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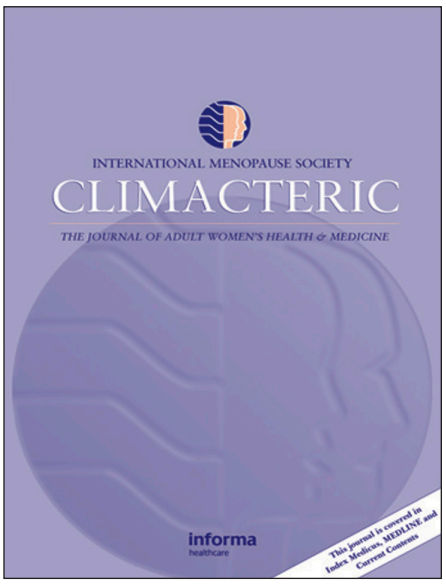

Primary prevention of cardiovascular disease with hormonal replacement therapy

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ABSTRACT

Many peri- and postmenopausal women suffer from a reduced quality of life due to menopausal symptoms and preventable diseases. The importance of cardiovascular disease in women must be emphasized, as it is the leading cause of mortality and morbidity in women. It is well-known that female hormones contribute to the later onset of cardiovascular disease in women. The effect of estrogens has for decades been understood from observational studies of postmenopausal women treated with hormonal replacement therapy (HRT). Later, treatment with HRT was disregarded due to the fear of side effects and an ambiguity of the cardiovascular advantages. Accumulating knowledge from the large number of trials and studies has elucidated the cause for the disparity in results. In this paper, the beneficial effects of HRT, with emphasis on CVD are explained, and the relative and absolute risks of side effects are discussed.

Primary prevention of cardiovascular disease with hormonal replacement therapy

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ABSTRACT

Many peri- and postmenopausal women suffer from a reduced quality of life due to menopausal symptoms and preventable diseases. The importance of cardiovascular disease in women must be emphasized, as it is the leading cause of mortality and morbidity in women. It is well-known that female hormones contribute to the later onset of cardiovascular disease in women. The effect of estrogens has for decades been understood from observational studies of postmenopausal women treated with hormonal replacement therapy (HRT). Later, treatment with HRT was disregarded due to the fear of side effects and an ambiguity of the cardiovascular advantages. Accumulating knowledge from the large number of trials and studies has elucidated the cause for the disparity in results. In this paper, the beneficial effects of HRT, with emphasis on CVD are explained, and the relative and absolute risks of side effects are discussed.

INTRODUCTION

Is it possible to improve quality of life, and reduce morbidity and mortality for peri- and post-menopausal women all at once? The easy answer is 'Yes'. Naturally, there is no one-size-fits-all solution, but for the vast majority of women, that is the case. Cardiovascular disease (CVD) is the leading cause of death in women. In Europe, 22% of all women die from Coronary Heart Disease (CHD) alone, and 52% of mortality in European women is due to cardiovascular disease (including CHD, stroke and other CVD). Cancer is the cause of death in 18% of all European women, and breast cancer accounts for 3% of the total number of deaths.(1) Correspondingly, quality of life in the total population is more severely affected by CVD than any other disease.(2) Thus, mediating cardiovascular disease in women yields an opportunity to reduce total mortality by a greater magnitude than reducing any other cause of death.

PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN

As statins are not useful for primary prevention for CVD in women (3;4), and the total beneficial effect of aspirin as primary prevention in women is no longer deemed positive, (5-7) primary prevention may seem reduced to lifestyle modifications.

Hormone Replacement therapy (HRT) as primary prevention in cardiovascular disease has long been considered not only controversial, but also by many physicians, inapt. This is largely due to the results from the Women's Health Initiative (WHI), which since first published in 2002 have been repeatedly published with minimal changes to the interpretation. Many papers regarding CV events in the WHI have since been published from the primary investigators, solely repeating conclusions that are not readily associated with the presented data, stressing risks that are not statistically significant despite the vast number of participants.(8)

Observational studies based on newly postmenopausal women taking HRT to relieve menopausal symptoms have consistently shown reductions in cardiovascular disease.(9) These finding have been questioned due to the results from WHI, despite the discordancy between the designs, most importantly, age and time since menopause. The mean time since menopause

of participants in WHI was 13 years and re-analyses from WHI did indeed find a (non-significant) reduction in CHD in the group of women within 10 years from menopause.(10)

Formerly, randomized trials have been made in women with established atherosclerosis. The Heart and Estrogen-progestin Replacement Study (HERS), the first large RCT of HRT and CVD was done in women with pre-existing CHD and a mean age of 66.7 years. The women were randomized to conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) versus placebo. The hazard ratio (HR) for CHD was 0.99 (95% confidence interval (CI), 0.80-1.22).(11) The Estrogen Replacement and Atherosclerosis (ERA) trial result—in women with verified CAD and a mean age of 65.8 year—were consistent with HERS and showed that neither unopposed CEE nor CEE+MPA reduced nor increased coronary artery atherosclerosis progression.(12) Thus, even in women with established atherosclerosis the net harm does not seem as evident as we have been led to believe.

