HHS Public Access

Author manuscript

Menopause. Author manuscript; available in PMC 2019 August 06.

Published in final edited form as:

Menopause. 2019 January ; 26(1): 5–6. doi:10.1097/GME.0000000000001264.

Hormone Therapy and Carotid Intima-Media Thickness: The Thick and Thin of it

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The timing hypothesis was developed after results from the Women's Health Initiative (WHI) clinical trials found a trend in lower incidences of cardiovascular disease outcomes in the younger women, closer to the age of natural menopause.[1] Coupled with similar findings from animal and observation studies, this hypothesis proposed that when starting hormone therapy (HT) closer to the age of menopause there may be a beneficial vascular effect in preventing or slowing atherosclerosis, while starting later may be harmful. To study this hypothesis, the Kronos Early Estrogen Prevention Study (KEEPS) was designed to assess atherosclerosis progression using imaging markers in recently menopausal women on oral conjugated estrogen, transdermal estradiol or placebo. Over the 4-year period, the study found early HT did not affect progression atherosclerosis as measured by carotid intima-media thickness (CIMT) between the groups, despite a favorable shift in some cardiovascular risk factors.[2] Additionally, all women increased CIMT over time (mean increase of 0.007 mm/year), consistent with age-predicted progression.[2,3]

In this recent study, Miller et al.[4] evaluated the impact on atherosclerotic progression after stopping HT or placebo in a subgroup of 76 participants from KEEPS using CIMT. Study results found that after a 3-year period of stopping HT there was no accelerate changes in arterial thickness and no differences between treatment groups over time. The authors did note that while there was no difference in progression between groups, for those randomized to oral estradiol, there was a significant increase in CIMT in the post-treatment follow up compared to the on-treatment years. Yet, overall there was no rebound effect or worsening of the vascular endothelium after stopping hormones.

The notion that withdrawal of estrogen could accelerate the progression of atherosclerosis is an interesting concept. One observational study using a national death registry from Finland suggested that stopping HT (mean follow up after discontinuation, 5.5 years) increased the risk of stroke and cardiovascular deaths, particularly in women under the age of 60 years.[5] What remained unknown in this study was why women discontinued HT, e.g. was it due to cardiovascular disease comorbidities, leading to the bias and challenge surrounding registry studies that do not evaluate causality of these associations. In the short-term estrogen, in the presence of a healthy vascular endothelium, acts as a vasodilator by binding to estrogen receptors within the vessel and producing nitric oxide.[6] Estrogen also decreases inflammatory markers and promotes vasodilation by relaxing vascular smooth muscle cells

Disclosures/Conflicts of Interest: None

with the release of nitric oxide.[7] However, while estrogen provides these actions it is not a determinant or regulator of endothelial coronary vascular resistance or blood flow.[8] Therefore, withdrawal of estrogen from a healthy endothelium would not be expected to be detrimental nor lead to progression of cardiovascular disease given then other signaling pathways are intact.

On the other hand, the Miller et al[4] findings are as one might have expected. The main KEEPS trial did not find a difference in CIMT between treatment groups with all group increasing over time consistent with chronological aging. If administration of estrogen did not differ in the trial, it is not as surprising that the withdrawal estrogen would also differ. The authors hypothesize that the lack of difference may have been due to the relatively low dose of hormones used, noting that within the oral estradiol users, a significant increase in CIMT was found after oral estradiol was discontinued. This might suggest that may progression of CIMT may differ by formulation. However, in our research, we have evaluated the dose, formulation and route of delivery of hormone therapy and cardiovascular outcomes and in direct comparison found similar rates of cardiovascular events and all-cause mortality.[9]

More compelling are the WHI clinical trial follow up data that have not indicated an increased cardiovascular disease events in the years after stopping at conventional oral dose of HT, much higher than that used in KEEPS.[10,11] In the most recent published finding, for the combined WHI trials, HT was not associated with and had almost null effect on all-cause mortality, cardiovascular mortality, and other mortality compared to placebo (hazard ratio [HR] 0.99 [95% confidence interval [CI] 0.94–1.03]; HR 1.00 [95% CI 0.92–1.08], and HR 0.95 [95% CI 0.88–1.02], respectively).[12]

The KEEPS data continues to add robust knowledge regarding HT use and now cessation of use at or around the time of menopause in healthy women. While the KEEPS results are intermediate outcomes and not clinical events, they are reassuring for healthy women want to initiate or whom now decide to stop HT around the time of menopause. These results do not prove that HT is safe or unsafe, yet are consistent with current guidelines and position statements.[13] HT is appropriate for use in healthy women at or around the time of menopause for bothersome symptoms and not for the prevention or treatment of cardiovascular disease. In a time, where women continue to be confused and fearful about using HT, these results provide menopause health-care providers data to be confident about starting and stopping HT as needed.

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