Cardiovascular Risk in Climacteric Women: When to Begin the Hormone Treatment?

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16.1 Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide. More people die of CVD than of any other causes.

In both sexes and at any age, the risk of developing a cardiovascular disease is influenced by numerous factors, such as plasma concentration of lipids and lipoproteins,

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R. D. Brinton et al. (eds.), *Sex Steroids' Effects on Brain, Heart and Vessels*, ISGE Series, https://doi.org/10.1007/978-3-030-11355-1_16

uric acid and fibrinogen, carbohydrate intolerance or diabetes mellitus, obesity, hypertension, family history, and habits such as smoking and a sedentary lifestyle.

In women, postmenopause further increases the relative risk of a cardiovascular disease.

Prevention is achieved through an early reduction in risk factors and changes in lifestyle, weight, and blood pressure. With this end in view, it is essential that gynecologists and cardiologists work together as a team [1].

Addressing the menopausal woman's cardiovascular health, JoAnn Manson [2] stressed the need for personalized medicine to allow the identification of appropriate candidates for menopausal hormone therapy (MHT).

She maintained that biological and/or clinical characteristics could modify the response to MHT and, therefore, that some women are more suitable candidates than others to receive the treatment. Hence, it is important to personalize the optimal dose, the formula, and the administration route. In addition, it is essential to determine the MHT effects on the cardiovascular disease early on, assess whether there is a particular group of women whose risk of CVD may increase or diminish with therapy, and clarify the differences between the research protocols according to the MHT administration route in relation to the cardiovascular system.

16.2 Basic Research Work

In their basic investigation using animal models with Monas, Clarkson et al. [3] demonstrated, as shown in Fig. 16.1, the effect of estrogens on coronary artery disease according to time of MHT initiation.

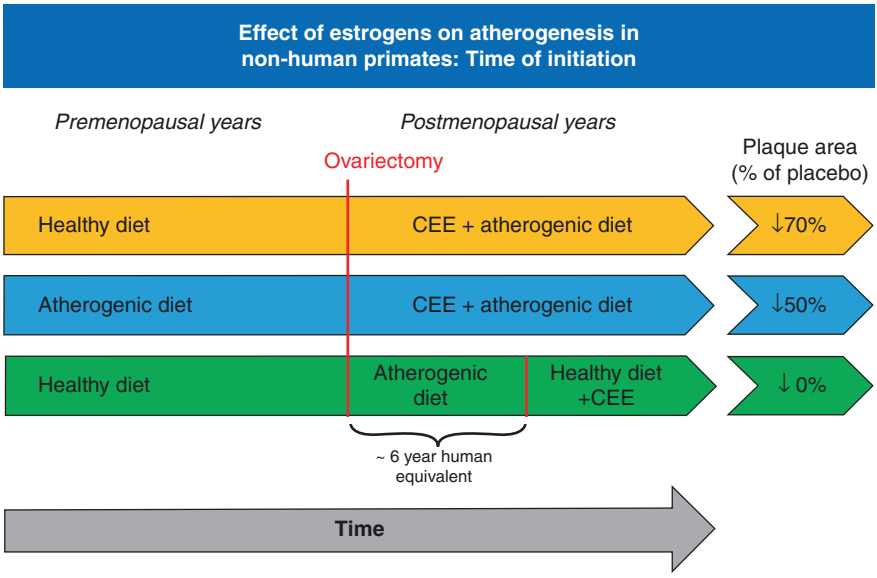


Fig. 16.1 Cardiovascular and metabolic risks and benefits. Adapted from Clarkson TB. *Menopause*. 2013 Mar;20(3):342–53