The consistency of the results from younger women in observational studies with the results from WHI in women closer to menopause and the disparity from results from older women or women with established atherosclerosis has been entitled the timing hypothesis.(13)

Trials such as the Estrogen in the Prevention of Atherosclerosis Trial (EPAT)(14) and Kronos Early Estrogen Prevention Study (KEEPS)(15;16) further support the beneficial effects of estrogen on the cardiovascular system and the perhaps parts of the biological mechanism responsible. In EPAT, a reduction in subclinical atherosclerosis progression was found in healthy postmenopausal women randomized to unopposed oral estradiol versus placebo(14) and the HDL and LDL profile improved with CEE treatment in KEEPS, (16) similar to what was found in women with established atherosclerosis on 17β-estradiol or 17β-estradiol +MPA.(17)

THE CHANGE IN PERSPECTIVE: THE WOMEN'S HEALTH INITIATIVE

In 2002, the initial results from The Women's Health Initiative (WHI) were published. WHI was a large randomized controlled trial (RCT) of women with a mean age of 63 years, 13 years postmenopausal. Women with an

intact uterus were randomized to CEE +MPA or placebo and women without a uterus were randomized to CEE mono therapy or placebo.

The E+P (CEE+MPA) trial was stopped prematurely after a mean of 5.2 years, due to concern for increased risk of breast cancer. The hazard ratio for women randomized to CEE+MPA vs. placebo for invasive breast cancer was 1.26 (95% CI: 1.00-1.59, and adjusted 95% CI: 0.83-1.92) (18), thus the possible increase of breast cancer was *not* significant in the trial including more than 16,000 women. In the smaller subgroup of hysterectomized women randomized to Estrogen alone vs placebo, the risk of invasive breast cancer was initially published showing a trend towards a decreased risk with a hazard ratio of 0.80 (95% CI: 0.65-1.04).(19) Later, the investigators published revised results, revealing a significantly reduced risk of invasive breast cancer; hazard ratio 0.77 (95% CI: 0.62-0.95).(20)

The risk of CHD in the total CEE+MPA trial was 1.23 (95% CI: 0.99-1.53; adjusted 95% CI: 0.85-1.97), (21) whereas the risk of CHD of the women randomized within 10 years of menopause was 0.88 (95% CI: 0.54-1.43) (21). That is indicative of a decreased risk of CHD in women starting HRT closer to menopause. Though the risk of CHD was not significantly decreased in this subgroup, it is worth noting that a large proportion of these 5494 women were more than 5 years postmenopausal; however, the authors do not provide the distribution. In the Estrogen alone trial, the hazard ratio for CHD in the total study population was 0.95 (95% CI: 0.78-1.16), and for women within 10 years of menopause 0.48 (95% CI: 0.20-1.17) (21).

Furthermore, the risk of cancer was not increased by the use of CEE+MPA (hazard ratio 1.03, 95% CI: 0.90-1.17) and the risk of fractures was significantly decreased; hazard ratio 0.76 (95% CI: 0.39-0.85).(18)

Importantly, mortality was not increased in the total population of women randomized to HRT, despite the mean age of 63 years at initiation. A closer look at the Kaplan Meier curve from the original publication of the E+P trial depicts the hazard ratio of 0.98 with the mortality curve for the E+P group slightly diverging towards a lower risk from the placebo group after 5½ years. Unfortunately, the trial was stopped prematurely.(18)For women aged 50-59, the mortality in the total study population was significantly decreased

in the HRT arm, with a hazard ratio of 0.70 (95% CI: 0.51-0.96), with no significant difference between the E alone compared to the E+P group. (21)

