

Controversial issues in climacteric medicine I

Cardiovascular disease and hormone replacement therapy

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Position Paper

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Cardiovascular disease (CVD) in women (including coronary heart disease (CHD), deep venous thrombosis and stroke) can be defined as a silent epidemic. Though thought of as a 'man's disease', CHD is the most common cause of morbidity and mortality in both women and men. In younger age groups, men are at significantly greater risk of developing CHD, but, as a woman ages, her risk for CHD approaches that of a man. The prevalence of CHD in women aged between 45 and 64 years is 1 in 7. Over the age of 65 years, the prevalence is 1 in 3. A significant number of women have atherosclerotic lesions in their vasculature even if they have no clinical signs of CHD. Mortality rises by age in both sexes. The male/female excess is 5 : 1 for those aged 35–44 years, but only 1.5 : 1 for those over 75 years. One in four women of age 60 and older will eventually die of CHD. A 50-year-old woman has a 46% risk of developing CHD and a 31% risk of death due to CHD. Women hospitalized with myocardial infarction (MI) have a mortality rate twice that of men. The high risk of death emphasizes the need for better understanding of heart disease in women. Only 50% of cases are related to predictable risk factors, suggesting the need for a different approach to risk factors in women. Despite the fact that CHD incidence

increases at the time of the menopause, the change is gradual rather than abrupt. Deaths from CHD and cancer are approximately equal in younger women but, over 65 years of age, CHD is the major cause of death. Though CHD overall represents a greater risk of morbidity and mortality, cancer remains a woman's greatest fear even among university graduates who are normally better informed of CHD risks.

Women have a different clinical presentation of an acute ischemic event as compared to men. Indeed, women have unstable angina more frequently than men, whilst men have acute ischemic syndromes more frequently. Women have a worse outcome after acute myocardial infarction, in part because they receive slower medical attention, with a greater delay in receiving care and later and less thrombolysis. In addition, they present more risk factors and higher rates of complications, due to their different pathophysiology or other yet unknown reasons. The development of atherosclerosis is delayed in women compared to men, and normal ovarian hormone production seems to counteract the development of atherosclerosis, while estrogen deficiency is associated with the development of atherosclerosis and CHD.

Despite the marked variation in trends observed over recent decades, marked differences

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in the mortality rate of cerebro-cardiovascular disease are still present. Substantial differences are observed both in mortality from cardiovascular and in cerebrovascular diseases in various areas of the world. The highest mortality rates for ischemic heart disease were registered in the United States (166/100 000 females), and Canada (131/100 000 females). The highest mortality rates from all ischemic heart disease within Europe were in North European countries, while Central and Eastern Europe had intermediate rates. The risk differs in different countries in different parts of the world, in relation to ethnic group, diet and life-style. Populations characterized by different patterns of mortality may have different HRT risk-benefit balances with regard to mortality. These epidemiological differences should be considered in the evaluation of the HRT benefit/risk profile in each country and ethnic group.

WOMEN AND CVD RISK FACTORS

Women share several CVD risk factors with men, such as family history, diet, obesity, smoking, unfavorable lipid profile, high homocysteine levels, high fibrinogen, low physical activity, diabetes mellitus and hypertension. In addition, women have the unique risk factor of the menopause. Women have a greater relative risk than men if they are diabetic, have raised triglyceride levels, low levels of high density lipoprotein (HDL), or if they are smokers. CHD is more common in countries with high saturated fat diets and high cholesterol levels. In addition, homozygous hypercholesterolemic patients are prone to early CHD, while cholesterol-lowering reduces CHD. We need to remember that a 1% decrease in low-density lipoprotein-cholesterol (LDL) gives a 2% decrease in CHD events in men. For CHD in women, low HDL and raised triglyceride levels are more important than LDL levels. We do not yet know whether the HDL level or the triglyceride level is the more important factor in women. Nevertheless, CHD prevention trials using statins have demonstrated that women benefit from LDL cholesterol reduction as much as men. Recent studies have revealed that intensive multiple interventions such as life-style modifications, including diet, weight reduction, smoking cessation and exercise, may reduce the risk of coronary heart disease and can result in fewer cases of heart disease in a very cost-effective manner. Aspirin, beta-blockers and cholesterol-lowering drugs are indicated for women with documented CVD.