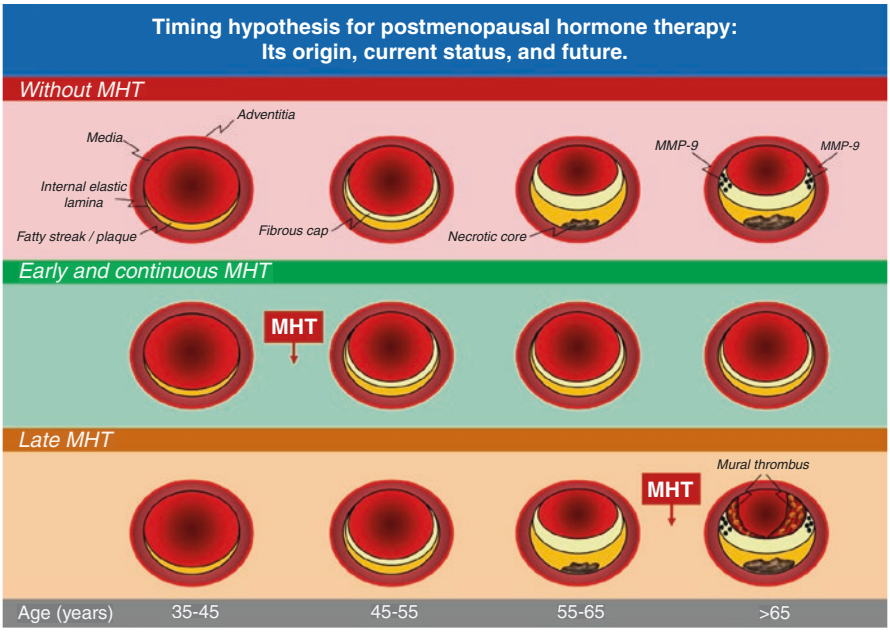


Fig. 16.2 Timing hypothesis for postmenopausal hormone therapy: its origin, current status, and future

The findings indicate the importance of initiating MHT immediately after menopause to allow for the removal of atheromatous plaques from a larger area.

In these animal models, according to the graph in Fig. 16.2, it can be seen that if MHT is undergone early on and continuously, the atheromatous plaques do not increase, whereas if the treatment initiates later on, progression is not only unhindered, but it also has a harmful effect. This is essentially due to estrogen-induced enzyme stimulation of matrix metalloproteases, which destabilizes the plaques and, therefore, poses a risk of embolism and its consequences (Fig. 16.2).

Mendelsohn et al. [4] reported the effect of estrogens (E2) on arteries in early menopause in comparison with late menopause as can be seen in Fig. 16.3.

It is clearly demonstrated that, in early menopause, estrogens produce an increase in vasodilation, a reduction in inflammatory factors, and a slowdown in the progression of the atherosclerotic lesion. On the other hand, in late menopause, estrogens can be seen to have the reverse effect, that is, a decrease in vasodilation, an increase in inflammatory factors, and greater instability in the atherosclerotic plaques (Fig. 16.3).

16.3 Clinical Trials

What do randomized controlled clinical trials, such as the Women's Health Initiative (WHI), show us?

In WHI, 64% of the enrolled women were older adults with more than 10 years of menopause. Furthermore, over 36% were hypertensive, 50% had been smokers, and most were obese, all of which features are risk factors for CVD [5].

