



Hormone replacement therapy and cardioprotection. A new dawn? A statement of the 'Gruppo di studio sulle malattie cardiovascolari nella donna' of the società italiana di cardiologia on hormone replacement therapy in postmenopausal women

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Cardiovascular disease is the leading cause of death in women in western countries. Despite preventive strategies, in the past decades, the incidence of cardiovascular events has shown a decline in men but a rise in women, matching the growth of the population of postmenopausal women. Several epidemiological findings suggest the causative pathophysiological role of ovarian hormone deficiency in the development of cardiovascular disease in women. Observational and randomized studies have suggested that hormone replacement therapy in early postmenopause could be beneficial from a cardiovascular point of view. Conversely, aging, time since menopause and presence of cardiovascular risk factors or cardiovascular disease may decrease its efficacy and increase the risk of cardiovascular events. It is plausible that the unfavorable effects of the estrogen/progestin combination used in the randomized studies are not related to the hormone preparation *per se* but rather to the use of hormones in the less receptive group of women, older and with cardiovascular risk factors. Clinical judgment, choice of the right dose and estrogen/progestin combination are of pivotal importance to

maximize the beneficial effect of estrogen replacement therapy/hormone replacement therapy, especially if given within a reasonable time after the menopause to the women who need the therapy for the relief of menopausal symptoms. *J Cardiovasc Med* 9:1–8 © 2008 Italian Federation of Cardiology.

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Introduction

Cardiovascular disease (CVD) is the primary cause of death in women in western countries and in Europe; more than one of two women dies from coronary heart disease (CHD) and stroke [1]. Although in the past 40 years, the age-adjusted mortality for cardiovascular disease has declined, the temporal trends of the incidence of CHD and cerebrovascular events have shown a decline in men but a rise in women, matching the growth of the population of postmenopausal women. Several epidemiological findings suggest the causative pathogenetic role of ovarian hormone deficiency in the development of CVD in women. Indeed, CVD risk increases after the menopause and, at any age, postmenopausal women have a significantly higher incidence of CVD compared with normomenstruating women [2,3]. The postmenopausal increase in cardiovascular disease after the menopause

is also matched by the increase in incidence of other diseases, such as osteoporosis and dementia, which are influenced by estrogen deficiency. These diseases were uncommon in women until few decades ago. This was due to the fact that until the '60–70s the population of postmenopausal women was small. Indeed, only in the recent years, with the sizeable increase in female life expectancy, there has been a sizeable proportion of postmenopausal women and therefore the manifestation of diseases that were rare until few decades ago.

Despite the wealth of studies proving the effect of estrogens [estrogen replacement therapy (ERT)] and estrogen–progestin associations [hormone replacement therapy (HRT)] on cardiovascular functions and surrogate CVD end points and despite the suggestions of a significant cardiovascular benefit of HRT gathered by

several observational studies conducted on early postmenopausal women, the results of recent randomized trials conducted with a fixed HRT formulation, not marketed in Italy, in populations of predominantly elderly postmenopausal women [4–13] failed to show a cardioprotective effect of ERT/HRT [13,14]. Furthermore, the Women's Health Initiative (WHI) studies have suggested a possible increase in cardiovascular disease in late postmenopausal women receiving ERT/ERT and have led to a contraindication of ERT/HRT also in early postmenopausal women. More recently, the WHI has reported that the effect of ERT/HRT differs according to time since menopause and age with a possible preventive effect in early postmenopausal women.

As the results of the randomized studies cannot be fully translated to clinical practice, the Working Group on Cardiovascular Disease in Women of the Societa' Italiana di Cardiologia has developed an expert document on the cardiovascular effect of ERT/HRT. The primary aim of this document is to highlight the risks and benefits associated with the use of ERT/HRT in early postmenopausal women.

Menopause as cardiovascular risk factor

In postmenopausal women, ovarian hormone deficiency induces changes in metabolic and hemodynamic functions, leading to a greater prevalence of hypertension, diabetes, hyperlipidemia and metabolic syndrome compared with the premenopausal period [2]. Menopause is associated with unfavorable changes in body weight and body fat distribution, insulin sensitivity, plasma lipid profile and sympathetic tone [15,16]. These modifications interact with each other, amplifying the primary effect of ovarian hormone deficiency and the negative consequence of aging. Postmenopausal women tend to gain weight starting within the first year of amenorrhea and their body fat is redistributed from a gynoid to an android pattern [11–17]. The causal relationship between body weight gain and estrogen deprivation is suggested by the evidence that women taking HRT have controlled BMI and their gynoid pattern of fat distribution [11–17] is preserved much better than women not on HRT. Increase in BMI and an increased proportion of visceral fat are strongly correlated with the development of arterial hypertension, insulin resistance and with a range of metabolic risk factors for CVD [18]. Accordingly, the improvement in insulin sensitivity produced by weight loss, exercise and insulin sensitizers is associated with a decrease in blood pressure values and improvement in endothelial function [18–20]. Because of the unfavorable changes related to the increase in body fat and body fat redistribution, lifestyle changes, including exercise programs and diet are one of the most important preventive strategies for cardiovascular disease in women. Studies conducted in Europe have almost invariably shown a clear effect of exercise and diet on cardi-

