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REVIEW

What the Women's Health Initiative has taught us about menopausal hormone therapy

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Our understanding of the complex relationship between menopausal hormone therapy (MHT) and cardiovascular disease (CVD) risk has been informed by detailed analyses in the Women's Health Initiative (WHI), the largest randomized, placebo-controlled trial evaluating MHT in postmenopausal women. Although the WHI demonstrated increased risk of CVD events with MHT in the overall cohort, subsequent secondary analyses demonstrated that these risks were influenced by the woman's age and time since menopause, with lower absolute risks and hazard ratios for younger than older women. As MHT is the most effective treatment for the vasomotor symptoms of menopause, it is important to understand its risks and how to conduct risk stratification for symptomatic women. In addition to reviewing the WHI findings, studies pre- and post-WHI are reviewed to describe the relationship between MHT and CVD risk in menopausal women. The absolute risks of adverse cardiovascular events for MHT initiated in women close to menopause are low, and all-cause mortality effects are neutral or even favorable for younger menopausal women. The WHI has advanced and refined our understanding of the relationship between MHT and CVD risk. Although MHT should not be used for CVD prevention, absolute risks of CVD are low when MHT is started close to menopause in healthy women and hazard ratios tend to be lower for younger than older women. For women in early menopause and without contraindications to treatment, the benefits of MHT are likely to outweigh the risks when used for menopausal symptom management.

KEYWORDS

Acute Coronary Care, Cardiovascular Risk, Menopausal Hormone Therapy, timing hypothesis, Women's Heart Disease

1 | INTRODUCTION

The Women's Health Initiative (WHI) was a landmark randomized, placebo-controlled trial designed to evaluate the risks and benefits of menopausal hormone therapy (MHT), when used for chronic disease prevention, in healthy postmenopausal women age 50 to 79 years (mean age, 63 years).[1–3] In the pre-WHI era, MHT was widely prescribed for symptom management and increasingly for chronic disease prevention, in part because multiple observational studies had demonstrated reduced incidence of cardiovascular disease (CVD) in symptomatic menopausal women who initiated MHT in early menopause.[4–10] Results from the WHI startled the medical community after showing an increased risk of CVD events in postmenopausal women treated with conjugated equine estrogens (CEE) in combination with medroxyprogesterone acetate (MPA).[2] Subsequently, prescriptions for MHT in postmenopausal women fell sharply,[11] and knowledge and training of clinicians in the medical management of menopause became a lower priority.[12]

In the post-WHI era, researchers have attempted to reconcile the discrepancy in findings between the observational studies and the WHI while further elucidating the complex relationship between MHT and CVD risk. An important theory that has received attention is the "timing hypothesis," which posits that age and time since menopause influence the MHT and CVD relationship, such that the risks are lower in women closer to menopause onset than in those distant from the transition. Randomized controlled trials including the Kronos Early Estrogen and Prevention Study (KEEPS)[13,14] and the Early Versus Late Intervention Trial (ELITE)[15] have specifically evaluated

different formulations and routes of MHT and their influence on surrogate markers of CVD risk, with findings of neutral or favorable effects of MHT in younger, healthy women close to menopause. This review aims to summarize current knowledge about MHT and CVD risk as a result of the WHI trial and related studies.

2 | PRE-WHI ERA

Risk of CVD and associated mortality increases in women after menopause.[16,17] It has been hypothesized, based on animal, clinical, and observational studies, that hormonal changes related to menopause may contribute to this risk, and that treatment with estrogen may mitigate it. Nonhuman primate studies showed that starting hormone treatment at the time of oophorectomy led to reduced coronary artery atherosclerosis, although similar findings were not found when hormones were started 2 years (equivalent of several human years) after oophorectomy.[18] Furthermore, estrogens have been shown to improve various atherosclerosis risk factors,[19] such as increasing high-density lipoprotein cholesterol while decreasing low-density lipoprotein cholesterol.[7] Indeed, in human observational studies, MHT has been associated with reduced risk of CVD events. In the pre-WHI era, upwards of 40% of symptomatic postmenopausal women were treated with estrogen therapy,[11] in part because observational studies demonstrated reductions in incidence of CVD and of all-cause mortality in menopausal women using MHT for symptom relief.[4–10,20]

