



## Review

## EMAS position statement: Managing the menopause in the context of coronary heart disease

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## ABSTRACT

**Introduction:** Cardiovascular disease (CVD) including coronary heart disease (CHD) and stroke is the most common cause of female death. Premenopausal CHD is very rare but when women enter the menopause the incidence of CHD increases markedly. CHD presents 10 years later in women than in men. The reason is still unclear but the protective effects of estrogens have been suggested.

**Aims:** To formulate a position statement on the management of menopause women in the context of coronary heart disease.

**Materials and methods:** Literature review and consensus of expert opinion.

**Results and conclusions:** Based on long term randomized placebo-controlled studies hormone therapy (HT) is not recommended for the primary or secondary prevention of CHD in postmenopausal women. In most countries the only indication for HT is the treatment of menopausal symptoms. Women with known CHD or with many coronary risk factors seeking HT because of troublesome climacteric symptoms should be evaluated for their individual baseline risk of developing breast cancer, venous thromboembolism and CHD recurrence. The same applies to non hormone therapy-based treatments where long term clinical studies are lacking. Risks should be weighed against expected benefit from symptom relief and improved quality of life. The lowest effective estrogen dose should be used during the shortest possible time. Transdermal administration is preferred if risk factors for VTE exist. Different progestogens might differ in their cardiovascular effects. Observational studies suggest that micronized progesterone or dydrogesterone may have a better risk profile than other progestogens with regard to thrombotic risk.

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### 1. Introduction

CVD including CHD and stroke is the most common cause of female death [1]. Worldwide, except in Africa, death from CVD

is more common than death from cancer, HIV/AIDS, malaria and tuberculosis combined. CVD is a disease of older women as it presents 10 years later than in men. Women currently live longer than men but for the first time ever this gender difference is decreasing in many countries such as Canada and Sweden [1–3].

Women are still underrepresented, under-diagnosed and under researched in clinical trials as recently shown in European and American reviews from 2010 [4,5]. According to the World Heart Federation, cardiovascular disease is indisputably the most serious

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neglected health problem for women worldwide. The lack of awareness among women is especially serious in low or middle-income countries where public health policy has been almost exclusively focused on maternal and child health.

A possible reason may be that CHD has traditionally been perceived as a male illness despite the fact that it ends the lives of as many women as men. For example, the WHO and Monica studies did not include women over 64 years in the CHD statistics and therefore women were not visible [6]. Since 6 out of 10 deaths from CHD can be prevented, it is of utmost importance that there is a general awareness in both genders about the disease. The most important risk factors for developing CHD are dyslipidemia, hypertension, smoking, stress, diabetes, obesity (especially abdominal), physical inactivity and poor diet with insufficient fruit and vegetable intake and high intake of animal fat. The level of alcohol intake may also play a role [7–9]. Emerging risk factors for CHD are C-reactive protein, lipoprotein (a), homocysteine, leukocyte count, fasting blood glucose, coronary artery calcium score, carotid intima-media thickness and periodontal disease. Premature menopause [10], pre-eclampsia, gestational diabetes and gestational hypertension are other important female CHD-risk factors as well as polycystic ovarian syndrome and metabolic syndrome [11,12].

The role of female sex hormones on cardiovascular disease has been debated for decades and publications arising from large prospective, randomised placebo controlled clinical trials at the beginning of this millennium reduced prescriptions of systemic HT both in Europe and the USA. Today, most cardiologists tend to discontinue HT as soon as a woman has had a cardiac event irrespective of the indications: such as early menopause or control of severe climacteric symptoms. Various types of HT (estrogen alone versus combined with progestogen, oral versus transdermal administration) have different actions on the cardiovascular system, lipid metabolism and coagulation factors. However, in clinical practice a comprehensive risk-benefit evaluation is very seldom performed.

Treatment options for menopausal symptoms include the following [13,14]:

- Life style changes such as removing triggers for vasomotor symptoms (alcohol, caffeine), maintaining a healthy weight, smoking cessation, techniques, acupuncture, increased physical activity but the evidence base is limited.
- Estrogen-based hormone therapy: alone or combined with a progestogen.
- Nonhormonal prescription medication such as clonidine, paroxetine, venlafaxine, gabapentin, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), and vaginal lubricants and moisturizers.
- Nonprescription medications such as isoflavone supplements, soy products, black cohosh, vitamin E but the evidence base is limited.
- Tibolone is used for menopausal symptoms, but clinical data with hard end-points like morbidity and mortality are limited [15]. In women over 60 with osteoporosis it does not affect CHD risk but increases the risk of stroke [15].

