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EMAS position paper

## Climacteric medicine: European Menopause And Andropause Society (EMAS) statements on postmenopausal hormonal therapy<sup>☆</sup>

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### Abstract

Hormonal therapy (HT) is one of the most frequently prescribed drug regimens for women after the age of 50 years. HT has been developed progressively since the 1960s to provide estrogen to those women (a) who require relief of symptoms which have resulted from reduced circulating estrogen or (b) to act as an anti-resorptive agent to counteract the effect of the increased bone turnover which occurs with falling menopausal estrogen levels and which results in loss of bone mass leading to postmenopausal osteoporosis. However, a large number of women pass through the menopausal transition without experiencing distress as a result of the natural fall in estrogen hormone levels and since the introduction HT has been thought to be associated with a number of health benefits that have been tested in clinical trials but not substantiated. In women experiencing distressing climacteric symptoms double-blind randomised controlled clinical trials with a variety of HT regimens have shown that HT of any type provides symptom relief with no alternative treatment of similar effect. The dose and regimen of HT need to be individualised and in general the appropriate dose is dependent on the menopausal age. Women experiencing urogenital estrogen deficiency symptoms require long-term treatment which is most easily achieved with local estrogen. With the perspective provided by the most recent epidemiological findings not least from the estrogen only arm of the Women's Health Initiative Study (WHI) EMAS supports research activities generating HT with new compositions including lower doses and a wider range of progestins in order to positively affect the balance of clinical benefit and risk. Currently, however, individualized and appropriate prescription of the available HT products together with life-style management will sustain possibilities for beneficial effects on climacteric symptoms, quality of life and degenerative diseases after the menopause.

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*Abbreviations:* BMD, bone mineral density; DVT, deep venous thrombosis; CCHT, continuous combined (estrogen + progestogen) therapy; CHD, coronary heart disease; CEE, conjugated estrogens; EMEA, European Agency for the Evaluation of Medicinal Products; EPT, estrogen progestin therapy; ET, estrogen only treatment; FDA, US Food and Drug Administration; HERS, The Heart and Estrogen/Progestin Replacement Study; HT, hormonal therapy; MPA, medroxyprogesterone; NHSBSP, National Health Breast Screening Programme; NIH, The National Institute of Health; RCT, randomised placebo-controlled clinical trial; WHI, women's health initiative; WHIMS, The Women's Health Initiative Memory Study

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## 1. Introduction

Hormone therapy has been prescribed since the early 1960s and approved for estrogen deficiency symptoms and prevention of postmenopausal osteoporosis based on information derived from double blind randomised clinical trials. The exact mechanisms of actions by sex steroids are still not fully known, but several are well established and causally related to risks and benefits. As a result of many observational studies over the past forty years, HT has been thought to be associated with a number of health benefits that have been tested in clinical trials but not substantiated. In addition both observational studies and recent large clinical trials have provided information on the risks associated with HT use in postmenopausal women that must be weighed against the expected benefits in creating an overall picture of benefit and risk for the woman considering using HT. Taken the most recent finding from the estrogen only arm of the WHI study into consideration and since estrogens remain the most efficient and cheapest therapy to alleviate climacteric symptoms and prevent osteoporotic bone fractures, it essential to improve the current knowledge on risks, benefits and unsolved clinical issues

## 2. Statement on recent epidemiological findings

The Nurses' Health Study and other large-scale observational (HT) studies have suggested a primary protective effect for heart disease in the magnitude of 40–50%. Other case control and cohort studies have suggested a small, but significantly increased risk of breast cancer if postmenopausal hormones are used for more than 5 years. Several studies have noted a decreased incidence of colon cancer and preliminary data suggest that HT provides protection against dementia. Recently, however, the HT paradigm on the balance of benefit and harm has been affected by information from new epidemiological studies, which have brought the results of foregoing studies into question. As a consequence the US Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) through recent statements on the appropriate use of these products emphasis that the minimum, effective dose and the shortest duration should be used.