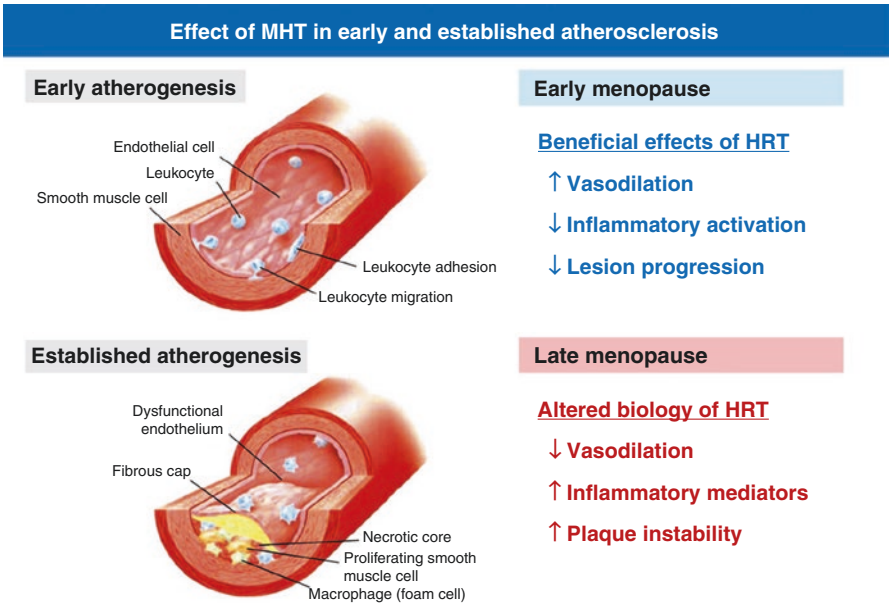


Fig. 16.3 Effect of MHT in early and established atherosclerosis

This is the reason WHI is not an ideal study for assessing MHT and primary prevention of CVD.

Contrariwise, observational studies, such as the cohort study of nurses [6], and randomized clinical studies, such as KEEPS [7] and ELITE [8, 9], recruited younger women with a healthier and more intact vascular endothelium, more favorably responsive to estrogen action.

Among the randomized controlled clinical trials of *secondary prevention of CVD and MHT*, that is, studies including patients with a history of CVD, we found HERS [10] and ERA [11]; we should also include WHI [5]. Though the latter was initially considered a study of primary prevention, in fact, it should not have been, given the aforementioned characteristics of its population.

Among the randomized controlled clinical trials of *primary prevention of CVD and MHT*, we found KEEPS [7], ELITE [8], and the DANISH STUDY [12]. We also included the observational cohort study of nurses in this group [6].

Taylor and Manson suggested a complex interplay of vasomotor symptoms, MHT, and cardiovascular risk [13].

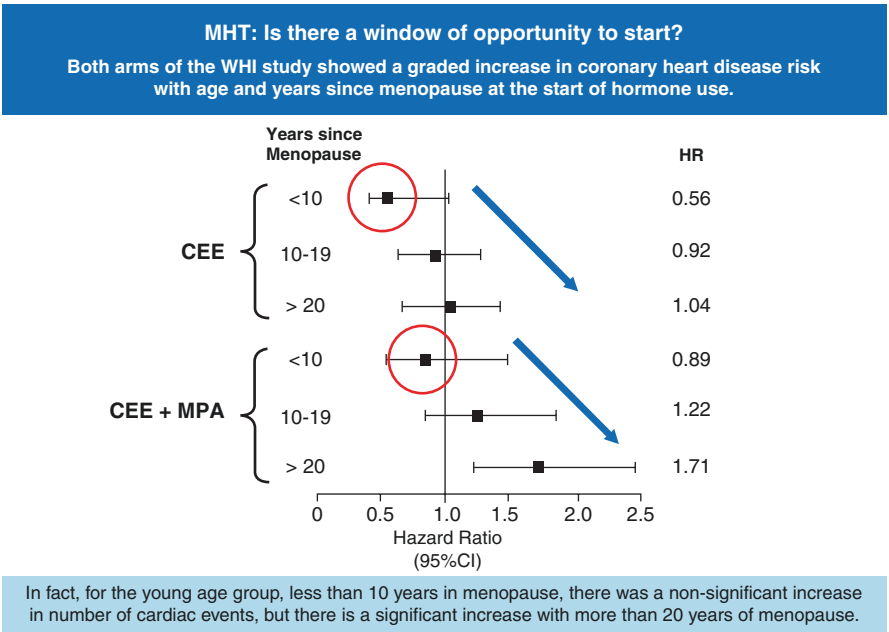
The results of the stratified secondary analysis of WHI show that conjugated equine estrogens (CEE) alone may be associated with a diminished risk of CVD in women in the 50–59 age range.