CLINICAL SUPPORT FOR THE TIMING HYPOTHESIS: DOPS

With the publication of the cardiovascular end points from the Danish Osteoporosis Prevention Study (DOPS) in 2012, (22) the circle was completed. DOPS was a Danish multi-center trial including 2016 women of whom 1006 were included in a randomized sub trial. The primary end point in the original study was osteoporosis, but cardiovascular end points and cancer were among the end points in the original protocol. (23) In the following, I will only focus on the randomized trial as it was published in 2012.(22) The 1006 women were randomized to HRT or placebo, and the trial was intended to continue for 20 years. The women in the treatment arm with intact uterus received sequential 17β-estradiol and norethisterone acetate (NETA), and hysterectomized women, continuous 17β-estradiol. The intervention was stopped in 2002 due to the results from the WHI and the change in opinion—world wide—to HRT. At inclusion, the women had a mean age of 50 years, and all were within 2 years of last menstrual bleeding; thus, these women represented the very women who consider HRT due to menopause, menopausal symptoms, or primary prevention of CVD or osteoporosis. During 10 years of intervention, the women randomized to HRT experienced half the rate of death, myocardial infarctions or heart failure than women randomized to placebo (HR: 0.48, 95% CI: 0.26-0.87, p=0.015). There was no increased risk of cancer in general or breast cancer in particular in the women randomized to HRT. Likewise, there was no increased risk of stroke (HR: 0.77, 95%CI: 0.35-1.70). The absolute number of venous thrombo-embolism was very low, and no statistically significant difference between the groups was observed. The women were followed until a total of 16 years since randomization and though almost all of the participants stopped HRT when advised to do so in 2002, there was a clear carry-over effect on mortality, myocardial infarction or heart failure so that the risk was still significantly reduced 6 years post exposure (HR: 0.61, 95% CI: 0.39-0.97, p=0.02). (Fig. 1). Persistently, no increased risk of cancer or stroke. During the 10 year intervention period 41 women died, 26 in the

control group and 15 in the HRT group (HR: 0.57, 95% CI: 0.30-1.08 p=0.087).

DOPS has been criticized for the small number of participants, but no other randomized trial has been made with as many women in close proximity to menopause (mean: seven months postmenopausal), with as long trial time (mean: 10.8 years randomized); moreover, finding statistically significant results in smaller populations underscores the clinical relevance. The open-label design has also been criticized. Blinding is not a serious concern when dealing with hard end points such as myocardial infarction, heart failure and especially mortality (which *cannot* be prone to outcome-assessor bias), but if anything this may only have resulted in detection bias, especially after 2002 where the awareness to HRT was associated with a general belief of negative outcome. As the positive carry over effect was significant, it is reassuring that the women randomized to HRT for 10 years did in fact experience reduced CV risk. Moreover, no trial of HRT, particularly comprising women with a uterus is completely blinded, thus this is not much different from any other trials of HRT.(24)

In consequence, the positive effects of HRT on the cardiovascular system in women close to menopause have been found in large observational studies, in randomized trials with paraclinical outcome and in RCT's with clinical outcome, all confirm the timing hypothesis.(13) Estrogen alone is preferable in hysterectomized women, as the progestins may alleviate some of the positive effects of estrogen. In addition, the type of progestogen influences the atherogenicity.(25;26)

HRT AS TO BREAST CANCER, VENOUS THROMBOEMBOLISM, STROKE AND OSTEOPOROSIS

Breast cancer

It is commonly believed that the risk of breast cancer is increased with the use of HRT—combination therapy (E+P), but not, and perhaps even decreased, with the use of estrogen only therapy (22;27). This has been found in some observational studies (28;29) as well as randomized trials (18). The actual association of HRT to risk of breast cancer is however not conclusive as results diverge on magnitude and importance.(30-33) As the a priory risk for a women in western society to develop breast cancer is approximately

10%, a relative risk increase of 20% results in an absolute risk increase of 2% (increasing the absolute risk from 10% to possibly 12%). Other factors, including lifestyle factors, such as obesity,(34) night time work,(30)etc. have much more effect on the risk of breast cancer than HRT (E+P).(30;35) Yet, the possible increase, which in absolute numbers is small, is being stressed as a major concern even though a greater proportion of peri- and postmenopausal women suffer from CVD, poorer sex life, osteoporosis, vasomotor symptoms and generally reduced quality of life. The drugs available for treating these conditions are associated with several side effects, but administered unquestioned. (32)

Venous thrombosis

Hormone therapy, premenopausal oral contraceptives as well as postmenopausal HRT is associated with and increased risk of venous thromboembolisms (VTE). The absolute risk of VTE is generally small, but obesity, factor V Leiden mutation and increasing age all increase the baseline risk of VTE and thus the absolute risk is further increased with use of oral hormone therapy. There may be a difference in the risk due to the types of estrogens and progestins used as well as the route of administration; and lesser risk seems to be associated with estradiol than CEE and progesterone than other progestogens. Transdermal administration of the estrogen compound is found to be less thrombogenic. In conclusion, in women close to menopause, who have not previously had a VTE or a family history of VTE, the concern of thrombosis should not restrain the initiation of HRT; and the risks of VTE can be mitigated if necessary.(36-40)