Pre-WHI data included 16 prospective cohort studies that evaluated the relationship between estrogen therapy and cardiovascular events (CVE). In what was considered a landmark study, Bush and colleagues followed a cohort of 2270 white women age 40 to 69 years at baseline for incident CVE.[20] Women treated with estrogen in this cohort were at a reduced risk of CVD-related deaths (relative risk [RR]: 0.34, 95% confidence interval [CI]: 0.12-0.81). Interestingly, the prevalence of CVD at baseline was actually higher in women who were treated with estrogen, which amplified the finding of reduced CVE in these women. In the Nurses' Health Study, nurses age 30 to 55 years were followed for CVE.[21] In this cohort, estrogen users had an RR of 0.5 (95% CI: 0.3-0.8) for CVE compared with non–estrogen users, a finding that persisted after controlling for other cardiovascular risk factors. In a similar study by Henderson and colleagues in 1991, a cohort of 8881 postmenopausal women with a median age of 73 years was followed for overall mortality.[22] In this cohort, mortality decreased with increasing duration of estrogen use. Similar results were found in prospective cohort studies conducted by the Kaiser Permanente Medical Program and the Leisure World Study. In contrast, the Framingham Heart Study reported an increased risk of CVE in postmenopausal women age 50 to 83 years treated with estrogen that was consistent across 3 age groups (50–59 years, 60–69 years, and 70–83 years).[23]

The majority of the pre-WHI-era observational studies showed a major benefit of MHT on CVE in symptomatic women on treatment, most of whom were within 2 to 3 years of menopause onset. However, no randomized controlled trials had vigorously evaluated the benefits and risks of MHT, which was the impetus behind the large-scale WHI trial.

3 | THE WOMEN'S HEALTH INITIATIVE

The WHI trial was designed to evaluate the risks and benefits of MHT for the prevention of chronic diseases, including the effects on CVD and invasive breast cancer, in postmenopausal women. The WHI enrolled 27 347 postmenopausal women age 50 to 79 years recruited from 1993 to 1998 at 40 US clinical centers. The 16 608 women with an intact uterus were randomized to receive CEE (0.625 mg/d) + MPA (2.5 mg/d) or placebo, whereas 10 739 women with a prior hysterectomy were randomized to receive either CEE alone or placebo. Clinical cardiovascular outcomes, including coronary heart disease, myocardial infarction (MI), coronary artery bypass grafting or percutaneous coronary intervention, cardiovascular deaths, and all-cause mortality, were reported in the intervention phase and postintervention phases. The intervention phase of the trial was stopped early because of increased risks for the CEE + MPA arm after a median of 5.6 years (interquartile range [IQR], 4.8–6.5 years) and in the CEE-alone arm after a median of 7.2 years (IQR, 6.4–8.1 years) due to an increased risk of stroke. The CEE + MPA arm had a median postintervention follow-up of 8.2 years (IQR, 6.6–8.2 years) and the CEE-alone arm had a median postintervention follow-up of 6.6 years (IQR, 3.8–6.6 years). Follow-up studies have since characterized the effect of MHT on chronic disease progression, all-cause mortality, and cause-specific mortality.[24]