In Table 16.1 and in Graph 16.1, Rossouw et al. [14] point out the risks as well as the metabolic and cardiovascular benefits of MHT according to age and time since menopause.

Table 16.1 Cardiovascular and metabolic risks and benefits

CHD events by age and time since menopause in the WHI studies		
	CEE	CEE/MPA
	RR (Cl)	RR (Cl)
Age (year)		
50–59	0.63 (0.36–1.09)	1.29 (0.79–2.12)
60–69	0.94 (0.71–1.24)	1.03 (0.74–1.43)
70–79	1.13 (0.82–1.54)	1.48 (104–2.11)
p value for trend	0.12	0.70
Time since menopause (year)		
<10	0.48 (0.20–1.17)	0.88 (0.54–1.43)
10–19	0.96 (0.64–1.44)	1.23 (0.85–1.77)
≥20	1.12 (0.86–1.46)	1.66 (1.14–2.41)
p value for trend	0.15	0.05

Adapted from Rossouw JE, et al. *JAMA*. 2008;299:1426



Graph 16.1 Effect of estrogens on atherogenesis in non-human primates: time of initiation

It can be seen that women did not have an increase in cardiovascular risk if MHT was initiated within 10 years of menopause and if they were under 60 years of age (RR 0.48 [CI 0.20–1.17] for CEE and RR 0.88 [CI 0.54–1.43] for CEE and medroxyprogesterone acetate [MPA]).

Santen et al. [15] at a wide-ranging consensus with the participation of endocrinologists, gynecologists, basic and clinical researchers, etc. concluded that basic

sciences, animal models, and observational studies support the hypothesis that MHT prevents atherosclerosis and reduces coronary events. Additionally, the analysis of subgroups suggests that the little benefit or the small increase in risk seen in CVDs in the WHI is the result of MHT use by elderly women or postmenopausal women.

A group of researchers of the WHI study [16], most of whom were epidemiologists, wanted to determine whether the effects of CEE, used alone by a group of female volunteers with a previous hysterectomy, would remain after the end of the treatment. To this end, they obtained a written statement of informed consent from 7645 women who had received CEE or placebo and followed them up until August 2009 (totaling 75 months), which means an analysis spanning 10.7 years of follow-up.

The age-stratified results are of considerable interest. The cohort was divided into three age groups: 50–59, 60–69, and 70–79 years. It should be emphasized that taking CEE is much more favorable to younger than to older women. For the former, with the exception of those taking placebo, it meant fewer CVDs and acute myocardial infarctions (AMI), fewer breast cancers, fewer mortalities, and fewer events contributing to the global index of chronic diseases. These data, when translated into absolute numbers, indicate that for every 10,000 women under 60 receiving CEE, there is an expected fallout of 12 AMIs, 13 deaths, and 18 events lowering the global index.

In 2012, Hodis et al. [17] published a study emphasizing the hypothesis that there is a time for preventing coronary disease with HT and they reached the conclusion that an early rather than a later prescription conditions the beneficial effects of HT. They further stressed that to maximize the beneficial effects of MHT on CVD and minimize risks, treatment should start during the "*window of opportunity*," that is, before age 60 and/or with less than 10 years of menopause and continue for 6 years or more.

16.4 Clinical Trials in Primary Prevention of CVD

The recent randomized controlled clinical trials in primary prevention are the following:

1. *ELITE* (Early vs. Late Intervention Trial with Estradiol) [8]
2. *KEEPS* (Kronos Early Estrogen Prevention Study) [7]
3. *DOPS* (Danish Osteoporosis Prevention Study) [12]

16.4.1 ELITE (Early vs. Late Intervention Trial with Estradiol) [8]

The ELITE study, whose chief researcher was Howard Hodis, enrolled 643 women. The inclusion criteria and the design were as follows:

- Women <6 or >10 years since menopause
- Serum estradiol <25 pg/ml
- Amenorrhea >6 months
- Oral estradiol (1 mg/day) or placebo with 4% vaginal progesterone gel or placebo for 10 days/month
- Assessment of the carotid intima-media thickness and of coronary calcification

The hypothesis being tested was whether 17β-estradiol could reduce atherosclerosis progression with therapy initiating in the immediate postmenopausal period when the endothelium is still healthy as opposed to a later initiation when the endothelium is unresponsive. Ultrasonography enables the measurement of the changes taking place in carotid thickness, and cardiac computed tomography (CCT) quantifies coronary artery calcium and arterial lesions.