ovascular risk in women and that the effect of these interventions is sustained for long-term [20]. Conversely most US studies have failed to show an adequate adherence to rehabilitation programs in women. These differences may be related to different cultural backgrounds and lifestyles but must suggest lifestyle changes as the primary intervention to counteract the increase in CVD risk occurring with menopause. However, more recently, data from the WHI in 73 743 postmenopausal women aging 50–79 years have shown that both walking and vigorous exercise are associated with substantial reductions in the incidence of cardiovascular events among postmenopausal women, and that this effect was present irrespective of race or ethnic group, age and BMI [21].

Although after the menopause the lipoprotein profile changes become more atherogenic, the importance of lipid changes occurring after the menopause has been overestimated in the past [22]. Serum concentrations of triglycerides, total cholesterol, low-density lipoprotein (LDL) and lipoprotein [Lp(a)] rise sharply within 6 months of menses cessation, whereas concentration of high-density lipoprotein (HDL) declines gradually [22]. However, like the majority of risk factors, changes in lipid profile are sex-specific and characterized by a different relative importance in men and women [23]. In women high triglycerides, Lp(a) and low HDL cholesterol levels are more important than total and LDL cholesterol in the development of CVD. Moreover, studies evaluating the effect of lipid-lowering therapy have failed to show any significant effect of these drugs in the reduction of cardiovascular mortality and morbidity in women at mild-to-moderate cardiovascular risk. Because of the mild effect of statins in preventing CVD in women with moderately elevated cholesterol, it has been calculated that, for primary prevention, the cost of therapy per life saved in women is significantly higher than that in men (1.500.000 vs. 250.000 EURO) and, therefore, has an unfavorable cost/benefit profile.

Arterial hypertension represents the single most important risk factor in elderly women, especially when coupled with insulin resistance or diabetes [24,25]. Blood pressure increases with age and, following middle age, both systolic and diastolic blood pressure appear to be higher in women than in men. Although before the age of 50 years arterial hypertension is more prevalent in men, by the age of 65 almost 60% of women become hypertensive [24]. The finding that postmenopausal women have higher systolic and diastolic blood pressure values than premenopausal women of the same age, suggests a negative effect of ovarian hormonal deprivation, which appears to be additional and independent of the aging process. However, the precise, single effect of menopause on blood pressure is difficult to evaluate, because both menopause and blood pressure are associated with aging

and influenced by common factors such as BMI, socioeconomic status and smoking [24]. Arterial hypertension in women is more frequent after the menopause and, after stratification for age and BMI, the odds of having hypertension are 2.2 after the menopause compared with premenopausal age [24]. Several possible mechanisms may explain the increase in blood pressure occurring after the menopause. In addition to the unfavorable changes in body weight and insulin resistance, postmenopausal estrogen deficiency may affect the balance between various vasoactive hormones, as well as the normal function of vascular smooth muscle cells. Also the increase in salt sensitivity and the activation of the rennin–angiotensin–aldosterone system (RAAS) occurring after the menopause play a significant role in the development of arterial hypertension [26]. Arterial hypertension has a greater impact on cardiovascular mortality and morbidity in women than in men and hypertensive women are four times more likely to develop CVD than age-matched normotensive individuals [25]. Conversely to what observed with interventions with hypolipidemic drugs, all therapeutic strategies aimed at reducing blood pressure levels have shown a beneficial effect on cardiovascular events in women as in men. Furthermore, in patients with metabolic syndrome an aggressive reduction in blood pressure is more effective in women than in men in reducing cardiovascular events [27].

