Is it time to revisit the recommendations for initiation of menopausal hormone therapy?

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Findings from the Women's Health Initiative studies led to menopausal hormone therapy (MHT) guidelines generally recommending the initiation of MHT be limited to women within 10 years of their menopause or before the age of 60 years. This recommendation has led to women who experience troublesome menopausal symptoms and who have not commenced MHT within these limits often being denied this type of therapy. Similarly, the majority of women who might benefit from the protective effects of MHT against bone loss and fracture are not offered this treatment option if they do not fit with these criteria. Based on review of the evidence that led to the conditional initiation of MHT, and subsequent studies, we propose that the recommendations regarding the initiation of MHT need to change to be more inclusive of women outside these chronological limits.

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With the widespread fear that menopausal hormone therapy (MHT) might cause breast cancer (instilled by the Women's Health Initiative [WHI] studies),[1,2] vast numbers of symptomatic women stopped or never tried MHT. Interpretation of the WHI findings also led to many guidelines recommending that MHT not be initiated beyond the age of 60 years or 10 years after menopause,[3] with the belief that initiation outside these limits might convey unacceptably greater risks of cardiovascular disease[4,5] and cognitive decline.[6,7] However, many women outside these limits have troublesome menopausal symptoms, with women experiencing natural menopause up to the age of 57 years.[8] The median overall duration of hot flushes and night sweats (ie, vasomotor symptoms) has been reported as about 7·4 years but 9–10 years for African American and Hispanic women, with about 40% of all women having vasomotor symptoms for at least 14 years.[9] Similarly, we found vasomotor symptoms affect 42% of women aged 60–65 years, being moderately-to-severely bothersome for 6·5% of women of this age,[8] and persist in approximately one-third of women aged 65–79 years.[10] With the average age of menopause increasing from 51 years in high-income countries,[11] the number of women with symptoms beyond 60 years of age might also increase.

With the increased awareness that not all MHT conveys the same risks, women older than 60 years who have not previously sought help because of fear of MHT-related side-effects might present for treatment of their vasomotor symptoms. We are also aware that younger women, more than 10 years after menopause, who were not previously offered MHT, are being denied MHT on the basis of years since menopause. In addition, MHT is a treatment option for the prevention of bone loss and fragility fracture, even when initiated many years beyond menopause.[1,12] This Viewpoint explores the evidence relating to the risks and benefits of initiating MHT after the age of 60 years, with the aim of stimulating discussion regarding the need to review current recommendations based on age or years since menopause.

The first WHI publication on hormone therapy, in 2002, reported an increased risk of breast cancer and adverse cardiovascular outcomes in women aged 50–79 years receiving combined MHT (conjugated equine oestrogen plus medroxyprogesterone acetate) versus placebo.[2] Vast numbers of women discontinued MHT, which fell further out of favour following early stoppage of the conjugated equine oestrogen-only trial 2 years later due to data suggesting an increased risk of stroke but no increase in breast cancer risk.[1] Subsequent stratified analyses by age group (50–59 years, 60–69 years, and 70–79 years) or years since menopause (<10 years, 10 to <20 years, or ≥20 years) suggested that conjugated equine oestrogen plus medroxyprogesterone acetate did not significantly increase the risk of heart disease in women aged 50–59 years or less than 10 years since menopause;[5] in addition, conjugated equine oestrogen conferred no increased risk of heart disease and a significantly lower risk of two secondary composite cardiac event outcomes.[4] There was also no significant increase in stroke risk in these two subgroups from conjugated equine oestrogen alone or conjugated equine oestrogen plus medroxyprogesterone acetate.[5]

These analyses led to the conditional recommendations for initiation of MHT. In 2012, the North American Menopause Society proposed that "systemic hormone therapy is an acceptable option for relatively young (up to age 59 [years] or within 10 years of menopause) and healthy women who are bothered by moderate to severe menopausal symptoms".[13] A year later, the International Menopause Society similarly stated, "benefits [of MHT] are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause".[14] Although both noted that the decision to use MHT was dependent on a benefit–risk analysis for each individual, specific guidance regarding MHT use in women older than 60 years (henceforth referred to as older women) or more than 10 years after menopause was not provided, nor was there a specific recommendation against its use.