The ELITE was specifically designed to test the hypothesis of "time of initiation" of MHT in relation to atherosclerotic progression and cognitive changes in postmenopause. It was a double-blind, placebo-controlled study in which women were randomized according to their time of menopause (<6 years, n = 271 or >10 years, n = 370) prior to enrollment in the study. The first results with respect to atherosclerosis pertained to the progression of the carotid intima-media thickness following 5–6 years of 1 mg/day of oral 17β-estradiol with or without 4% vaginal progesterone gel in contrast with placebo.

The second results relative to atherosclerosis included the CCT scans with or without contrast enhancement taken of the participants who completed the study.

In 2016, the final results of the ELITE studies were published [9]. They emphasized that estradiol use was associated with a slower progression of subclinical atherosclerosis than placebo (measured as CIMT) when MHT started within 6 postmenopausal years, but not when it began 10 or more years after menopause.

Estradiol had no significant effect on atherosclerosis as measured by CCT in any of the groups of postmenopausal women.

The ELITE study provided evidence substantiating the hypothesis that multiple benefits are obtainable when MHT begins around the onset of menopause ("*time hypothesis*" or "*window of opportunity*") and that MHT does not increase the cardiovascular risk in healthy and recently menopausal women [9].

The authors maintain that further evidence is needed to support the relationship between MHT duration and cardiovascular events. They also stress that more studies of micronized natural progesterone and of synthetic progestins are necessary.

16.4.2 KEEPS (Kronos Early Estrogen Prevention Study) [7]

The KEEPS study is another study of primary prevention, whose working hypothesis was that there is a "*window of opportunity*" in early menopause for hormone therapy to have a cardioprotective effect.

The study had the following objectives:

- To determine the effects of MHT started by 737 recently menopausal women (mean age: 52 years) on atherosclerotic progression
- To compare the effects of CEE via the oral route (OR) and of E2 via the transdermal route (TD) with placebo in relation to risk factors for CVD and venous thromboembolism (VTE)
- To assess the safety of micronized natural progesterone

The KEEPS found that, in the treatment groups, neither the oral route nor the transdermal route affected arterial pressure in contrast with the high CEE doses

used in the WHI. The oral route was associated with an increase in HDL-chol and a decrease in LDL-chol, albeit with a rise in TG. The transdermal route was neutral relative to the biomarkers with the additional advantage that it improved sensitivity to insulin (insulin resistance decreased) as calculated by HOMA-IR [7].

During the 48 months of hormone replacement therapy (HRT) vs. placebo, there were no effects on atherosclerosis progression as measured by carotid ultrasound and there was a tendency toward diminished accumulation of coronary calcium as quantified by CCT.

The conclusion was that HRT with the doses used in the population of healthy recently menopausal women neither slows down nor speeds up atherosclerosis progression as assessed by imaging. The study showed the favorable effects of MHT in recently menopausal women. The need for individualizing decision-making with respect to MHT is stressed, given that the oral and the transdermal routes have different effects and different women have different symptom profiles and treatment priorities [7].

16.4.3 DOPS (Danish Osteoporosis Prevention Study) (Effect of Hormone Replacement Therapy on Cardiovascular Events in Recently Menopausal Women: Randomized Trial) [12]

The DOPS is a study of 1006 healthy recently menopausal women aged 45–58 years, 502 of whom received HRT. These were divided into two groups, as follows: Group 1, 2/1 mg of 17β E2 + 1 mg of norethisterone acetate (NETA), 10 days, and Group 2, 2 mg of E2/day (hysterectomized); and 504 comprised the control group.