The EMAS considers the clinicians' main goal is to provide a safe and effective advice for the alleviation of the climacteric symptoms. This advice may include the use of drugs. Even if relative risks and benefits of drugs may appear to be impressive the more relevant absolute risks are generally less impressive since they put the effect in the context of the actual numbers of people affected. In addition the benefits and risks may or may not apply to a given individual or situation in clinical practice. As for HT there are no absolute indications and only few absolute contraindications. Now is the time to both on a European as well as on a global scale to re-appraise the risk/benefit associated with HT.

Observational studies have the advantages of being able to include large numbers of subjects and long-term follow-up, but the disadvantages of incomplete adjustment for confounding factors such as time trends, heterogeneity between users and non-users (*healthy user effect*) and imprecise information on HT dosage and type. The National Institutes of Health (NIH) established the WHI in 1993 as a randomised placebo-controlled clinical trial (RCT) to address the effect of HT in preventing the most common causes of death, disability and impaired quality-of-life in postmenopausal women. The WHI addressed the effect of HT on cardiovascular disease, cancer, and osteoporosis. It is a 15-year multi-million dollar endeavour, and one of the largest prevention studies of its kind. The WHI set out to examine the long-term effect of estrogen plus progestin therapy (EPT), on the prevention of heart disease and hip fractures, while monitoring for possible increases in risk for breast and colon cancer. The EPT regimen was given as continuous combined hormone therapy (CCHT) (0.625 mg CEE + 0.5 mg MPA) 16,000 women were randomised to the EPT regimen or placebo. A separate study of estrogen alone (ET) in women who had a hysterectomy was also established with random allocation of 11,000 women to ET (0.625 mg of CEE) or placebo. The publication of the EPT arm of the WHI in July 2002 after premature termination of the study and subsequent more detailed papers from WHI have led to increased uncertainty among health professionals and women over the role of HT. The reason for stopping the EPT arm of the trial was the combination of the risk of invasive breast cancer and the lack of the expected benefit with regard to cardiovascular disease prevention, which had been

suggested by observational studies. Using a global index the WHI investigators concluded that the risks exceeded the benefits of the combined regimen.

In February 2004 the NIH has also instructed the participants in the ET part of the WHI to stop taking their medication earlier than planned and to begin the follow-up phase of the study. The NIH has determined that the results would not likely change if the estrogen trial continued to its scheduled completion in 2005. Furthermore, enough data have been obtained to assess the overall risks and benefits of the use of estrogen in this trial. The report, to be published will include data collected through the end of February 2004 representing an average of nearly 7 years treatment.

RCT studies are widely acknowledged as the “gold standard” of clinical trials because they use the study design least affected by bias and therefore having the greatest objectivity. Therefore, the WHI study results have been widely accepted as valid without careful analysis on biological plausibility. However, since the first study results were published, EMAS has reconsidered the data and finds that the original reports on EPT raise many questions and concerns in relation to the study population, compliance, data reporting and analysis which are relevant to the conclusions drawn from the WHI results. They have also indicated a possibility of both a protective and a deleterious effect of HT on cardiovascular disease. Since a majority of the women studied in WHI are above 60 years of age and were commencing on HT well beyond the menopause it is especially difficult to determine the implications of the WHI results for women who have been on long-term HT since early menopause at around 50 years of age. There appears to be widespread agreement that when women are using HT in the early postmenopause (50–60 years of age) for menopausal symptom relief the negative risk/benefit balance described in the overall WHI results becomes less relevant.

The observational Million Women Study has provided detailed information about a diverse range of HT regimens and routes of administration (with the exception of vaginal preparations) from women aged between 50 and 64 years attending the NHS Breast Screening Programme (NHSBSP) in the UK. According to the results of the study an increase in the breast cancer risk is independent of HT route of administration (oral, transdermal, or implant), HT content (estrogen–progesterone types, tibolone), or

therapy regimens (intermittent/continuous). The relative risk is observed to be higher with estrogen progestin therapy (EPT) (RR = 2.00) than with estrogen only therapy (ET) (R = 1.30). Even though the study is of large-scale extensive criticism has been raised on the design. In particular, there are concerns that the study over-estimates the risk of breast cancer associated with a short exposure to HT. The results of the study were based on responses to a baseline questionnaire and duration of HT use was defined at study entry. Thus, changes in use during prospective follow-up were not taken into account.