Hormone replacement therapy and cardioprotection

As ovarian hormone deficiency is associated with unfavorable changes in a broad range of risk factors for cardiovascular disease and as ovarian hormone replacement improves these changes, it has been suggested that HRT may confer cardioprotection. Since the late 70s and until the publication of the WHI, estrogen and estrogen–progestin replacement therapy have been widely prescribed in early postmenopausal women for the relief of menopausal symptoms. In the 90s, their use was extended, in particular in the United States, to several years after menopause with the understanding that both replacement regimens might reduce the occurrence of CVD. This belief was supported by the large body of evidence demonstrating a favorable effect of ovarian hormones on lipid profile and vascular function and by several observational studies showing a significant reduction in cardiovascular events with ERT and HRT [5–10]. Because of the supposed benefit in primary prevention, it has been hypothesized that HRT may be beneficial in postmenopausal women with coronary artery disease. However, the HERS study [28] failed to show any protective effect of HRT in late postmenopausal women (mean age 67.5 years) with proven coronary artery disease. The study [28] has also suggested a potential initial harm of HRT when started in late postmenopausal women with proven cardiovascular disease; however, this initial harm was not seen in those women receiving statins.

More recently the presentation to the lay press and to the scientific community of the results of the WHI has generated confusion regarding the cardiovascular effect of HRT in postmenopausal women [29]. The WHI is a National Institute of Health (NIH) sponsored study aimed at evaluating the effect of ERT/HRT with conjugated equine estrogens and medroxyprogesterone acetate and other preventive strategies on several outcomes in a population of women not usually prescribed with HRT, namely late postmenopausal free of menopausal symptoms. The mean age of women included in the WHI study was 63.3 years; however, the vast majority of women were of more than 60 years of age at inclusion and more than 30% were above 70 years of age. The study included one arm evaluating the effect of estrogen/progestin HRT in women with a uterus and one arm evaluating the effect of ERT with conjugated equine estrogens. The estrogen–progestin arm of the study was discontinued because of a supposed increase in the Global Index [13], an index of cumulative events that has never been validated and whose definition has been changed several times throughout the study. The estrogen only arm of the study had been stopped 2 years thereafter without any sound specific reason [14].

In contradiction to the wealth of data, the WHI study found a number of results concordant with those of the observational studies but instead of documenting a protective effect of HRT against CHD, it set a warning on a possible increase in CVD risk induced by such therapy in late postmenopausal women [13,14]. However, the initial findings of the possible increased cardiovascular risk suggested by the estrogen/progestin arm of the study have not been confirmed by the estrogen only arm of the study [14]. Overall the WHI showed that ERT and HRT do not reduce cardiovascular events in late postmenopausal women [29]. However, the study has shown that in early postmenopausal women, those within 10 years since menopause, ERT and HRT have no arm [30]. Furthermore, the recent analysis of the two arms of the study suggested a possible benefit of ERT on total mortality in postmenopausal women in whom replacement therapy was started before the age of 60 years [30]. This analysis also suggested that in early postmenopausal women – women very similar to those included in the observational studies and those who have always been prescribed with HRT in Europe and in Italy – ERT may reduce cardiovascular risk.

It is important to underline that the combined WHI trials showed an overall increase risk of stroke with both ERT and HRT. This increased risk, albeit not significantly increased in the combined analysis of the ERT/HRT arms, was not observed in those women of 50–59 years of age at the start of ERT [30].

The findings of the WHI studies suggesting no arm of ERT/HRT in early postmenopausal women and a possible beneficial effect of ERT is also supported by the results of the WHI-Coronary Artery Calcium Study (WHI-CACS) [30]. The study, which is a sub-study of the WHI aimed at assessing the effect of HRT on the progression of atherosclerosis, has shown that ERT/HRT in women aged 50–59 years significantly reduces the degree of coronary calcifications [30]. Therefore, the overall results of the WHI study on cardiovascular outcomes suggest that two factors, time to initiation of HRT since menopause and estrogen/progestin associations, are of importance to explain the widely divergent findings on the cardiovascular effects of observational studies and randomized controlled studies.

An important difference between the observational and randomized studies is represented by the characteristics of participants recruited. Women included in the observational studies chose to take ovarian hormones because of menopausal symptoms, on the contrary, in the randomized trials the absence of menopausal symptoms was a prerequisite for inclusion in the study. In Italy, the mean age at start of ERT/HRT is 52.6 years, 10 years less than that in the WHI study. Studies performed in Italy reported that less than 1% of women attending menopause clinics had features similar to those included in the randomized studies [31,32].