As the limitations regarding MHT initiation pertained primarily to potential adverse effects on cardiovascular disease and cognition, we have focused on these outcomes. Notably, however, the WHI Studies found the

	Intervention phase		13-year cumulative follow-up	
	Hazard ratio (95% CI)	Rate difference, events per 10 000 person-years†	Hazard ratio (95% CI)	Rate difference, events per 10 000 person-years†
Conjugated equine oestrogen plus medroxyprogesterone acetate				
Coronary heart disease				
Age 60–69 years	1·01 (0·73–1·39)	NA	0·97 (0·79–1·18)	NA
Age 70–79 years	1·31 (0·93–1·84)	NA	1·17 (0·95–1·44)	NA
10 to <20 years since menopause	1·19 (0·83–1·7)	NA	Not provided	Not provided
≥20 years since menopause	1·52 (1·07–2·17)	26	Not provided	Not provided
Total myocardial infarction				
Age 60–69 years	1·05 (0·74–1·47)	NA	0·99 (0·80–1·24)	NA
Age 70–79 years	1·46 (1·00–2·15)	21	1·34 (1·05–1·72)	19
Stroke				
Age 60–69 years	1·45 (1·00–2·11)	11	1·16 (0·92–1·45)	NA
Age 70–79 years	1·22 (0·84–1·79)	NA	1·10 (0·87–1·38)	NA
10 to <20 years since menopause	1·23 (0·83–1·82)	NA	Not provided	Not provided
≥20 years since menopause	1·31 (0·88–1·96)	NA	Not provided	Not provided
Pulmonary embolism				
Age 60–69 years	1·69 (1·01–2·85)	8	1·14 (0·82–1·58)	NA
Age 70–79 years	2·54 (1·27–5·09)	18	1·52 (1·01–2·30)	10
10 to <20 years since menopause	2·02 (1·11–3·68)	10	Not provided	Not provided
≥20 years since menopause	2·33 (1·19–4·59)	16	Not provided	Not provided
Conjugated equine oestrogen alone				
Stroke				
Age 60–69 years	1·55 (1·10–2·16)	18	1·25 (0·97–1·60)	NA
Age 70–79 years	1·29 (0·90–1·86)	NA	1·12 (0·85–1·46)	NA
10 to <20 years since menopause	1·53 (0·96–2·44)	NA	Not provided	Not provided
≥20 years since menopause	1·21 (0·89–1·65)	NA	Not provided	Not provided

NA=not applicable (results not statistically significant). *Adapted from Manson and colleagues.[13] †Difference in estimated absolute excess risks (conjugated equine oestrogen plus medroxyprogesterone acetate or conjugated equine oestrogen alone minus placebo) where there is a significant increase in risk.

Table 1: **Women's Health Initiative study* findings for incident cardiovascular disease outcomes from menopausal hormone therapy**

global index of monitored events for combined MHT was not modified by age at initiation but was reportedly more favourable for women aged 50–59 years for conjugated equine oestrogen alone.[15] There was also no effect modification by age or time since menopause onset for cancer mortality in the WHI trials in the cumulative follow-up.[15]

The WHI clinical trials data do not support adverse MHT effects in older women for the primary outcomes of coronary heart disease (CHD), which included non-fatal myocardial infarction and CHD death. Specifically, there were no differences between either conjugated equine oestrogen plus medroxyprogesterone acetate or conjugated equine oestrogen alone versus placebo for women aged 60–69 years or 70–79 years during the intervention phase or at the 13-year cumulative follow-up (table 1).[15] Notably, a finding of significantly increased CHD risk for women aged 70–79 years in the intervention phase reported in an earlier age-stratified analysis[5] was no longer present in the 2013 analysis of updated intervention phase data.[15] Regarding years since menopause, a statistically significant increased risk of CHD was limited to the intervention phase for conjugated equine oestrogen plus medroxyprogesterone acetate initiated 20 years or more after menopause.[15] For the secondary endpoint of myocardial infarction, a marginally significant increase in risk during the intervention phase and in the 13-year cumulative follow-up was limited to those aged 70–79 years.[15] There was no increase in mortality from cardiac or vascular causes in older women taking conjugated equine oestrogen plus medroxyprogesterone acetate or conjugated equine oestrogen alone compared with placebo during the intervention or over the 18-year cumulative follow-up.[16] All-cause mortality was also not increased in either the intervention phase by age or time since menopause or at the 13-year[15] and 18-year[16] cumulative follow-ups.

