclerosis even though they may not have experienced a clinical coronary event<sup>7</sup> (Figure 1). The secondary prevention randomized clinical trials, including the WHI study, did not find HT to be protective of CAD, and, in the case of the Heart and Estrogen/progestin Replacement Study (HERS) and the WHI study, both studying the effects of conjugated equine estrogens (CEE)+ medroxyprogesterone acetate (MPA), there were more events in the first year of use, also called ‘early harm’. Various angiographic trials of women with CAD also showed no beneficial effect<sup>8–10</sup>.

Hypotheses have been generated to explain the phenomenon of ‘early harm’. Acute exposure to standard doses of HT in women with significant atherosclerosis is expected to result in an inflammatory reaction, with an increase in matrix metalloproteinase (MMP) activity resulting in a breakdown of the wall of the atherosclerotic plaque, with subsequent rupture and thrombosis. Moreover, in the setting of significant atherosclerosis in older women, natural cardioprotective mechanisms of estrogen action are not operative. Figure 2 depicts a normal coronary vessel in the left panel, where estrogen action may prevent atherosclerosis, and a vessel with advanced atherosclerosis in the right panel, which is vulnerable to rupture, as described above, and where estrogen action is not possible<sup>11</sup>. The

putative mechanism of plaque instability induced by estrogen, and the provocation of MMP activity, is enhanced by the knowledge that statins provide plaque stability and inhibit MMP activity<sup>12</sup>. Further statins have been suggested to prevent the early harm induced by estrogen in women with cardiovascular disease, as shown in HERS<sup>13</sup>. It is clear, therefore, that the age of the woman, and more specifically the number of years since menopause, that dictates the state of the coronary vessels, and significantly influences the effects of estrogen.

Women in the observational trials, where a beneficial effect of HT had been reported, were younger and generally healthier than those in the randomized trials noted above. They were within 5 years of menopause and the majority was receiving HT for menopausal symptoms. The observational trial in the WHI that assessed the effects of estrogen and progestogen among 93 676 women showed results which were more similar to the older observational data showing a trend towards protection. The majority of women were using CEE or CEE/MPA<sup>14,15</sup>.

Attempts have been made to reconcile the differences between the observational and clinical trial data in the WHI trial. Adjustment for age, timing and duration of therapy was shown to bring the point estimates closer together in the case of coronary disease<sup>14,15</sup>. A recent reanalysis of data from the Nurses’ Health Study also showed that timing of initiation was critical to the findings. Women who initiated estrogen-alone or estrogen + progestogen therapy near to the time of menopause showed a protective effect of the therapy on CAD, with hazard ratios (HR) of 0.66 (95% confidence interval (CI) 0.54–0.80) and 0.92 (95% CI 0.56–0.92), respectively<sup>16</sup>. On the

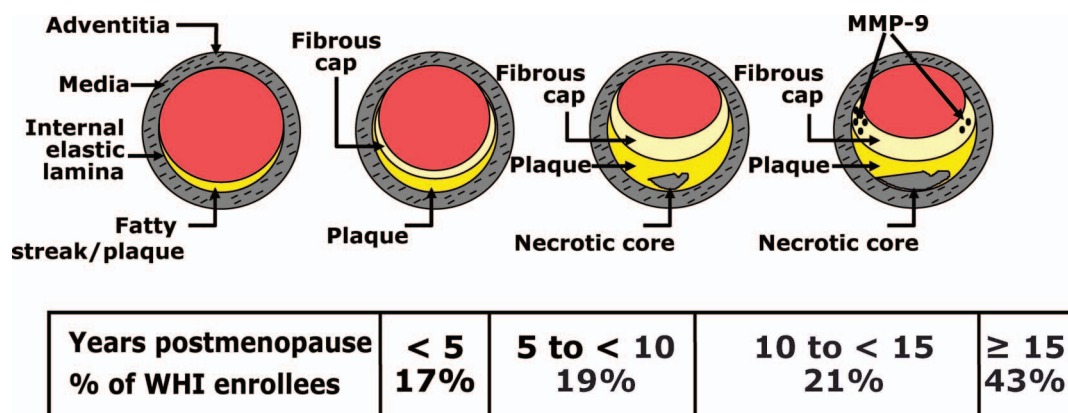


Figure 1 Relation of years since menopause to progression of atherosclerosis in the Women’s Health Initiative (WHI) study

