

Are we there yet? Menopausal hormone therapy for primary cardiovascular disease prevention

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FEAR OVER FACTS

Since the publication of Women's Health Initiative (WHI) data, a pervasive fear of doing harm has limited the use of all menopausal hormone therapies (MHT) despite newer evidence that is reassuring. Oestrogen therapy (ET), even for women who have a physiological requirement for it, as in those with POI (Premature Ovarian Insufficiency) or surgical (bilateral salpingo-oophorectomy) POI, has markedly dwindled, despite their elevated risk of premature death from cardiovascular disease (CVD).^{1,2} Now, less than 10% of women with surgical POI use ET, while before 2002, greater than 90% of surgical POI women did.³ This significant shift of not taking ET postsurgical POI had resulted in over 50 000 premature deaths, before age 70, from CVD of women who underwent surgical POI.⁴ This number represents a sizeable portion of women: spontaneous POI affects 1% of women before age 40, and early menopause (before 45 years) affects 5% of women.⁵ A recent American Heart Association (AHA) statement supports MHT for reduced CVD risk if started within 10 years of natural menopause or after surgical POI, especially in women younger than 45.⁶

Almost half of the women in the WHI cohort had early surgical POI with bilateral oophorectomy (BSO) by age 50.² Using conjugated equine oestrogens plus medroxyprogesterone acetate in the WHI cohort was not found to be protective with a HR of 1.24 (CI 1.00 to 1.57). However, the mean age of enrolled women was 63 years, and they were on average 12 years postmenopausal. However, when analysed by subgroups, HR became less than one, with a HR of 0.89 in women who underwent menopause within 10 years and a HR of 0.95 in women with hot flashes, aged 50–59. But these HRs did not reach significance because the sample size was too small in this age range: only a third (31%) of the WHI cohort consisted of this

younger age group of fewer than 10 years since menopause or aged 50–59.²

When the WHI data were reanalysed by age, MHT was found to be cardioprotective by outcomes in menopausal women aged 50–54, especially in those with surgical menopause, and that cardiovascular complications were only seen in women who had started MHT a decade postmenopause.⁷ The Nurses' Health Study, an ongoing observational study consisting of almost 60 000 women, shows that those women who received MHT have a significant decrease in their relative risk of coronary disease with an OR of 0.45, bound by narrow CI of 0.34 to 0.60.⁸ Also, the most considerable increased risk of CVD was found in women with the earliest menopause, between ages 40 and 44, with a HR of 1.30 (CI 1.22 to 1.39; $p < 0.0001$) in an extensive pooled analysis from 15 observational studies with over 300 000 women.⁹

These observational data, along with increased heart disease death rates of middle-aged women aged 45–65,¹⁰ have resurrected interest in treating menopausal women with MHT. However, MHT is not recommended for the primary prevention of CVD as per the American College of Cardiology (ACC), AHA¹¹ and the North American Menopause Society (NAMS)¹² even though the ACC/AHA prevention guidelines list premature menopause (age <40) as a CVD risk enhancer and permit the use of MHT for newly menopausal women with symptoms.¹³

With the mounting observational data and the WHI reanalysis, Gersch *et al* write a timely review: Postmenopausal Hormone Therapy for Cardiovascular Health: The Evolving Data in this issue of Heart and ask cardiology societies for an official hormone therapy recommendation for cardioprotection beyond the current stance of 'the lowest dose for the shortest time'.¹⁴

SYMPTOM RELIEF VERSUS HORMONE REPLACEMENT

Recent evidence from extensive observational studies suggests potential differential effects based on the type of oestrogen,

route of administration or MHT formulations. The WHI observational study found non-significant trends for lower coronary heart disease rates, stroke and CVD mortality for transdermal estradiol compared with oral estrogens.¹⁵ Transdermal MHT also shows no increase in venous thromboembolism risk in observational studies, even in women with obesity or an underlying thrombophilia, likely by avoiding the hepatic first-pass effect not increasing levels of coagulation factors or hepatic-binding globulins.

A key distinction must be made between symptom relief (natural menopause) or replacement hormone therapy (surgical menopause from BSO or spontaneous primary ovarian failure (POI)). POI, surgical menopause and normal menopause all lead to oestrogen deficiency, but normal menopause is not a pathological state, unlike the former conditions. Oestrogen deficiency treatment is called hormone replacement therapy (HRT) if the underlying cause is POI or early surgical menopause. These prescribed hormones replace those that were naturally present, as opposed to MHT, which would be used to treat natural menopause.