In contrast to the pre-WHI observational studies, WHI results indicated a small but significant increase in all CVE in women treated with MHT, both with CEE + MPA (hazard ratio [HR]: 1.13, 95% CI: 1.02-1.25, $P = 0.02$) or CEE alone (HR: 1.11, 95% CI: 1.01-1.22, $P = 0.03$) during the intervention phase of the trial.[25] Table 1 shows HRs for cardiovascular outcomes in the intervention and cumulative 13-year follow-up period. In the extended follow-up there was a small but significant increase in cardiovascular events in the CEE + MPA group only (CEE + MPA, HR: 1.08, 95% CI: 1.00-1.15, $P = 0.05$; CEE-only, HR: 1.06, 95% CI: 0.98-1.15, $P = 0.12$).[25] Although the increase in CVE was surprising, an important aspect of the WHI design may at least partially explain this finding. The average age of WHI participants was 63 years, which is significantly older than the average age of menopause in North America (51 years), and many were not symptomatic with vasomotor symptoms. In contrast, most observational studies showing benefit of MHT enrolled younger, symptomatic participants closer to onset of menopause. The overall WHI cohort, therefore, was not representative of the younger symptomatic women in the observational studies.

Stratifying the WHI cohort by age provides signals for trends supporting the theory that the timing of MHT initiation may influence CVE risk. This “timing hypothesis” was first described based on nonhuman primate studies in the 1990s.[18] In the WHI, when stratified by age, there was a *reduction* in MI and all-cause mortality in women age 50 to 59 years treated with CEE alone, compared with the women age 70 to 79 years, who had trends toward increased risks. For CEE + MPA, a trend for MI risk was apparent by time since

TABLE 1 CV outcomes in the WHI hormone therapy trials during the intervention and extended follow-up phase

	CEE + MPA Arm					CEE-Only Arm				
	No. of Events (annualized %)					No. of Events (annualized %)				
	CEE + MPA, n = 8506	Placebo, n = 8102	Difference/ 10 000 PY	HR (95% CI)	*P* Value	CEE, n = 5310	Placebo, n = 5429	Difference/ 10 000 PY	HR (95% CI)	*P* Value
Intervention										
CHD	196 (0.41)	159 (0.35)	6	1.18 (0.95-1.45)	0.13	204 (0.55)	222 (0.58)	−3	0.94 (0.78-1.14)	0.53
Total MI	168 (0.35)	129 (0.29)	6	1.24 (0.98-1.56)	0.07	164 (0.44)	173 (0.45)	−1	0.97 (0.79-1.21)	0.81
CABG or PCI	198 (0.42)	200 (0.45)	−3	0.95 (0.78-1.16)	0.64	249 (0.68)	255 (0.67)	0	1.00 (0.83-1.19)	0.96
All CV events	786 (1.70)	663 (1.52)	19	1.13 (1.02-1.25)	0.02	877 (2.51)	813 (2.24)	27	1.11 (1.01-1.22)	0.03
CV deaths	79 (0.16)	70 (0.15)	1	1.05 (0.76-1.45)	0.77	109 (0.29)	112 (0.29)	0	1.00 (0.77-1.31)	0.98
All-cause mortality	250 (0.52)	238 (0.53)	−1	0.97 (0.81-1.16)	0.76	301 (0.80)	299 (0.77)	3	1.03 (0.88-1.21)	0.68
Extended follow-up										
CHD	487 (0.48)	430 (0.45)	3	1.09 (0.96-1.24)	0.19	487 (0.48)	430 (0.45)	3	0.94 (0.82-1.09)	0.43
Total MI	389 (0.39)	324 (0.34)	5	1.15 (0.99-1.34)	0.06	285 (0.47)	288 (0.47)	1	1.01 (0.86-1.19)	0.90
CABG or PCI	506 (0.50)	471 (0.50)	1	1.04 (0.92-1.18)	0.50	405 (0.68)	396 (0.65)	3	1.03 (0.90-1.19)	0.65
All CV events	1606 (1.70)	1446 (1.60)	10	1.08 (1.00-1.15)	0.05	1267 (2.30)	1227 (2.15)	15	1.06 (0.98-1.15)	0.12
CV deaths	293 (0.28)	286 (0.29)	−1	0.97 (0.83-1.14)	0.73	243 (0.39)	257 (0.41)	−1	0.97 (0.82-1.16)	0.75
All-cause mortality	1011 (0.98)	966 (0.99)	−1	0.99 (0.91-1.08)	0.87	403 (1.66)	426 (1.73)	−7	0.99 (0.90-1.10)	0.92