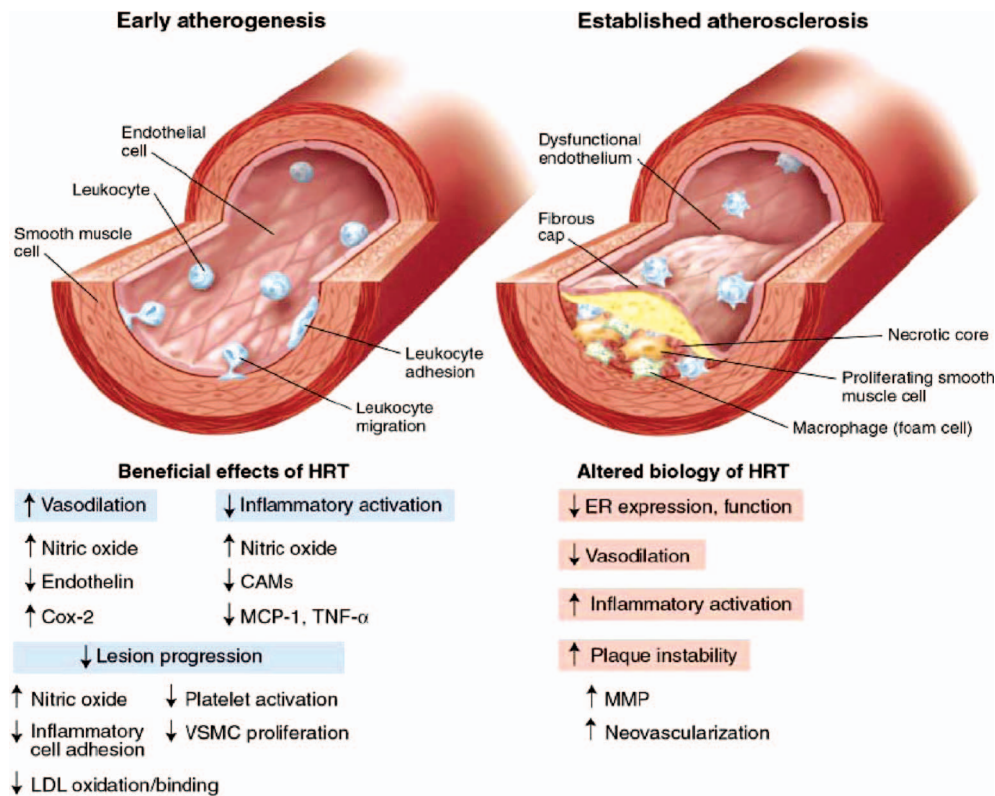


Figure 2 Effect of hormone therapy in early and established atherosclerosis<sup>11</sup>

other hand, women who were similar to those women studied in the WHI study and who were 10 or more years from menopause had non-significant effects of estrogen-alone and estrogen + progestogen therapy: HR 0.87 (95% CI 0.69–1.10) and HR 0.90 (95% CI 0.62–1.29), respectively<sup>16</sup>.

In the observational studies, there was also no evidence for ‘early harm’ except for a non-significant trend for early harm in the minority of the cohort who had prevalent coronary disease<sup>17</sup>. A criticism of these analyses is that surveillance of these cohorts was not as close in the first 1–2 years. Yet, in a prospective trial of over 7333 women receiving randomized HT and followed closely for 2 years, this group of younger (mean age 53 years), recently menopausal women did not have more coronary events: HR 0.17 (95% CI 0.004–0.97)<sup>18</sup>.

When further analyses have been carried out in the WHI study, women in the CEE + MPA trial who were within 10 years of menopause had a hazard ratio of 0.89 (95% CI 0.5–1.4). Similarly, in the CEE-alone trial, the 50–59-year-old group had a HR of 0.63 (95% CI 0.36–1.08), which was similar to the point estimate in most observational

data. Age of menopause, which is a more important parameter to assess, was less precise in this latter cohort because of hysterectomy status. A further analysis of the 50–59-year-old group in the CEE-alone trial showed a statistically significant reduction in a global coronary score (including data on coronary events, revascularization and angina): HR 0.60 (95% CI 0.45–0.96)<sup>19</sup>.

In a recent pooled analysis of 23 randomized clinical trials, including the WHI study, it was reported that, among women in these trials who were within 10 years of menopause, there was a significant reduction in coronary events: odds ratio 0.68 (95% CI 0.48–0.96)<sup>20</sup> (Figure 3). In the older women in this analysis, the odds ratio was 1.03 (0.91–1.16)<sup>20</sup>.