Clinical and experimental evidence suggests that most of the cardioprotective and antiatherogenic effects of ovarian hormones are receptor-mediated and endothelium-dependent [33–41]. Experimental studies conducted on monkeys indicated that estrogen administration delays atherosclerosis progression if administered soon after menopause but has no effect if given late. One possible explanation for the lack of an effect of estrogens late after menopause is related to the age-related increase in methylation of the promoter region of the estrogen receptors, as well as of the estrogen receptors in vascular areas with atherosclerosis [35,42,43]. This process diminishes the estrogen-receptor-mediated effects attenuating or abolishing the protective effect of estrogens on the vessel wall. It has been shown that estrogen-receptor expression in the arterial wall diminishes sharply with time since menopause [35,43]. Furthermore, atherosclerotic human coronary arteries show a greatly reduced density of estrogen receptors with estrogen deficiency [44–46]. Thus, women who have been postmenopausal for several years are clearly exposed to a longer period of ovarian hormone deprivation that may lead to a reduced number and activity of vascular estrogen receptors. In addition, they could have accumulated more extensive atherosclerotic damage or developed endothelium dysfunction, resulting in an overall reduced vascular responsiveness to estrogens. It has been shown that time since menopause (>5 years) influences vascular response to estrogens and, in women of

more than 60 years of age, ERT/HRT may increase the vascular inflammatory response [47–52].

It is well known that menopause negatively influences BMI, glucose metabolism, blood pressure and coagulation, increasing the likelihood of venous thromboembolism (VTE). Women included in the WHI studies were mostly overweight or obese. The association of late menopause with increased body weight and oral HRT may have heightened the risk of VTE observed in the study. A long time since menopause is associated with a reduced protective effect of estrogens, in presence of an unaltered unfavorable effect upon coagulation shifting the balance toward a procoagulant effect. Therefore, whereas in early postmenopausal women ERT/HRT may be cardioprotective because of the favorable responsiveness of the endothelium to estrogens, which buffers the possible detrimental effect upon coagulation, in late postmenopausal women ovarian hormones have either a neutral or even a detrimental effect because of the predominance of the inflammatory, procoagulant or plaque-destabilizing effects over the vasoprotective effects.

It is well known that estrogens may have a procoagulant effect. However, the thromboembolic risk in women receiving ERT/HRT has been overemphasized after the WHI study. Indeed, the absolute risk of VTE with ERT/HRT is very less because of the extremely low prevalence of the disease. Although genetic polymorphisms may contribute to estrogen-associated increase in prothrombotic risk in women receiving ERT/HRT, most of these women have already been exposed to greater procoagulant stimuli like pregnancy (nine-fold increase) or oral contraception during their fertile life [53–55]. Therefore, the majority of women eligible to receive HRT have undergone a physiological screening for prothrombotic mutations during their fertile life and the risk of undiagnosed polymorphisms for thrombophilia is extremely low in postmenopausal women. Recently, the Estrogen and Thromboembolism Risk (ESTHER) study has suggested that BMI, diabetes and venous insufficiency were the most important predictors of VTE in women receiving HRT [56,57]. The risk of VTE with HRT was also increased by cigarette smoking and presence of prothrombotic mutations [57]. More recently, the investigators of the ESTHER study have suggested that different estrogen–progestin associations and different routes of administration may have different effects on the risk of thrombosis associated with HRT [58]. The ESTER study was not designed to detect differences between treatments and, therefore, these latter results should be taken with caution.

Hormone regimen

The somewhat divergent results of the ERT and HRT arms of the WHI have highlighted the importance of the hormone regimen. The unfavorable effects of the

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estrogen/progestin combination used in the randomized studies appear to be related not to the hormone preparation *per se* but to the use of that hormone regimen in the wrong group of women. Indeed, it is well known that the vascular effects of hormones may differ in women with different time since menopause and with different clinical characteristics [47–51]. Most of the women included in the study were hypertensive and the majority of them were inadequately treated as only a small minority had target blood pressure levels. The use of a progestin with a mineralocorticoid effect in hypertensive women or in those at increased risk of hypertension was associated with an increase in blood pressure levels that *per se* may be responsible for some of the negative effects like stroke seen in the late postmenopausal women – those of more than 60 years of age. Medroxyprogesterone acetate is seldom used in Europe and the association of conjugated equine estrogens and medroxyprogesterone acetate is not in the Italian market. In Europe, HRT formulations contain different dosage of estrogens and a wide range of progestins and newer progestin-like drospirenone have been shown to reduce blood pressure in hypertensive women receiving antihypertensive medications [58–61].

Women receiving HRT in Europe are different and are managed differently from those in the United States and, therefore, a careful selection of women to prescribe with HRT by the gynecologists together with the appropriate choice of HRT regimens may minimize risk and increase the benefits. The WHI investigators acknowledged that in women of 50–59 years of age, ERT/HRT may reduce the overall mortality [30]. This statement represents a U turn in the analysis of the WHI and moves toward a European interpretation of the effect of ERT/HRT [62]. In fact, replacement therapy in Europe and in Italy is utilized and it has always been prescribed for women of age less than 60 years and in presence of menopausal complaints.