Abbreviations: CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease (defined as nonfatal MI and CHD death); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; PCI, percutaneous coronary intervention; PY, person-years; WHI, Women's Health Initiative. Data from Manson et al.[25]

menopause. Table 2 shows HRs for cardiovascular outcomes in the intervention and extended follow-up phases stratified by age group. For those age 50 to 59 years, there was a significant reduction in total MI in the intervention and extended follow-up phase in the CEE-alone arm. Coronary heart disease, coronary artery bypass grafting or percutaneous coronary intervention, and all-cause mortality showed similar trends during the intervention phase in the CEE-alone trial. The age-stratified data from the WHI provide support for the timing hypothesis, where risks associated with MHT are related to the time of initiation since menopause, such that risks of MHT are low in women <10 years from menopause and age <60 years, and higher for older women further from menopause.

Extended follow-up studies have also demonstrated lower risks of MHT in younger women (age 50–59 years). In the extended post-intervention follow-up of 13 years, women in the CEE-alone group who were younger (age 50–59 years) had better outcomes for MI (50–59 years, HR: 0.6, 95% CI: 0.39-0.91; 60–69 years, HR: 1.03, 95% CI: 0.82-1.31; 70–79 years, HR: 1.25, 95% CI: 0.95-1.65; $P = 0.007$), all-cause mortality (50–59 years, HR: 0.78, 95% CI: 0.59-1.03; 60–69 years, HR: 1.02, 95% CI: 0.87-1.19; 70–79 years, HR: 1.06, 95% CI: 0.90-1.24; $P = 0.1$), and the global index (50–59 years, HR: 0.82, 95% CI: 0.68-0.98; 60–69 years, HR: 1.03, 95% CI: 0.92-1.15; 70–79 years, HR: 1.10, 95% CI: 0.97-1.25; $P = 0.01$). In terms of absolute events per 10 000 person-years, women age 50 to 59 taking CEE alone had 11 fewer heart attacks, 11 fewer cases of heart disease, and 12 fewer deaths than similar-age women taking placebo. These significant reductions in events for younger women did not extend to women age 60 to 69, who had a neutral effect of CEE on these outcomes; nor to women age 70 to 79, who had a trend toward increased risk of these events. During the 18-year follow-up, results demonstrated no difference in long-term all-cause and cause-specific mortality in women treated with MHT vs placebo.[24] In fact, when compared with placebo, the use of oral CEE alone over 7 years was associated with a 26% lower risk of Alzheimer's disease or dementia mortality and a 45% reduction in breast cancer mortality over this long-term follow-up.

The increased risk of CVE demonstrated in the WHI had profound effects on clinical practice. Prescriptions for MHT declined sharply after the release of the WHI data,[11] and the use of MHT decreased by as much as 80%.[26,27] Subsequently, medical school and residency training in menopause management has also declined,[12,27] leading to a situation where many primary-care providers lack core competencies in the management of menopause and related symptoms. Mounting evidence since the WHI, as reviewed below, supports the timing hypothesis and has influenced the most recent menopause guidelines. However, it is important to emphasize that current guidelines do not endorse use of MHT for the express purpose of preventing CVD or other chronic diseases of aging.