The small, statistically significant increase in stroke risk during the intervention phases for women aged 60–69 years at random treatment assignment with conjugated equine oestrogen alone and conjugated equine oestrogen plus medroxyprogesterone acetate was no longer seen by the 13-year cumulative follow-up.[15] Stroke was not increased in women aged 70–79 years in these analyses in either treatment group.[15] There was no statistically significant effect on stroke according to time since menopause.[15]

The risk of venous thromboembolism, defined as a composite outcome of pulmonary embolism and deep vein thrombosis, was only reported for the WHI intervention phases. Compared with placebo, the incidence of venous thromboembolism was approximately double for women taking conjugated equine oestrogen plus medroxyprogesterone acetate in all age groups.[17] Venous thromboembolism risk also increased with age irrespective of treatment assignment.[17] For conjugated equine oestrogen only, the increased risk of venous thromboembolism in older women did not differ from results obtained with placebo, and the risk from taking conjugated equine oestrogen was not modified by age (p=0·99).[18] An increased pulmonary embolism risk was seen with conjugated equine oestrogen plus medroxyprogesterone acetate during the intervention phase if initiated from the age of 60 years or more than 10 years after menopause. However, women aged 50–59 years with no history of MHT use before random assignment to treatment groups had a similarly significantly increased pulmonary embolism risk.[15] The increased risk of pulmonary embolism only remained

significant for women initiating conjugated equine oestrogen plus medroxyprogesterone acetate from the age of 70 years by the 13-year cumulative follow-up.[15] Pulmonary embolism risk was not significantly increased by conjugated equine oestrogen alone for any age group or time since menopause during the intervention phase or 13-year follow-up analysis.[15]

Overall, WHI trials data suggest that initiation of oral MHT at age 60 years or older or more than 10 years after menopause does not increase CHD risk, cardiovascular mortality, or all-cause mortality. Although an increased risk of venous thromboembolism was reported for conjugated equine oestrogen plus medroxyprogesterone acetate, this increase was not meaningfully different to that seen for younger women. The increased risk of pulmonary embolism was limited to conjugated equine oestrogen plus medroxyprogesterone acetate and did not persist for women younger than 70 years in the 13-year analysis. An increased risk of stroke in women aged 60–69 years in both trials had also resolved at follow-up. The absolute risk of these outcomes varied between 8 and 26 more events per 10 000 women per year for those taking MHT versus those taking placebo. The Council for International Organizations of Medical Sciences recommendations regarding drug safety would classify the frequency of these adverse events as uncommon or rare.[19]

The potential for MHT to accelerate cognitive decline has been raised as a reason to avoid MHT in older women. The Women's Health Initiative Memory Study (WHIMS), a WHI substudy, found a two-fold increased risk of probable dementia in women aged 65 years and older randomly assigned to conjugated equine oestrogen plus medroxyprogesterone acetate compared with those assigned to placebo (table 2).[7] This increased risk equated to 23 extra cases per 10 000 women-years.[7] The incidence of mild cognitive impairment was not significantly different in those taking conjugated equine oestrogen plus medroxyprogesterone acetate and those taking placebo.[7] For conjugated equine oestrogen alone, there was no significant increase in the risks of probable dementia or mild cognitive impairment, compared with placebo.[20]

The reported two-fold probable risk of dementia reported for conjugated equine oestrogen plus medroxyprogesterone acetate in WHIMS[7] would be expected to translate to greater mortality from dementia over a decade later. However, at the cumulative 18-year follow-up, this combination was not associated with death from Alzheimer's disease or other dementias in older women.[16] Conjugated equine oestrogen alone was not associated with dementia-related death in women aged 60–69 years at random assignment to treatment group, but for those aged 70–79 years at assignment, the risk of death from Alzheimer's disease or other dementias was significantly reduced.[16]

An ancillary study to WHIMS, commenced 3 years after WHI treatment assignment, assessed the effect of conjugated equine oestrogen plus medroxyprogesterone acetate or conjugated equine oestrogen alone on comprehensive neuropsychological test performance in participants aged 65 years and older.[6,21] The mean follow-up period was 1·35 years, and only 40% completed the final assessment at 2 years. The only statistically significant finding was a greater rate of decline in one domain of the California Verbal Learning Test score over a mean follow-up of 1·35 years for conjugated equine oestrogen plus medroxyprogesterone acetate compared with placebo (score range 0–48, mean difference –0·52 units per year, SE 0·20; p=0·009).[6] For the 40% that completed all three visits over 2 years, this difference did not achieve statistical significance.[6] Conjugated equine oestrogen alone had no adverse effect on any cognitive test outcome.[21]

Systematic reviews and meta-analyses of clinical trials for the outcomes discussed have mostly combined different formulations and doses of oral MHT, and data from the WHI studies dominate the analyses due to their size.