Raloxifene has no effect on climacteric symptoms and no cardiac preventive effects as shown in the RUTH-study on 10,101 cardiovascular high risk women followed during 5.6 years [16]. In this position statement only estrogen either alone or combined with progestogens will be discussed. No evidence-based data on the effects on CHD of non-estrogen based therapies are currently available.

The aim of this position statement is to try to clarify the role of HT on CHD in menopausal women.

## 2. Hormone therapy (HT)

Reviews and consensus statements about HT and CHD have previously been discussed in the cardiology literature [17,18].

### 2.1. Primary prevention

Early observational studies such as the Nurses' Health Study [19] and a more recent Danish study [20] showed that HT reduced the risk of CVD.

The biological and physiological rationale for this was well documented in many studies but most were undertaken in animals. The anti-atherogenic, vessel-dilating and lipid-lowering effects of estrogen were also well established [21]. Furthermore the discovery of the different estrogen receptors, especially ER alpha and ER beta, lead to great hopes regarding the cardiovascular benefits of HT with clinical end points such as reduced risk of myocardial infarction [21].

This led to the randomized placebo-controlled Women's Health Initiative (WHI) study, which was initiated by the National Institutes of Health (NIH) in 1991. This was a large complex series of clinical research projects to examine strategies for the primary prevention and control of some of the most common causes of morbidity and mortality among healthy postmenopausal women aged 50–79 with a mean age of 63 years [22,23]. It consisted of a randomized controlled trial and an observational study. The randomized trial considered not only HT but also calcium and vitamin D supplementation and diets with low fat content. HT (unopposed and combined) was hypothesized to reduce the risk of CHD and other cardiovascular diseases and, secondarily, to reduce the risk of hip and other fractures, with increased risk of breast cancer being studied as a possible adverse outcome.

The randomized HT trial involved 10,739 women taking conjugated equine estrogens (0.625 mg) alone and 16,608 women taking conjugated equine estrogens (0.625 mg) in combination with medroxyprogesterone acetate (2.5 mg). Many of the women had never taken HT before. A global index was designed balancing risks and benefits to include CHD, breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death caused by other causes [22]. It was not designed to study the effects of HT in women with early ovarian failure before the age of 45 [10].

The combined WHI arm showed an early, albeit transient, increase in coronary events. Overall, there was no significant effect of HT. The excess absolute risk at 50–59 years was 5, 60–69 years 1, and 70–79 years 23 cases of nonfatal myocardial infarction and death due to coronary heart disease per 10,000 women per year [24].

The WHI used oral medroxyprogesterone acetate as the progestogen and there is little information about other progestogens with different routes of administration (transdermal, intrauterine) which may have different effects on lipids, glucose, insulin metabolism and coagulation [25]. Thus data from WHI cannot necessarily be extrapolated to other combined HT regimens.

In the estrogen-alone study a non-significant reduction in CHD was found, which was most marked in the younger (50–59 years) age group [26]. In this sub-group, there was a significant reduction in a composite of coronary events and procedures, and there were no significant increases in events in the older age groups. The reduced absolute risk at 50–59 years was 10, and at 60–69 years 5, with an excess risk of 4 cases in those aged 70–79 years per 10,000 women per year [26].

In an ancillary substudy of the estrogen alone arm computed tomography of the heart was undertaken in 1064 women aged 50–59 years at randomization. Imaging was then repeated at 28 of 40 centers after a mean of 7.4 years of treatment and 1.3 years after the trial was completed (8.7 years after randomization). Coronary-artery calcium (or Agatston) scores, which are a surrogate marker of CHD, were measured at a central reading center without knowledge of randomization status. The calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo [27].

In reanalyses it was observed that the increased risk of CHD occurred principally in older women and those many years beyond the menopause [24,28].

Thus no increased risk of CHD was seen in women between the ages of 50 and 59 years or in those within 10 years of menopause. The data provide reassurance regarding the cardiovascular safety of HT use for bothersome hot flushes and night sweats in otherwise healthy women at the time of the menopausal transition.