4 | THE TIMING HYPOTHESIS: POST-WHI

In follow-up to the WHI subanalysis findings, 2 important clinical trials have been conducted to specifically evaluate the safety of MHT in early, healthy postmenopausal women: KEEPS[13,28] and ELITE.[15] Surrogate markers of CVD risk, such as measuring progression of atherosclerosis, are informative in clinical practice and were used in these trials to evaluate the effects of MHT on CVD risk. KEEPS was a 4-year randomized, placebo-controlled, double-blind prospective trial that aimed to evaluate effects of MHT on progression of atherosclerosis as measured by carotid intima-media thickness (CIMT) and coronary arterial calcification (CAC). From 9 US clinical centers, 727 healthy women age 42 to

TABLE 2 CV outcomes in the WHI hormone therapy trials during the intervention and extended follow-up phase according to age at randomization

	CEE + MPA Arm					CEE-Only Arm				
	No. of Events (annualized %)					No. of Events, (annualized %)				
	CEE + MPA, n = 8506	Placebo, n = 8102	Difference/ 10 000 PY	HR (95% CI)	*P* Value	CEE, n = 5310	Placebo, n = 5429	Difference/ 10 000 PY	HR (95% CI)	*P* Value
Intervention										
CHD					0.81					0.08
50–59 y	38 (0.23)	27 (0.17)	5	1.34 (0.82-2.19)		21 (0.17)	35 (0.28)	−11	0.60 (0.35-1.04)	
60–69 y	79 (0.37)	73 (0.37)	0	1.01 (0.73-1.39)		100 (0.61)	108 (0.63)	−3	0.95 (0.72-1.24)	
70–79 y	79 (0.82)	59 (0.63)	19	1.31 (0.93-1.84)		83 (0.97)	79 (0.90)	7	1.09 (0.80-1.49)	
Total MI					0.55					0.02
50–59 y	32 (0.19)	23 (0.15)	4	1.32 (0.77-2.25)		17 (0.14)	31 (0.25)	−11	0.55 (0.31-1.00)	
60–69 y	70 (0.33)	62 (0.31)	2	1.05 (0.74-1.47)		76 (0.46)	82 (0.48)	−2	0.95 (0.69-1.30)	
70–79 y	66 (0.69)	44 (0.47)	21	1.46 (1.00-2.15)		71 (0.83)	60 (0.69)	14	1.24 (0.88-1.75)	
CABG or PCI					0.67					0.06
50–59 y	34 (0.20)	32 (0.20)	0	1.03 (0.63-1.68)		29 (0.24)	51 (0.41)	−17	0.56 (0.35-0.88)	
60–69 y	92 (0.43)	103 (0.52)	−9	0.85 (0.64-1.13)		129 (0.79)	116 (0.69)	11	1.13 (0.88-1.46)	
70–79 y	72 (0.75)	65 (0.70)	5	1.08 (0.77-1.51)		91 (1.07)	88 (1.02)	5	1.07 (0.79-1.43)	
All-cause mortality					0.20					0.04
50–59 y	35 (0.21)	48 (0.31)	−10	0.67 (0.43-1.04)		35 (0.29)	50 (0.40)	−11	0.70 (0.46-1.09)	
60–69 y	111 (0.51)	94 (0.47)	5	1.07 (0.81-1.41)		130 (0.78)	134 (0.77)	0	1.01 (0.79-1.29)	
70–79 y	104 (1.06)	96 (1.02)	4	1.03 (0.78-1.36)		136 (1.55)	115 (1.29)	26	1.21 (0.95-1.56)	
Extended follow-up										
CHD					0.99					0.12
50–59 y	93 (0.26)	69 (0.21)	5	1.27 (0.93-1.74)		42 (0.21)	64 (0.32)	−11	0.65 (0.44-0.96)	
60–69 y	201 (0.44)	199 (0.46)	−2	0.97 (0.79-1.18)		183 (0.67)	188 (0.67)	0	1.00 (0.82-1.23)	
70–79 y	193 (0.98)	162 (0.84)	14	1.17 (0.95-1.44)		138 (1.03)	141 (1.03)	0	1.01 (0.80-1.28)	
Total MI					0.46					0.007
50–59 y	75 (0.21)	57 (0.17)	4	1.25 (0.88-1.76)		35 (0.17)	58 (0.29)	−11	0.60 (0.39-0.91)	
60–69 y	165 (0.36)	158 (0.36)	0	0.99 (0.8-1.24)		140 (0.52)	139 (0.49)	2	1.03 (0.82-1.31)	
70–79 y	149 (0.76)	109 (0.57)	19	1.34 (1.05-1.72)		110 (0.82)	91 (0.67)	16	1.25 (0.95-1.65)	
CABG or PCI					0.34					0.40
50–59 y	102 (0.29)	96 (0.29)	0	1.01 (0.76-1.34)		71 (0.36)	83 (0.42)	−6	0.83 (0.60-1.14)	
60–69 y	246 (0.54)	244 (0.57)	−3	0.98 (0.82-1.18)		212 (0.80)	192 (0.69)	10	1.12 (0.92-1.37)	
70–79 y	158 (0.81)	131 (0.69)	12	1.18 (0.94-1.49)		122 (0.93)	121 (0.90)	2	1.03 (0.80-1.33)	
All-cause mortality					0.23					0.10
50–59 y	141 (0.39)	149 (0.44)	−5	0.88 (0.70-1.11)		90 (0.45)	115 (0.56)	−12	0.78 (0.59-1.03)	
60–69 y	452 (0.97)	429 (0.97)	−1	0.99 (0.87-1.13)		301 (1.08)	308 (1.07)	1	1.02 (0.87-1.19)	
70–79 y	418 (2.07)	388 (1.97)	9	1.04 (0.91-1.20)		313 (2.26)	302 (2.15)	11	1.06 (0.90-1.24)	