### 3. Benefits of HT

#### 3.1. *Treatment of vasomotor symptoms*

There is compelling evidence that HT, ET or EPT, alleviates climacteric symptoms especially vasomotor symptoms: the number of hot flushes being substantially reduced. Improvement is usually obtained within 4 weeks. Relief of vasomotor symptoms is the commonest indication for HT. Incidence and intensity of postmenopausal symptoms vary between countries and ethnicities. In Europe approximately 80% of postmenopausal women will experience symptoms and half will consult their doctors to get advice and relief. Although self-limiting 20% of all women will still endure distressing vasomotoric symptoms more than 4 years following the menopause HT has a beneficial effect on the perceived quality-of-life, in women with climacteric symptoms. The beneficial effect on vasomotor symptoms is independent of route of administration, late perimenopausal period or after menopause.

#### 3.2. *Urogenital symptom*

Symptoms such as vaginal dryness, soreness, superficial dyspareunia, and urinary frequency and urgency respond well to estrogens which may be given topically. Improvement may take several months. Long-term treatment is often required as symptoms can recur on cessation of therapy.

#### 3.3. *Osteoporosis*

There is evidence from randomised controlled trials that HT, including ET (oral and transdermal, nat-

ural estrogens and CEE), with or without added progestogen reduces the risk of fractures of both spine and hip as well as other osteoporotic fractures. BMD is a predictor of fracture risk. Data from prospective cohort studies indicate that a reduction of the *T*-score for BMD in the hip of 1 standard deviation (S.D.) is associated with a 2–3-fold increased risk of hip fracture. The increase in BMD during HT is dose dependent. BMD is possibly increased even with very low dosages in older women. After discontinuation of HT, bone mass is lost at a rate similar to that seen in untreated women and the most recent epidemiological studies suggest that for HT to be an effective method of preventing fracture in all age groups of women who are most susceptible the treatment needs to be long-term and therefore may need to involve different options at different stages of life. While alternatives to HT use are available for the prevention and treatment of osteoporosis, estrogen may still remain the best option particularly in young and/or symptomatic women. Calculations of absolute risks based on the results from the RTC part of the WHI trial indicate that 5 years of use of combined HT reduces the incidence of hip fracture by about 1 per 1000 for women aged under 70 and by about 8 per 1000 for women aged 70–79 years. No detailed information on the magnitude of the fracture risk reduction is available from the ET part of the WHI study.

### 3.4. Colorectal cancer

Previous observational data have shown a reduced risk of colorectal cancer in women taking HT. Evidence from the EPT WHI trial shows a significantly reduced risk of 30% for women taking HT compared with those taking placebo. It is unknown how long the effect of combined HT persists after treatment is stopped or how HT affects mortality from colorectal cancer.

## 4. Risks of HT

### 4.1. Breast cancer

The EPT part of the WHI trial and several observational studies, including the Million Women Study, have confirmed the association between HT and breast

cancer risk. HT appears to confer a similar degree of risk as that associated with late natural menopause (2.3% compared with 2.8% per year, respectively). There is good evidence that the excess relative risk increases with duration of use, returning to baseline levels within a few, at most five, years after stopping the intake. The increased risk of breast cancer with longer-term exposure, however, seems to be limited in most studies to lean women (i.e., BMI < 25 kg/m<sup>2</sup>). The magnitude of the excess relative risk is greater when the estrogen has been combined with a progestin, either when given sequentially or continuously, and regardless of type of progestin. In contrast the ET part of the WHI trial has showed no increased the risk of breast cancer during the time period of the study. Calculations of absolute risks of breast cancer from risk estimates in the Million Women Cohort Study revealed that among 1000 women aged 50, 32 new cases of breast cancers would be expected by the age of 65 without HT, whereas after 5 and 10 years of HT an additional 2 and 5 women, respectively, would develop a breast cancer when taking ET, and 6 and 19 women, respectively, when taking EPT. The results of the Million Women Study should be interpreted in the context of completed/ongoing placebo-controlled HT trials. The risk of breast cancer associated with continuous combined HT reported by the EPT part of the WHI Study investigators provides the most reliable estimation in that this was a placebo-controlled trial. In the study, during a mean of 5.2 years follow-up, the absolute excess risk attributable to HT was eight breast cancer cases in 10,000 women per year. This part of the study reported that HT-associated cancer were significantly larger and more likely to be node positive compared with placebo-associated cancers. The increased risk of breast cancer risk due to HT is not significantly different from other risk factors such as alcohol use, obesity, lack of exercise, late first child-birth and late menopause. Mortality is the most important cancer outcome. It is unlikely that any randomised trials will ever be large enough to evaluate this end point reliably. The estimated 10-year survival difference is very small (1.5%).