Stroke

In the WHI, an increased risk of stroke was found in women on HRT, (18) but in DOPS including younger women, for a longer period of time, as well as in HERS including women with a mean age of 67 years, there was no increased risk.(22;43) It is generally believed that HRT is safe in younger women, but as the baseline risk of stroke increases with age, if HRT does increase the risk of stroke it is not advisable in women over 70 years of age.(44) However, estrogen has been shown to be protective in stroke (45;46) and as the risk may very well depend on formulation (the type of progestin) and route of administration (lower risk with transdermal estrogen), (37;47-

49) women within 10 years of menopause should not be withheld HRT out of fear of stroke. Furthermore, in a large cohort of women with atrial fibrillation, women with an increased risk of stroke, use of HRT did not result in an increased risk of stroke, mortality, thromboembolism or bleeding.(50)

Osteoporosis and quality of life

The effect of HRT on bone is irrefutable.(18;51-54) Yet, the benefit with respect to osteoporosis and fractures was deemphasized in the WHI. As the rapid decrease in Bone Mineral Density happens in early menopause(55), late onset of treatment cannot be expected to have as dramatic effect on osteoporotic fractures as HRT starting in early menopause. Nonetheless, despite the late onset of HRT in the WHI, the effect on fractures was significant (18). As quality of life is severely affected by osteoporotic fractures (56;57) the undisputed effect on bone of HRT has for decades been enough reason for numerous women to initiate HRT. HRT ameliorates the menopausal symptoms and improves quality of life.(58;59) The positive effect of HRT on quality of life is more pronounced in women closer to menopause.(60)

CONCLUSION

For women close to menopause, those who are most severely affected by menopausal symptoms, the benefits of HRT outweigh the risks. As CVD is accountable for most deaths and disability in women, it is especially due to the beneficial effects on CVD along with improved quality of life. This has been shown in large observational studies of women initiating HRT close to menopause in addition to RCTs with surrogate end-points as well as clinical outcome.

The side effects are—in absolute numbers—small, especially in the younger women, where the overall benefit also manifests in reduced mortality.(61) Trials with surrogate end-points such as intima media thickness and lipid levels aid in the identification of biological mechanisms and are supportive of the studies and trials with clinical outcome. Existing data supports the timing hypothesis, so to maximize the cardiovascular benefit of HRT, treatment should be initiated close to menopause, accordingly also preventing the rapid decline in BMD and relieving menopausal symptoms.

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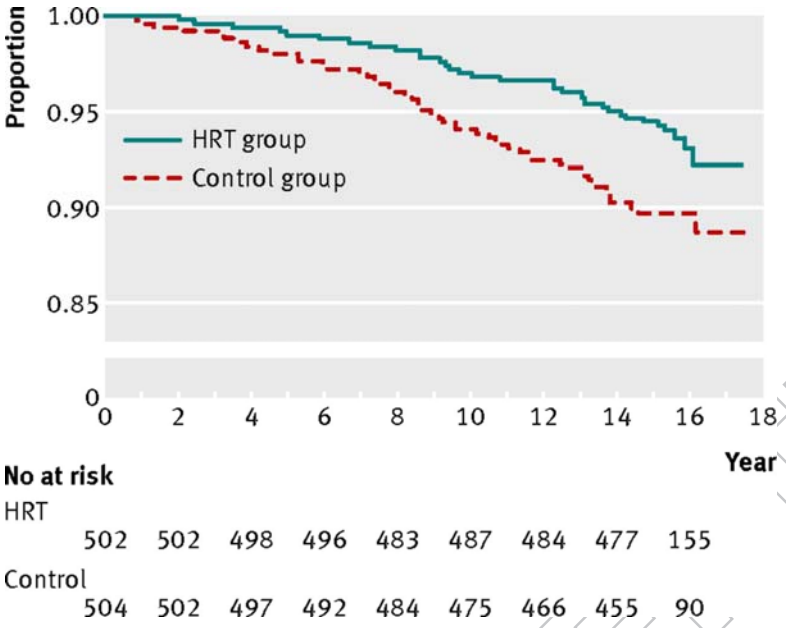
Figure Legend

Fig. 1. Kaplain Meier curve of composite cardiovascular end-point in DOPS: Death, Myocardial infarction or Heart Failure. From: BMJ 2012;345:e6409



No at risk

HRT	502	502	498	496	483	487	484	477	155
Control	504	502	497	492	484	475	466	455	90