Abbreviations: CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease (defined as nonfatal MI and CHD death); CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; MPA, medroxyprogesterone acetate; PCI, percutaneous coronary intervention; PY, person-years; WHI, Women's Health Initiative. *P* values for trend by age.

58 years (mean age, 52 years) who were within 3 years after menopause were recruited. The women were randomized into 3 arms, along with cyclical micronized progesterone: oral CEE (0.45 mg/d, a lower dose than used in the WHI), transdermal estradiol (50 μg/d), or placebo. There were no beneficial or deleterious effects of MHT on atherosclerosis progression assessed by CIMT or CAC. In addition, neither CEE nor transdermal estradiol affected systolic or diastolic blood pressure, unlike the WHI, which found increases in blood-pressure levels with the higher-dose oral CEE. Oral CEE in KEEPS, but not transdermal estrogen, was also associated with a favorable change in lipid profile. Participants receiving oral CEE experienced an increase in high-density lipoprotein cholesterol ("good" cholesterol) and a decrease in low-density lipoprotein cholesterol ("bad" cholesterol); however, they also experienced an increase in triglycerides. Transdermal estrogen had a neutral effect on these biomarkers. As expected, there were improvements in vasomotor symptoms, sexual function, mood, and bone

density with MHT vs placebo, and no significant differences were seen in adverse events, including breast cancer, MI, transient ischemic attack, stroke, or venous thromboembolism (although numbers of clinical events were small).

The ELITE study was designed specifically to test the timing hypothesis, by comparing women early in menopause (<6 years past menopause) treated with MHT and older women (≥10 years past menopause) started on MHT.[15,29] The randomized, double-blind, placebo-controlled trial used a 2 × 2 factorial design to evaluate oral MHT effects on subclinical atherosclerosis by measuring CIMT every 6 months and cardiac computed tomography. Six hundred forty-three healthy postmenopausal women who were without CVD at baseline were randomized to oral estradiol (1 mg/d 17 β-estradiol, plus progesterone 45 mg vaginal gel once daily for 10 days of each 30-day cycle for women with a uterus) vs placebo for 6 to 7 years. CIMT progression from the effect of estradiol (with or without progesterone) differed between the early and late postmenopausal groups (P = 0.007 for the interaction) after a median of 5 years. For women ≥10 years past menopause, the rate of progression of atherosclerosis by CIMT was similar in the estradiol and placebo groups (0.0100 and 0.0088 mm per year, respectively; P = 0.29). In keeping with the timing hypothesis, for the group of women closer to menopause (<6 years), mean CIMT progression was slower for women on MHT compared with placebo (0.0044 mm/y vs 0.0078 mm/y; P = 0.008). Differences were not seen for CAC, total stenosis, and plaque as measured by computed tomography between the estradiol and placebo group in either postmenopausal stratum.