EPT causes an increased density of the mammographic image and may reduce the sensitivity or specificity of mammographic screening.

In women treated for breast cancer observational studies suggest that HT has no significant effect on

survival compared with non-users, but this was not confirmed by the EPT part of the WHI trial.

#### 4.2. Endometrial cancer

Intake of ET by women with an intact uterus causes a dose and duration dependant increase in the risk of endometrial hyperplasia and cancer. An early adverse effect on the endometrium, i.e., endometrial hyperplasia that is seen as a precursor of endometrial cancer, may be observed within 6 months of treatment. It is unclear how long the effect persists after stopping. This excess risk is reduced or eliminated by adding a progestogen, the preventive effect appears to be greater the more days per cycle the progestogens are used. In the WHI trial, women exposed to continuous combined EPT had no significant difference in the risk of endometrial hyperplasia and endometrial cancer compared with women receiving placebo. The totality of the evidence is that unopposed estrogens causes endometrial cancer, a risk that can be avoided by adding a progestin.

#### 4.3. Ovarian cancer

Results from observational studies and from the EPT WHI trial indicate that HT may be associated with a slightly increased albeit not significant risk of epithelial ovarian cancer. The effect of different added progestins, or types of HT, or routes of administration are currently unknown.

#### 4.4. Venous thromboembolism

HT increases risk of venous thromboembolism (VTE) three-fold with the highest risk occurring in the first year of use. The overall risk in menopausal women years 50–59 is of the order of 3–4 in 10,000 per year and the mortality is 1–2%. The absolute rate increase corresponds to 1.5 VTE events per 10,000 women in 1 year impacted by age and BMI at baseline. The absolute risk of pulmonary embolism (PE) based on data from all trials implies that in 1000 women 50–59 years taking HT for 5 years there would be an additional two cases. A single case-control study has suggested that transdermal HT was not associated with an increased risk of VTE.

#### 4.5. Cardiovascular disease

Results from the RTC study on secondary prevention, The Heart and Estrogen/Progestin Replacement Study (HERS) showed that estrogen plus progestin does not confer cardiac protection and may increase the early risk of coronary heart disease (CHD) among postmenopausal women with established disease taking HT as CCHT (0.625 mg CEE + 2.5 mg MPA), at least during the first year of intake. The EPT part of the WHI trial results showed no difference in overall risk women without established disease, but a trend towards early increase and a later ( $\geq 6$  years) decrease. The absolute rates of CHD were 39 cases and 33 cases of non-fatal myocardial infarction and death due to coronary heart disease per 10,000 women per year for hormone therapy and placebo, respectively. The preliminary information from the ET WHI study similarly indicate no impact of CEE on the CHD rate. Those trial data are in contradiction the numerous previously published observational data that have showed a reduction of 30–40% of any type of HT on CHD risk. The overall WHI trial evidence that both ET and EPT increase the risk of stroke with an excess of eight more strokes per year for every 10,000 women on HT. When separating by stroke subtypes in the WHI, EPT was associated with an excess risk of ischemic stroke only and the relative risk did not vary by subgroups of women. In women 50–59 years not taking HT, ischemic stroke is expected to occur in 3 out of 1000 women during 5 years. Five years use of HT would yield 1 additional case of stroke.

### 5. Uncertainties

#### 5.1. Cognitive function

In a sub-study of the EPT part of the WHI, the WHI Memory Study (WHIMS), about 5000 women aged 65–79 years were examined with cognitive tests. There was no evidence of improvement of cognitive function nor prevention of dementia in the women using this kind of HT. The EPT part of the WHI study found a two-fold increased risk of dementia (possibly of thrombotic origin) in women. However, this increased risk was only significant in the group of women over the age of 75 years. Preliminary data suggest that for the WHIMS participants who were on

ET when compared to the women who were taking the placebo, there was a trend toward increased risk of probable dementia and/or mild cognitive impairment. It is not clear why these results are the opposite of earlier findings from observational studies. HT may delay or reduce the risk of Alzheimer's disease (AD) in women commenced in the early postmenopause when the pathological processes that lead to AD are being initiated. Therefore more evidence is required, especially from younger postmenopausal women taking appropriate doses and different regimens before definitive advice can be given in relation to AD.