Two systematic reviews, often interpreted as providing evidence regarding the timing of MHT initiation, combined data for women initiating MHT more than 10 years after menopause with data for women using MHT who had a mean age of 60 years or older at baseline and women who initiated MHT from the age of 60 years.[22,23] One of the reviews reported no increase in CHD or all-cause mortality in women commencing

	Hazard ratio (95% CI)	Rate difference, events per 10 000 person-years*
Conjugated equine oestrogen plus medroxyprogesterone acetate		
Probable dementia[7]		
Age ≥65 years	2·05 (1·21–3·48)	23
Mild cognitive impairment[7]		
Age ≥65 years	1·07 (0·74–1·55)	NA
Death from Alzheimer's disease or other dementias[16]		
Age 60–69 years	0·90 (0·67–1·22)	NA
Age 70–79 years	0·92 (0·73–1·17)	NA
Conjugated equine oestrogen alone		
Probable dementia[20]		
Age ≥65 years	1·49 (0·83–2·66)	NA
Mild cognitive impairment[20]		
Age ≥65 years	1·34 (0·95–1·89)	NA
Death from Alzheimer's disease or other dementias[16]		
Age 60–69 years	0·75 (0·51–1·09)	NA
Age 70–79 years	0·73 (0·54–0·98)	Not provided

NA=not applicable (results not statistically significant). *Difference in estimated absolute excess risks (conjugated equine oestrogen plus medroxyprogesterone acetate or conjugated equine oestrogen alone minus placebo) where there is a significant increase in risk.

Table 2: **Women's Health Initiative study findings for dementia-related outcomes from menopausal hormone therapy**

MHT more than 10 years after menopause, compared with placebo.[22] The risk of stroke was increased (relative risk [RR] 1·21, 95% CI 1·06–1·38), as well as the risk of venous thromboembolism, with the latter risk not differing by time since menopause (1·96, 1·37–2·80 for >10 years and 1·74, 1·11–2·73 for <10 years).[22] The other systematic review and meta-analysis comparing MHT with placebo reported no significant increase in risk of CHD or all-cause mortality and no increase in risk of myocardial infarction or death from cardiovascular disease in late users, defined as women using MHT who were older than 60 years or had initiated MHT more than 10 years after menopause.[23] Being a late user was associated with significantly increased stroke risk (summary estimate 1·17, 95% CI 1·01–1·37); an increased risk of venous thromboembolism was also limited to late users (1·79, 1·39–2·29).[23] This review did not include the age-stratified WHI venous thromboembolism data.

We did not identify systematic reviews or individual randomised controlled trials reporting dementia incidence in older women initiating other forms of MHT. Observational studies of dementia risk after starting MHT in later life have conflicting results, with findings that MHT either increases[24] or has no significant effect[25–28] on dementia risk in older women. A systematic review and meta-analysis of observational studies examining the effect of MHT on dementia risk associated with late-life use reported no significant difference in risk of dementia for users of oestrogen alone or oestrogen plus progestogen, compared with placebo, when stratified by formulation.[29]

A 2021 meta-analysis of randomised controlled trials examining the effect of MHT on cognition found a small but significant association between MHT and decreased global cognition (standardised mean difference –0·05, 95% CI –0·08 to –0·01) but no association with any specific cognitive domain in women older than 60 years.[30] This review only examined the effect of MHT overall, rather than presenting a stratified analysis for different formulations of MHT.

Transdermal hormone delivery bypasses first-pass hepatic metabolism and has a neutral effect on the production of coagulation factors.[31] To the best of our knowledge, randomised controlled trials of the effect of transdermal oestrogen or different types of progestogens on risk of cardiovascular disease, including stroke and venous thromboembolism, in older women are absent. In the WHI Observational Study, no significant differences in any of the cardiovascular disease outcomes were seen when directly comparing transdermal oestradiol with conjugated equine oestrogen.[32] Observational studies of women aged up to 64[33] years and 69 years[34] reported no increased risk of myocardial infarction with transdermal oestradiol with or without progestogen, compared with placebo.