If using MHT in women with natural menopause, one must weigh patient-specific benefits and risks, such as underlying risk factors of heart disease, breast cancer or liver disease.

Based on many recent double-blinded randomised placebo-controlled trials and reanalysed WHI data that shows no adverse events in women aged 50–54 years, NAMS recommends low dose MHT for short periods for management of severe menopause symptoms in low-risk women, especially when vasomotor symptoms are present (figure 1).¹²

TIMING IS EVERYTHING: IMAGING, MHT, AND CAC

Two trials have assessed the effect response of MHT on carotid intima medial thickness (CIMT), which changes with age and is an established measurement of atherosclerosis progression.

The first prospective randomised controlled trial, The Early versus Late Postmenopausal Treatment with Estradiol, to test the timing hypothesis, first proposed by Clarkson that the advantageous effects of MHT depend on when MHT is started, and better to begin before plaque builds up, showed less progression of CIMT over placebo. Still, it took 5 years of treatment to see a statistical difference.¹⁶

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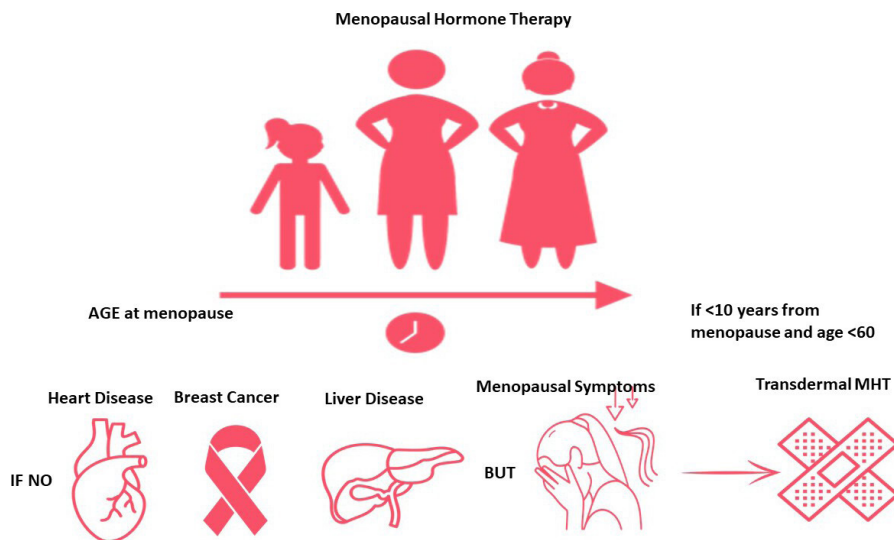


Figure 1 Menopausal hormone therapy strategy

Another trial, The Kronos Early Estrogen Prevention Study (KEEPS), showed that MHT, either low dose oral or transdermal used in early menopausal women, did not affect cIMT progression. However, KEEPS excluded women with a coronary artery calcium (CAC) score of ≥ 50 Agaston units, a marker for subclinical atherosclerosis. The cIMT measurements did not show atherosclerotic progression in either group, perhaps because only 4 years of follow-up occurred, which may be too short of a time to reveal progression in a low-risk cohort.¹⁷

There is support to use CAC to risk stratify asymptomatic postmenopausal women based on studies that show postmenopausal women with higher levels of E2 had reduced CAC scores, independent of age and other coronary heart disease risk factors.¹⁸

This imaging evidence suggests that the sequelae of MHT on atherosclerosis evolution and CVD events varies by the time of menopause: beneficial in those women younger than 60 or less than 10 years out from menopause, but null or harmful if initiated at older ages or after a long time since menopause.

LEVEL OF EVIDENCE: REACHING STATISTICAL SIGNIFICANCE

The WHI studies combined follow-up occurred through March 2019, with over 18 years of follow-up. While the WHI follow-up data shows that timely use of MHT in women aged 50–59 lowers cardiovascular deaths, the overall event rate (CVD death) is too low¹⁹ and did not reach statistical significance.²⁰

Although the current observational data point to the cardioprotective

effects of timely MHT for the postmenopausal woman, whether hard endpoints of myocardial infarction, heart failure or death are delayed or reduced by using timely MHT still needs to be prospectively studied.²¹ Until we have these hard endpoints as proof, the implications of the original WHI studies still hold that using MHT in women older than 60 or who have more than 10-years of postmenopause carries the highest risk. In younger women, we need personalised risk/benefit discussion and shared decision-making, ideally using MHT for the shortest possible time at the lowest possible dose to control symptoms.