The objective was to evaluate the long-term effect of MHT on CVD in recently menopausal women, and the endpoints were mortality, heart failure, and AMI.

This study is considered the first randomized controlled clinical trial of healthy women treated in immediate postmenopause with 17β E2 and NETA, and it is the only one with 10 years of randomized treatment. In addition, the women were followed up for 6 more years after the end of therapy [12].

The findings suggest that starting MHT in early menopause reduces the risk of a combined endpoint of mortality, AMI, and heart failure. Early initiation of MHT and its prolonged use did not increase the risk of breast cancer or cerebrovascular accident (CVA).

16.5 The International Menopause Society (IMS) Comments on the Danish Study [12]

Commenting on DOPS, Prof. Howard Hodis said it was the only randomized controlled study (RCT) designed for the long term and which included women close to menopause for the MHT. He added that it provided evidence that the preventive benefits surpassed the risks and that the study confirmed the data accumulated in the

last 50 years indicating that MHT reduces CVD and mortality when prescribed for women in immediate postmenopause.

He went on to say that the study produced additional evidence to contradict the concept that "a lower dose and for the shortest possible time" is preferable. This postulate, which never had a scientific basis, can keep women from obtaining the benefits associated with long-term use of MHT: a reduction in cardiovascular diseases, bone fractures, and total mortality [12].

Prof. John Stevenson remarked that the study, which had a 16-year follow-up, had no significant adverse events. This is evidence that MHT, when prescribed for women around the onset of menopause, in the long term produces consistent benefits as demonstrated by other studies. The importance of this study is its long duration, its initiation in early menopause, and its therapy individualization [12].

16.6 Consensus on MHT and CVD

In 2012, experts from the most representative societies related to menopause (the American Society for Reproductive Medicine, the Asia Pacific Menopause Federation, the Endocrine Society, the European Menopause and Andropause Society, the International Menopause Society, the International Osteoporosis Foundation, and the North American Menopause Society) got together and wrote a short and simple document about the points of consensus on MHT.

This Global Consensus Statement on Menopausal Hormone Therapy was published in specialty journals such as Maturitas [18] and the most important CVD-related points are the following:

- The RCT and observational studies, along with meta-analyses, show that estrogens, as those used in MHT, may reduce CVDs and the causes of mortality in women younger than 60 and with less than 10 years of menopause.
- The data on estrogens + progestogens in this population show a similar tendency, but some RCTs did not find a significant increase or decrease in CVDs.

In 2016, a revision of this consensus was published with the inclusion of FLASCYM (Federación Latinoamericana de Sociedades de Climaterio y Menopausia) [19] aiming to update and broaden the previous consensus points.

It corroborates MHT, including tibolone and the association of conjugated equine estrogens (CEEs) with a SERM (bazedoxifene), as the most effective therapy for treating vasomotor symptoms associated with menopause. However, the benefits outdo the risks when women start therapy before age 60 or with less than 10 years of menopause.

It emphasizes the difference between ET and combined MHT, the difference in risk of VTE and ischemic stroke between the oral and transdermal routes, and the fact that MHT should be individualized and its duration should be a function of treatment objectives and safety issues.

16.7 Final Considerations

- In the menopausal transition, the risk of a CVD increases.
- Hormonal changes increase the vulnerability of the cardiovascular system.
- The gynecologist is the primary care physician for:
  - Identifying the risk factors for CVD
  - Educating women to age in a healthy way
  - Treating or preventing the progression of emerging CVDs
- The MHT poses no danger to the cardiovascular system; on the contrary, if it is given to the right woman and at the right time, it may reduce the risk of CVD: the "*window of opportunity*" should be emphasized.
- Every woman is unique and has her own risk profile; thus, MHT should be tailored to her and her preferences, adjusting to the responses.
- If followed, these recommendations should lead to a better quality of life and increase the life expectancy of our patients.

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