The effects of transdermal oestradiol on stroke risk might be dose dependent. A large nested case–control study of women with a mean age of 70 years found transdermal oestradiol patches releasing 50 µg per day or less did not affect the risk of stroke, compared with no use, whereas an increased stroke risk was seen with oestradiol patches releasing more than 50 µg.[35] However, transdermal oestradiol appeared to convey less stroke risk than oral oestrogen in this study (RR 0·74, 95% CI 0·58–0·95).[35] In a nested case–control study of younger women, mean age 56 years, transdermal oestradiol was not associated with greater stroke risk, and there was no dose effect.[36] Risk of venous thromboembolism has not been found to increase with transdermal oestradiol in observational studies of women with a mean age above 60 years after adjustment for multiple confounders, including age, obesity, and smoking status.[37,38] Systematic reviews and meta-analyses of observational studies have found that transdermal oestradiol does not increase venous thromboembolism risk [39,40] Norpregnane-derived progestogens, but not other progestogens, have been associated with greater risk of venous thromboembolism (RR 2·42, 95% CI 1·84–3·18).[40] Position statements from 2020[41] and 2022[42] suggest that when considering MHT for older women, transdermal preparations and low-risk progestogens are preferred.

Although specific dose guidelines for initiating MHT in older women are scarce, the available data suggest that non-oral oestradiol offers the safest option, initiated at the lowest available dose.[3] Another important consideration is that in the WHI clinical trials, women were excluded if they had had an acute myocardial infarction or cerebrovascular event in the previous 6 months, a previous venous thromboembolism, a personal history of cancer, or life expectancy of less than 3 years.[2] Nonetheless, one-third of the participants had obesity, over one-third had either hypertension or treated hypertension, and 10% were current smokers.[2] Hence, the WHI clinical trial participants comprised a community-based sample, excluding women considered to be at the highest risk of an adverse health event. Therefore, regarding initiating MHT at any age, a full health assessment is required to evaluate each person's risk–benefit profile before MHT is prescribed.

The risk of a minimal trauma fracture increases with age, and in women in their mid-50s, this risk increases steadily, with up to one in two postmenopausal women reported to have an osteoporotic fracture in their remaining lifetime.[43,44] Bone-specific therapies are highly effective in preventing bone loss and fragility fracture. However, with the progressive increase in life expectancy, fracture prevention potentially needs to occur over decades following menopause. Ideally, these therapies should be instituted as late as possible to maximise the benefit and minimise the side-effects of their long-term use, such as atypical femoral fracture.[45] Although newer options are available, they are costly and less well studied. Oral MHT significantly protects against total fracture in individuals older than 60 years.[1,12,46] Transdermal MHT also increases bone mineral density and reduces bone turnover after menopause,[47–49] and, in large observational

studies, reduces fracture risk.[50,51] Denial of MHT based solely on age or years since menopause might leave many women who cannot tolerate or access bone-specific medications without effective therapy.

The WHI studies have provided the greatest body of information regarding MHT use in women from the age of 50 years. The initial findings were rapidly translated into clinical guidelines, notably in the context of conjugated equine oestrogen and medroxyprogesterone acetate being the most prescribed MHT in North America at that time. Review of these early findings, the comprehensive 13-year and 18-year follow-up studies, and other available data suggests that restricting the initiation of any MHT use to women younger than 60 years and within 10 years of menopause is overly cautious. Rather than this strong chronological focus, individual risk factors should be the primary consideration when discussing the benefits and risks of initiating MHT with each woman.

In this Viewpoint, we have not discussed breast cancer risk reported in the conjugated equine oestrogen plus medroxyprogesterone acetate WHI study as it was not meaningfully affected by age or years since menopause.[2] We also limited our discussion to recommendations regarding oestrogen and progestogen, as the prescribing of these hormones was our primary issue to consider. Although newer, non-hormonal treatments for vasomotor symptoms might be excellent alternatives, they might not be effective in all women, do not protect against fracture, and might be unavailable or too costly.

While acknowledging that no pharmacotherapy is without some risk, given the availability of safer MHT preparations, including transdermal and ultra-low dose oral oestradiol preparations, progesterone, and other progestogens, we propose that the recommendations regarding the initiation of MHT need to change.

Contributors

ST and SRD contributed equally to the content through discussion, literature review, and drafting and finalising the manuscript. Both authors have directly accessed and verified the underlying information included in this paper.

Declaration of interests

SRD has prepared and delivered educational presentations for Besins Healthcare, Abbott, and Mayne Pharma; has been on advisory boards for Theramex, Astellas, Abbott Laboratories, Mayne Pharma, and Gedeon Richter; and has received institutional grant funding from Ovoca Bio and Lawley Pharmaceuticals. ST declares no competing interests.

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