### 5.2. *Quality-of-life*

Results from observational studies had suggested a beneficial effect on quality-of-life in women with vasomotor symptoms. This area is difficult to evaluate because of the different measures used, varying levels of menopausal symptomatology, a large placebo effect and extrinsic factors which may alter women's responses.

It should be noted that women included in the WHI trial were in general late post-menopausal and were not included on the basis of climacteric symptoms; only 12–13% of the women had moderate to severe vasomotor symptoms. In a subset of some 1500 participants quality-of-life measurements were performed baseline and after 1 and 3 years. At 3 years there was no effect of EPT on perceived general health, vitality, mental health, depressive symptoms or sexual satisfaction. There was only a small benefit on sleep disturbances.

## 6. Clinical statements

- In women with climacteric symptoms, HT of any type provides symptom relief with no alternative treatment of similar effect. In most cases benefits will therefore outweigh any of the risks pertaining to those years of HT exposure because the treatment positively affects quality-of-life. The dose and regimen of HT need to be individualised and in general the appropriate dose is dependent on the menopausal age. This should be considered before and annually during treatment to adapt to the principle of prescribing the lowest effective dose. Among

the early postmenopausal women an estradiol dose corresponding to 1–2 mg taken orally is generally needed for to obtain sufficient symptom relief. In deciding on what is an appropriate duration of treatment it is reasonable to consider discontinuation after 2–3 years. If symptoms return, then further use of HT is appropriate, reconsidering lowering the estrogen dose.

- Current data support an overall beneficial risk benefit ratio of HT in women with natural or iatrogenic premature menopause. In particular the risk of breast cancer after HT is used corresponds to the risk found in premenopausal women of similar age who have not suffered an iatrogenic or premature menopause.
- Urogenital symptoms due to atrophy can alternatively be treated with local low-potency/dose estrogens, for which systemic risks have not been identified.
- There is good evidence that current use of HT (ET and EPT) reduces the relative risk of osteoporotic fractures regardless of the presence or absence of risk factors. This reduced risk is not substantially different across different age groups and across subgroups with low, moderate, or high fracture risk based on clinical risk factors. The absolute risk reduction differs across the different age groups. There is evidence that within 5 years after stopping HT, the continuing fracture preventing effect is vanished. Consequently in women at significantly increased fracture risk an alternative strategy for long-term prevention should be applied when HT is discontinued.
- HT increases risk of breast and endometrial cancer. The excess risk depends on duration of therapy and is enhanced for breast cancer and reduced or eliminated for endometrial cancer when EPT is used compared to ET preparations. The risk of breast cancer returns to baseline levels within a few, at most five, years after stopping the intake. The EPT data and the preliminary data from the ET part of the WHI study emphasise the significant impact of the progestin (MPA) on breast cancer risk. This is in accordance with results from studies on breast cancer density. However, currently ET should only be used in hysterectomised women due to the risk of bleeding disturbances and the subsequent cancer concern and need for invasive diagnostics. The dose

and type of progestin chosen for EPT needs new and scrutinised attention. Topical ET application for urogenital symptom relief does not impact the risk of breast or endometrial cancer.

- According to the recent RCT studies HT should not be prescribed as CHD prevention. Epidemiological data provide evidence of an increased risk of VTE, in particular during the first years of treatment and a slightly increased risk of ischemic stroke independent of age and treatment duration.
- There is insufficient evidence of a beneficial effect of HT on cognitive function or risk of dementia. HT should not solely be prescribed for these purposes.
- Over and above defining the best clinical HT strategy EMAS warrants special attention to the possibility of increasing quality-of-life and to prevent not only CHD and osteoporotic fractures but also breast cancer by life-style management with particular emphasis on exercise, the dietary intake and cessation of smoking.

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