Age at menopause should be taken into account as part of CVD risk stratification. However, using cardioprevention as the justification for MHT is not advisable. ‘An official MHT recommendation for cardioprotection,’ as Gersh *et al* request, would affirm these supporting studies, which emphasise the crucial role of timing of MHT relative to the onset of menopause, with the initiation of MHT in women younger than 60 or within 10 years of menopause associated with reduced CVD risk.¹⁴ However, further research assessing MHT use, by formulation, route and administration duration, on cardiometabolic effects in women both premenopause, during and postmenopause is still needed.

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REFERENCES

- 1 Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999–2010. *Obstet Gynecol* 2012;120:595–603.
- 2 LaCroix AZ, Chlebowski RT, Manson JE, *et al*. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. *JAMA* 2011;305:1305–14.
- 3 Faubion SS, Kuhle CL, Shuster LT, *et al*. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015;18:483–91.
- 4 Sarrel PM, Njike VY, Vinante V, *et al*. The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *Am J Public Health* 2013;103:1583–8.
- 5 Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986;67:604–6.
- 6 El Khoudary SR, Aggarwal B, Beckie TM, *et al*. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American heart association. *Circulation* 2020;142:e506–32.
- 7 Chester RC, Kling JM, Manson JE. What the Women’s Health Initiative has taught us about menopausal hormone therapy. *Clin Cardiol* 2018;41:247–52.
- 8 Bhupathiraju SN, Grodstein F, Rosner BA, *et al*. Hormone therapy use and risk of chronic disease in the nurses’ health study: a comparative analysis with the women’s health Initiative. *Am J Epidemiol* 2017;186:696–708.
- 9 Zhu D, Chung H-F, Dobson AJ, *et al*. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health* 2019;4:e553–64.
- 10 Curtin SC. Trends in cancer and heart disease death rates among adults aged 45–64: United States, 1999–2017. *Natl Vital Stat Rep* 2019;68:1–8.
- 11 Mosca L, Benjamin EJ, Berra K, *et al*. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American heart association. *Circulation* 2011;123:1243–62.
- 12 Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American

- College of Cardiology/American heart association Task force on clinical practice guidelines. *Circulation* 2019;140:e596–646.
- 13 The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause* 2018;25:1362–87.
 - 14 Gersh FL, O’Keefe JH, Lavie CJ. Postmenopausal hormone therapy for cardiovascular health: the evolving data. *Heart* 2021;107:1115–22.
 - 15 Shufelt CL, Merz CNB, Prentice RL, *et al.* Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women’s Health Initiative observational study. *Menopause* 2014;21:260–6.
 - 16 Hodis HN, Mack WJ, Henderson VW, *et al.* Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016;374:1221–31.
 - 17 Harman SM, Brinton EA, Cedars M, *et al.* KEEPS: The Kronos Early Estrogen Prevention Study. *Climacteric* 2005;8:3–12.
 - 18 Budoff MJ, Chen GP-W, Hunter CJ, *et al.* Effects of hormone replacement on progression of coronary calcium as measured by electron beam tomography. *J Womens Health* 2005;14:410–7.
 - 19 Poornima IG, Mackey RH, Allison MA, *et al.* Coronary Artery Calcification (CAC) and Post-trial cardiovascular events and mortality within the Women’s Health Initiative (WHI) Estrogen-Alone Trial. *J Am Heart Assoc* 2017;6:e006887.
 - 20 Manson JE, Aragaki AK, Rossouw JE, *et al.* Menopausal hormone therapy and long-term all-cause and cause-specific mortality: the women’s health Initiative randomized trials. *JAMA* 2017;318:927–38.
 - 21 Naftolin F, Friedenthal J, Nachtigall R, *et al.* Cardiovascular health and the menopausal woman: the role of estrogen and when to begin and end hormone treatment. *F1000Res* 2019;8. doi:10.12688/f1000research.15548.1. [Epub ahead of print: 03 Sep 2019].