Subgroups of women defined by years since menopause in the WHI study were then analyzed. A cardioprotective effect of estrogen plus progestogen among women within 10 years of menopause was apparent only after 6 years of use. No suggestion of a decreased risk was found within the first 2 years including women who initiated therapy within 10 years after menopause. The so called therapeutic window for HT may therefore be questioned [29,30]. Prentice et al. [29] however urge caution in the interpretation of the analysis for several reasons: multiple testing issues, hazard ratios pertaining to 5 or more years from hormone therapy initiation were derived mainly from the observational study, few recently postmenopausal women without prior HT who were followed in WHI during their early years of hormone use, so corresponding hazard ratios were imprecisely estimated and may have depended on modeling assumptions [29].

In summary, overall the WHI-study showed no benefit for HT in the primary prevention of CHD. There are no data regarding other estrogens or progestogens and non-oral administration which could potentially have different effects on cardiovascular risk as has been observed for venous thromboembolism [31]. Findings of studies examining the effects of the timing of use of HT are awaited. The prospective, randomized, controlled trial Kronos Early Estrogen Replacement Study (KEEPS) is testing the hypothesis that HT when initiated early in menopause reduces progression of atherosclerosis [32]. The Early Versus Late Intervention Trial With Estradiol (ELITE) study is examining the effects of oral 17beta-estradiol on the progression of early (subclinical) atherosclerosis and cognitive decline in healthy postmenopausal women [33].

## 2.2. Secondary prevention

The role of HT on secondary prevention of CHD was intensively studied in the 1990s and the early part of this decade. Angiographic, surrogate markers (mostly lipids) and cohort studies such as the Nurses' Health study [34] suggested a role of estrogen in the secondary prevention of CHD [35–39]. Several randomised trials have now been undertaken using both oral and transdermal therapy and none have shown benefit. Most have been small [40–43].

The largest one (HERS), involving 2769 women, used conjugated equine estrogens and medroxyprogesterone acetate in the same dose as in the WHI studies [43]. After 4 years fatal or non fatal heart disease combined did not differ between the groups. However, like in many other studies, there was a 50% excess of coronary events in the HT group during the first treatment year suggesting early coronary harm. This effect was not evident in statin users. After 6.8 years, HT did not reduce risk of cardiovascular events in women with CHD [44]. So, this study failed to demonstrate any cardioprotective benefit of HT in elderly women with proven CHD.

Despite the paucity of data, symptomatic women with early ovarian failure who have had a coronary event may be denied HT leading to poor quality of life as well as increased risk of osteoporosis and dementia [10]. Benefits and risks need to be evaluated on an individual basis. The transdermal route may be preferred because of fewer effects on coagulation [31].

There are no data for secondary prevention with hard endpoints like morbidity and mortality with regard to tibolone [15]. For raloxifene there are no cardiac preventive effects as shown in the RUTH-study of 10, 101 cardiovascular high-risk women followed up for 5.6 years [16].

Observational studies suggest that micronized progesterone or hydroprogesterone may have a better risk profile than other progestogens with regard to thrombotic risk [45,46].

## 3. Summary recommendations

- Cardiovascular disease is the main cause of death in women. Postmenopausal status is associated with a higher prevalence of coronary heart disease.
- Randomized controlled trial data show that HT does not have a role in the primary prevention of CHD in women over 50, but most information is limited to conjugated equine estrogens and medroxyprogesterone acetate.
- HT does not have a role in the secondary prevention of CHD; but the number of patients involved in randomized controlled trials is small.
- The lowest effective estrogen dose should be used for menopausal symptoms (17beta-estradiol 0.5–1 mg orally daily, conjugated equine estrogen 0.3–0.625 mg daily orally, or 25–50 µg 17beta-estradiol transdermally).
- Transdermal HT should be the first choice in women either at increased risk of CHD or with pre-existing disease because of its lesser effects on coagulation.
- Regular follow up by a specialist service is recommended.

## Contributors

K S-G and MR prepared the initial draft which was circulated to all EMAS board members for comment and approval, production was coordinated by Margaret Rees.

## Competing interests

None declared.

## Provenance

EMAS position statement.

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