Additional studies since the WHI have also supported the timing hypothesis. For example, the Danish Osteoporosis Prevention Study (DOPS) randomized recently postmenopausal women to hormone treatment or placebo to evaluate osteoporosis, but also looked at cardiovascular risks and events. After 10 years, women receiving hormonal treatments had a significantly reduced risk (HR: 0.48, 95% CI: 0.26-0.87, P = 0.015) of cardiovascular events such as heart failure and MI with no increased risk of venous thromboembolism, cancer, or stroke.[30] In subgroup analysis of women closer to menopause (age 50–59 years), cardiovascular events were fewer in the treated groups compared with placebo.

These post-WHI studies lend further support to the safety of MHT in healthy women early in menopause and have influenced recent menopause guidelines, including the 2017 hormone therapy position statement of North American Menopause Society (NAMS).[31] This guideline moves away from the post-WHI recommendation to "use the smallest dose possible for the shortest period of time" to using the type, dose, and duration of MHT that is appropriate and individualized to symptomatic women in menopause. The NAMS guideline states, "For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is most favorable for treatment of bothersome [vasomotor symptoms] and for those at elevated risk for bone loss or fracture."

Despite the fact that the risks of MHT in young, early menopausal women are now more clear, women are still not being treated for their menopausal symptoms. Many women feel that their clinicians do not recognize the impact of menopause symptoms on quality of life and also report reluctance of clinicians to prescribe MHT.[32] This is not surprising, considering that both internal medicine and obstetrics and gynecology residents acknowledge a low comfort level with managing menopause symptoms and have limited training opportunities in this area.[12,33,34] Fortunately, more recent analyses from MHT trials have somewhat increased clinicians' comfort with prescribing MHT.[35] As the number of postmenopausal women in the United States is increasing and expected to exceed 50 million by the year 2020, most of whom will experience menopausal symptoms, and the direct and indirect healthcare costs associated with untreated vasomotor symptoms is estimated at nearly $400 million annually,[36] it is critically important that clinicians responsible for the primary care of women re-engage in menopause management.

5 | CONCLUSION

The WHI was the largest trial to date to evaluate the effects of MHT and has significantly informed our understanding of 2 formulations of MHT (CEE alone and CEE + MPA). Understanding the design of the WHI, including the type of hormones used, as well as the fact that the average age of women was 63 at enrollment, helps to clarify the basis for discrepancies between findings from basic science and observational studies prior and subsequent to the WHI, specifically related to the cardiovascular safety profile of MHT and the timing hypothesis. WHI subanalysis, along with KEEPS and ELITE findings, indicate that MHT is low risk for symptomatic women in early menopause and is likely to have a favorable benefit–risk profile for women without contraindications. MHT is effective at reducing symptoms of menopause and improving quality of life, and it is important for women to share in decision-making about their symptom management. It is time now to get menopause management back on track by assuring practicing clinicians and trainees are equipped with current evidence regarding menopause management and available treatment options.

Conflicts of interest

The authors declare no potential conflicts of interest.

REFERENCES

1. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. *Control Clin Trials*. 1998;19:61–109.
2. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–333.
3. Anderson GL, Limacher M, Assaf AR, et al; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–1712.
4. Barrett-Connor E, Bush TL. Estrogen and coronary heart disease in women. *JAMA*. 1991;265:1861–1867.
5. Bush TL, Barrett-Connor E. Noncontraceptive estrogen use and cardiovascular disease. *Epidemiol Rev*. 1985;7:89–104.

6. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med*. 1991;20:47–63.
7. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial [published correction appears in *JAMA*. 1995;274:1676]. *JAMA*. 1995;273:199–208.
8. Grodstein F, Manson GE, Colditz GA. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med*. 2000;133:933–941.
9. Wolf PH, Madans JH, Finucane FF, et al. Reduction of cardiovascular disease–related mortality among postmenopausal women who use hormones: evidence from a national cohort. *Am J Obstet Gynecol*. 1991;164:489–494.
10. Speroff L. Postmenopausal hormone therapy and primary prevention of cardiovascular disease—Nurses' Health Study 20-year follow-up. *Maturitas*. 2001;38:221–224.
11. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA*. 2004;291:47–53.
12. Hsieh E, Nunez-Smith M, Henrich JB. Needs and priorities in women's health training: perspectives from an internal medicine residency program. *J Womens Health (Larchmt)*. 2013;22:667–672.
13. Harman SM, Black DM, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women. *Ann Intern Med*. 2014;161:249–260.
14. Santoro N, Allshouse A, Neal-Perry G, et al. Longitudinal changes in menopausal symptoms comparing women randomized to low-dose oral conjugated estrogens or transdermal estradiol plus micronized progesterone versus placebo: the Kronos Early Estrogen Prevention Strategy. *Menopause*. 2017;24:238–246.
15. Hodis HN, Mack WJ, Henderson VW, et al; ELITE Research Group. Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med*. 2016;374:1221–1231.
16. Moreau KL, Hildreth KL, Meditz AL, et al. Endothelial function is impaired across the stages of the menopause transition in healthy women. *J Clin Endocrinol Metab*. 2012;97:4692–4700.
17. Rossi R, Grimaldi T, Origliani G, et al. Menopause and cardiovascular risk. *Pathophysiol Haemost Thromb*. 2002;32:325–328.
18. Clarkson TB, Prichard RW, Morgan TM, et al. Remodeling of coronary arteries in human and nonhuman primates. *JAMA*. 1994;271:289–294.
19. Hodis HN, Mack WJ, Lobo RA, et al; Estrogen in the Prevention of Atherosclerosis Trial Research Group. Estrogen in the prevention of atherosclerosis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 2001;135:939–953.
20. Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation*. 1987;75:1102–1109.
21. Stampfer MJ, Willett WC, Colditz GA, et al. A prospective study of postmenopausal estrogen therapy and coronary heart disease. *N Engl J Med*. 1985;313:1044–1049.
22. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med*. 1991;151:75–78.
23. Wilson PW, Garrison RJ, Castelli WP. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: the Framingham Study. *N Engl J Med*. 1985;313:1038–1043.
24. 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;318:927–938.
25. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. *JAMA*. 2013;310:1353–1368.
26. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of symptoms of the menopause: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100:3975–4011.
27. Santen RJ, Stuenkel CA, Burger HG, et al. Competency in menopause management: whither goest the internist? *J Womens Health (Larchmt)*. 2014;23:281–285.
28. Miller VM, Black DM, Brinton EA, et al. Using basic science to design a clinical trial: baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). *J Cardiovasc Transl Res*. 2009;2:228–239.
29. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. *Menopause*. 2015;22:391–401.
30. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ*. 2012;345:e6409.
31. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017;24:728–753.
32. Cumming GP, Currie H, Morris E, et al. The need to do better—are we still letting our patients down and at what cost? *Post Reprod Health. 2015;12*;21:56–62.
33. Christianson MS, Washington CI, Stewart KI, et al. Effectiveness of a 2-year menopause medicine curriculum for obstetrics and gynecology residents. *Menopause*. 2016;23:275–279.
34. Hess R, Chang CC, Conigliaro J, et al. Understanding physicians' attitudes towards hormone therapy. *Womens Health Issues*. 2005;15:31–38.
35. Taylor HS, Kagan R, Altomare CJ, et al. Knowledge of clinical trials regarding hormone therapy and likelihood of prescribing hormone therapy. *Menopause*. 2017;24:27–34.
36. Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause*. 2015;22:260–266.

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