Taken together, these data strongly suggest that the presumed discrepancy between the findings of the observational studies, showing coronary benefit, and the randomized clinical trials, showing no benefit and possibly early harm, is likely explained by the timing of initiation of HT and the age and health status of the woman. Extrapolating this back further in terms of age of menopause, it is now quite clear that premature

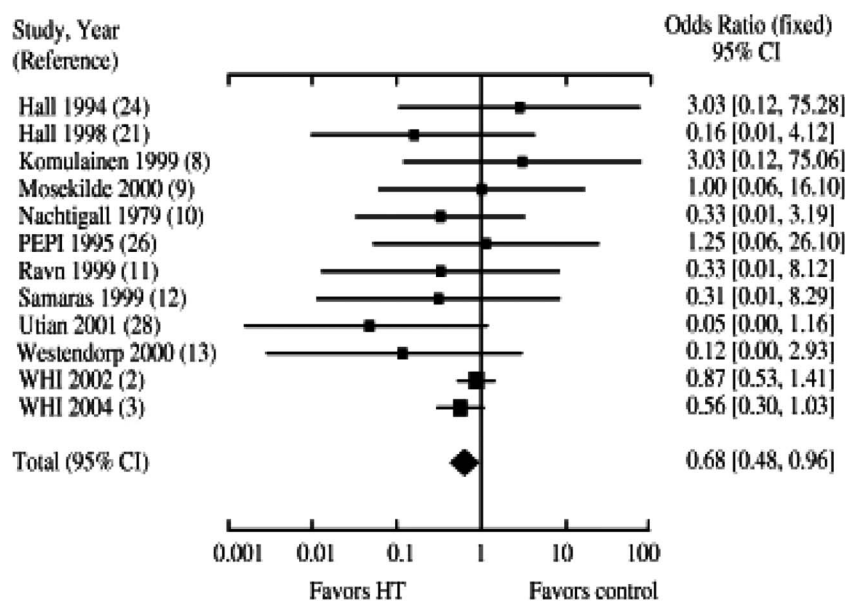


Figure 3 Pooled analysis from 23 randomized trials: younger women<sup>20</sup> (within 10 years of menopause)

menopause (either natural or surgical) results in a significantly increased risk for CAD and mortality. A recent meta-analysis showed that the risk of cardiovascular disease with a spontaneous early menopause was 1.27 (95% CI 1.14–1.43) and was 4.55 (95% CI 2.56–8.01) with bilateral oophorectomy prior to age 50; the risk of myocardial infarction, specifically, with early menopause was 2.03 (95% CI 1.51–2.73)<sup>21</sup>. Increased subclinical atherosclerosis, as evidenced by carotid intima media thickness after bilateral oophorectomy, has been shown to be related to the age at which menopause occurred<sup>22</sup>. Of interest, it was noted among several studies that this increased risk of CAD with early menopause was not evident if women were prescribed HT<sup>23–25</sup>.

### OTHER THERAPIES

It is clear that HT does not have a beneficial effect in women who have established CAD, i.e. no secondary preventative benefit, and may indeed cause some harm. In this setting only, statin therapy has been shown to have a beneficial role<sup>26</sup>. Raloxifene, also, has not been shown to be beneficial<sup>27</sup>. Does any agent have a benefit for primary prevention? Unlike data in men, aspirin in women was not shown to be beneficial in a 10-year study<sup>28</sup>. The risk of myocardial infarction with aspirin was 1.02 (95% CI 0.84–1.25). Similarly and contrary to common belief, in women there is no statistical evidence that statins

are beneficial for primary prevention of coronary heart disease. Data from 11 435 women in six randomized clinical trials show a non-statistical effect on coronary heart disease events: HR 0.87 (95% CI 0.69–1.019); for myocardial infarction the HR is 0.61 (95% CI 0.22–1.68), for CAD mortality the HR is 1.07 (95% CI 0.47–2.40) and for total mortality the HR is 0.95 (95% CI 0.62–1.46)<sup>26</sup>. Thus, it is an attractive notion to consider that estrogen (with important distinctions regarding type, dose, and route) prescribed near the onset of menopause may be found to have a beneficial primary preventative benefit on CAD. While this is not proven, ongoing clinical trials, using carotid intima media thickness as an intermediate endpoint, may provide these answers in the next few years. These trials are the Kronos Early Estrogen Prevention Study (KEEPS) and the Early versus Late Intervention Trial with Estradiol (ELITE).

### CONCLUSIONS

Recent data and analyses since the initial publications of the HT trials of the WHI study strongly suggest that the timing of initiation of HT is critical to the effects of HT on CAD in postmenopausal women. Young healthy women who initiate HT within a few years of menopause, typically for menopausal symptoms, may have a beneficial effect on CAD; at the same time, it is clear that HT should not be used in older women for the secondary prevention of

coronary heart disease. Because an analysis of the effects of CEE and CEE/MPA in women aged 50–59 years in the WHI trial appears to show more CHD benefit for CEE versus CEE/MPA, it has been suggested that there may be a detrimental effect of progestogens. While other clinical and basic data may lend some credence to this

notion, there are no prospective clinical trial data, including data from the WHI study, to prove this assertion.

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