One important point of relevance for the cardiologist is represented by women with elevated cardiovascular risk. The Cardiovascular Health Study [41] found that women with multiple cardiovascular risk factors seem to have a reduced vascular response to estrogens. Women recruited in the randomized studies had a high incidence of uncontrolled risk factors such as arterial hypertension and obesity compared with women included in the observational studies. This condition may have reduced the effectiveness of the cardioprotective effect of estrogens and increased the negative cerebrovascular effects of progestins related to their mineralocorticoid-like effects upon blood pressure. The effect of HRT upon blood pressure is a very relevant issue as the changes in systolic blood pressure observed in individuals randomized to such treatment in WHI are likely to explain the small increase in stroke in elderly women included in the study.

As mentioned, women included in the WHI had often uncontrolled arterial hypertension; this circumstance may have heightened the mineralocorticoid effect of medroxyprogesterone. The mineralocorticoid effect of progestins may be enhanced by the effect of estrogens on the production of angiotensinogen that in turn may increase the production of angiotensin and aldosterone. Therefore, progestins with antiminerocorticoid and antialdosterone effects should be preferred in the treatment of postmenopausal women, especially if they have family history of arterial hypertension or if they report weight gain or bloating with other estrogen/progestin combinations.

Hormone replacement therapy and cancer risk

Despite the fact that breast cancer is a rare cause of death in women after the age of 50 years compared with cardiovascular disease (6/100 deaths compared with 72/100 breast cancer vs. cardiovascular disease in women 50 years of age or more). After the publication of WHI a lot of attention. A major difference when discussing cardiovascular and breast cancer risk is that cardiovascular disease also includes mortality for cardiovascular events, whereas breast cancer statistics reports only the occurrence of breast cancer. Furthermore, to date there is no evidence that HRT may increase the risk of death related to breast cancer.

The degree of association between breast cancer and postmenopausal HRT remains a major but still controversial issue. All the hypothetical risks of HRT in perimenopausal women are definitely low, falling in the rare category for the criteria of the Council for International Organizations of Medical Sciences (CIOMS) [63]. Women should be reassured that the possible risk of breast cancer associated with HRT is less (less than 0.1% per annum) [64]. Available evidence suggests that HRT for less than 5 years has little, if any, impact on breast cancer risk. In the WHI, this increased risk, in absolute terms, was in the rare category, being 4–6 additional invasive cancers per 10 000 women per year of HRT use for 5 or more years [13]. The increase in breast cancer risk was significantly related to HRT use before the participation in the trial, and confined to women using HRT for 5–10 years before the 5.2 years of the WHI duration [13]. There are insufficient data to evaluate the possible differences in the incidence of breast cancer using different types and routes of estrogen, natural progesterone and progestogens and androgen administration [64]. However, in the estrogen only arm of the WHI, no increase in risk of breast cancer was demonstrated after an average of 7.1 years of use, with six fewer cases of invasive breast cancer per 10 000 women per year of estrogen alone use, which is not statistically significant [14]. As far as the uterine effects of HRT are concerned, the use of unopposed systemic estrogen in postmenopausal women with an intact uterus is associated

with increased (5–13 fold) endometrial cancer risk, linked to the dose and duration of use. Adequate concomitant progestogen administration completely abolishes this risk [30,64]. Continuous combined estrogen–progestogens regimens are associated with a lower incidence of endometrial hyperplasia and cancer than occurs in the normal population.

Regarding the long-term effects of HRT on cancer incidence, there is an increasing body of evidence suggesting a protective effect of HRT not only on colon cancer but also on lung cancer [30,65–69]. So far, the relevance of the HRT protective effect (25% risk reduction) on lung cancer (no.1 killer for cancer death in women) has been overlooked by the medical community as well as by the media coverage [70]. Therefore, physicians and consumers are not aware of these important positive actions of HRT on cancer risks. These issues should be fully explained when HRT use is discussed with the women concerned about HRT use.

Conclusion

In conclusion, the results of the WHI show that in women of less than 60 years of age, ERT/HRT is safe from a cardiovascular standpoint and may be prescribed without fear. The cardiologist, however, should not prescribe ERT/HRT for women, as this must be initiated by the gynecologist according to the clinical presentation. Cardiologists should counsel gynecologists for the control of cardiovascular risk factors and give advice for the choice of the more appropriate estrogen/progestin combination and the adjunctive therapy to curb cardiovascular risk according to the risk profile of each woman.

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Since December 2007 the Study Group on Cardiovascular Disease in Women of the Italian Society of Cardiology has become Study Group on Gender in Cardiovascular Disease

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