EDITORIAL

Should hormone therapy be recommended for prevention of cardiovascular disease?

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International guidelines are in general agreement that the clinical indication for hormone therapy is treatment of moderate-to-severe vasomotor symptoms and that current evidence does not support the use of hormone therapy for the prevention of chronic disease, including cardiovascular disease (CVD).[1] An updated Cochrane Review on hormone therapy for the prevention of CVD offers additional information for recently postmenopausal women, with the addition of six studies to the 13 included in the previous version of the review.[2] The update includes one new randomised controlled trial (RCT) – the Danish Osteoporosis Prevention Study (DOPS)[3] – and five older RCTs that were previously excluded because they report CVD as an adverse event rather than as a prespecified outcome.

The review authors discuss the finding that while hormone therapy provides no protection against CVD overall, there may be benefit for survival and coronary heart disease (CHD) in the subgroup of postmenopausal women who start hormone therapy within 10 years of menopause (between 50 and 59 years).[2] They note that this finding should be considered in the context of increased risk of venous thromboembolism in this population and no reduction in overall mortality.

The concept that hormone therapy may reduce CVD in recently postmenopausal women but potentially increase CVD in older women has been called the 'timing hypothesis'.[4] The hypothesis arose from preclinical data showing reduced atherosclerosis when oestrogen was administered immediately after surgical menopause, but advancing disease when it was delayed following oophorectomy.[5] It is predicated on the assumption that menopause itself increases the risk of CVD, and this assumption is largely based on 40-year-old observations from the Framingham study.[6] However, other large cohort studies have not demonstrated that natural menopause increases the risk of CVD,[7] questioning the basis of the timing hypothesis. The concept of a 'critical window' has been extended to other purported benefits of hormone therapy, including reducing dementia, improving cognition, and preventing mood disorders.[8][9][10] However, supporting evidence is limited.

The Cochrane Review looked at oral hormone therapy, consisting of oestrogen alone or in combination with a progestogen, compared with either a placebo or a no-treatment control. Participants were postmenopausal women (with spontaneous or induced cessation of menstrual bleeding for a continuous period of six months or more), with or without evidence of existing CVD. To assess the impact of the timing of hormone therapy, the trials were stratified according to whether hormone therapy was started < 10 or ≥ 10 years after the menopause. If these data were not available, the mean age of participants at baseline (< 60 versus ≥ 60 years of age) was used as a surrogate. The review found that hormone therapy gave no overall benefit for prevention of primary or secondary CVD events and an increased incidence of stroke, pulmonary embolism, and venous thromboembolism.

Based on the hypothesis that early commencement of hormone therapy may show a different risk-benefit profile, and that women aged 50 to 59 years are most troubled by menopausal symptoms, the review authors present subgroup analyses of outcomes for younger postmenopausal women commencing hormone therapy. In this subpopulation, starting hormone therapy within 10 years of menopause was associated with a reduced risk of death and CHD. There was no increase in stroke in this age group, but venous thromboembolism was increased in hormone therapy users. The authors add that the benefit seen in survival and CHD for this group comes from combining five primary prevention trials with follow-up ranging from 3.4 to 10.1 years and with greater cardiovascular benefit associated with longer follow-up. Cardiovascular events show an early peak in a small population of hormone therapy users who then stop treatment,[11] so any potential cardiovascular benefit for other users would not be apparent without much longer follow-up. The review confirms that it is not possible to comment whether short-duration hormone therapy confers cardiovascular benefits in younger postmenopausal women, only that hormone therapy taken for between 3.4 to 10.1 years may be beneficial.

Cardiovascular events are uncommon in women aged 50 to 59 years. To measure the risk of CVD or CHD in this age group the review authors needed to pool data from trials using different oestrogens and progestogens and different doses and delivery systems, assuming a 'class effect' of hormone therapy. However, recent evidence suggests that the risk-benefit profile of hormone therapy differs depending on whether oestrogen is taken alone or in combination with a progestogen.[12] Also, in clinical practice the choice of oestrogen alone or in combination with progestogen will depend on whether endometrial protection is required. Most data informing the Cochrane Review come from the two large Women's Health Institute (WHI) trials, which have now reported for an extended post-intervention follow-up and have

stratification by age.[12] Outcomes after a median of 13 years of cumulative follow-up show marked differences in the risk-benefit profile for combined therapy compared with oestrogen alone. The WHI 'global index' of risks and benefits included multiple outcomes (CHD, invasive breast cancer, stroke, pulmonary embolism, dementia in women aged ≥ 65 years, gallbladder disease, urinary incontinence, hip fractures, and diabetes), most of which dissipated after hormone therapy was stopped. However, for women using combined therapy the risk of breast cancer continued, whereas for oestrogen-only hormone therapy breast cancer risk reduced. Neither regimen affected all-cause mortality. The global index for women aged 50 to 59 years who had used oestrogen plus progestogen was 10 extra adverse events per 10,000 women-years (hazard ratio 1.08; 95% confidence interval 0.94 to 1.24), compared with 26 fewer adverse events for those taking oestrogen only (hazard ratio 0.82; 95% confidence interval 0.68 to 0.98). Of these, the 11 fewer cases of CHD per 10,000 women-years was statistically significant. The WHI studies, as with the Cochrane Review, included a caveat: the study participants took unopposed oestrogen for a median duration of < 6 years, and the results cannot be extrapolated to longer or shorter treatment durations. These findings emphasise the need to counsel women about hormone therapy based on their age and hysterectomy status and to consider changing risk profiles over the duration of treatment.[11]

In the Cochrane Review's 'Implications for research' section, the authors discuss the KEEPS and ELITE studies.[13][14][15] KEEPS (the Kronos Early Estrogen Prevention Study) was an RCT comparing daily oral or transdermal oestrogen, both with cyclic progesterone treatment, versus placebo. This is the only published study directly addressing the timing hypothesis. The study used surrogate endpoints for CVD, as clinical endpoints are rare in this younger population and would likely be unfeasible in terms of study size and follow-up duration. The primary endpoint was annual change in carotid artery intima–media thickness, and secondary endpoints included changes in markers of CVD risk. There was no change in the primary endpoint in women taking hormone therapy, and there were mixed findings for the secondary endpoints. The investigators concluded: "Four years of [menopausal hormone therapy] does not protect against progression of atherosclerosis."[16] Even if hormone therapy could reduce progression of early atherosclerosis it may still increase the risk of CHD events, perhaps due to effects on thrombosis and plaque rupture.[11]

Recent conclusions from the WHI cumulative follow-up studies state that "Even though hormone therapy is a reasonable option for the management of moderate to severe menopausal symptoms among generally healthy women during early menopause, the risks associated with hormone therapy, in conjunction with the multiple testing limitations attending subgroup analyses, preclude a recommendation in support of its use for disease prevention even among younger women."[12] This advice is consistent with international guidance on hormone therapy for prevention of CVD in women of any age, and the findings of this Cochrane Review do not provide sufficient evidence to change existing clinical recommendations for hormone therapy use.

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Declarations of interest

The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request) and declare that they have no conflicts of interest.

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