MENOPAUSE AND CARDIOVASCULAR RISK

Presumably because of the protective effects of estrogen, women tend to develop CHD about 10 years later than men. Being a male over 45 years of age is considered a risk factor for CHD, whereas females are not considered at risk until they reach 55 years of age. This '10-year advantage' can be lost, however, if a woman starts menopause prematurely or if she has other risk factors, such as smoking or diabetes mellitus. Although few well-designed longitudinal studies have shown some conflicting results, large cross-sectional studies indicate that, in addition to the effect of aging, menopause is *per se* associated with lipid modifications such as an increase in total cholesterol, LDL cholesterol and triglycerides that can cause an increased risk of developing CVD. This increase in total cholesterol results from increases in levels of low-density lipoprotein cholesterol (LDL-C), and increases in very-low-density lipoprotein (VLDL) and lipoprotein(a). The oxidation of LDL-C is also enhanced. High-density lipoprotein cholesterol (HDL-C) levels may decrease over time, but these changes are small and insignificant relative to the increases in LDL-C. The coagulation balance is not altered significantly with menopause because a counterbalance of changes occurs: some procoagulation factors increase (factor VII, fibrinogen), but so do certain fibrinolytic factors such as antithrombin III and plasminogen. In addition, at the time of menopause, changes in vascular reactivity take place: prostacyclin production decreases, endothelin levels increase, and the endothelium-dependent vasodilation is impaired. At the same time, increases in blood pressure and body weight and changes in body fat distribution, plus alterations in insulin sensitivity and glucose metabolism have been reported; in healthy, non-obese, postmenopausal women, carbohydrate tolerance decreases as a result of an increase in insulin resistance.

HRT AND THE LIPID PROFILE

Estrogen replacement can improve the lipid profile in postmenopausal women. The various estrogen formulations, and the route of administration, seem to have different effects on lipid profile over time, although the exact weight of these differences and their clinical significance for CVD risk are still open to discussion. No conclusive evidence suggests that the addition of progestogens, at the doses needed to exert endometrial

protection, attenuates in a clinically significant way the effects of estrogen on lipid profiles, although the effect may vary depending on the type and the dose of different progestogens. Besides the negative effect on HDL-C, data are available on some beneficial effects of tibolone on the lipid profile, but to date there is no information on cardiovascular events.

HRT AND CARBOHYDRATE METABOLISM

Menopausal women exhibit features of the metabolic syndrome X. Postmenopausal women have greater insulin resistance than premenopausal and menopause is followed by a progressive fall in insulin sensitivity. Estrogen replacement increases insulin sensitivity in postmenopausal women, while estrogen-progestin regimens may decrease insulin sensitivity; however, the data are very limited. Thus, progestins may negate the beneficial actions of estrogen on glucose tolerance: this effect is related to the type, route of administration and dose of progestin. In women with type 2 diabetes, ERT and some forms of HRT have recently been shown to improve glucose control, HDL and LDL cholesterol, with minimal or no increase in blood triglycerides. However, all of the existing studies in diabetic women have a small number of participants and are short-term studies. There was clear agreement by the expert panel that more research is needed to determine the effects of estrogen/hormone replacement on glucose metabolism and cardiovascular risk in diabetic women.

HRT AND BLOOD PRESSURE

In addition to the age-related increase in blood pressure levels, women show a more evident increase in both diastolic and, chiefly, systolic blood pressure during the climacteric transition. This phenomenon seems to be principally related to the menopause-related increase in body weight and central, android body fat distribution. HRT has a neutral effect on blood pressure in normotensive women. However, limited data are available concerning the effects of HRT on blood pressure in borderline and hypertensive postmenopausal women.

HRT AND BODY WEIGHT

Overweight and obesity are associated with an increase in morbidity and mortality. In particular, the central distribution of body fat may be

considered as an independent predictor of cardiovascular disease in women. Evidence for an increase in body weight, and a shift to a more central, android fat distribution in normal women throughout the climacteric period has been reported. Perimenopausal hormonal changes rather than the aging process seem to be relevant for the accelerated increase in body weight and body fat, and these can be counteracted, at least in part, by HRT. Most interventional studies indicate that HRT can attenuate the accumulation of central body fat in postmenopausal women compared with control or placebo-treated women.

HRT AND VASCULATURE

In the past several years, exciting new scientific information has emerged regarding how estrogens are able to influence directly and indirectly blood vessel function and structure. Recent studies have shown that the cells of the blood vessels and the heart also contain estrogen receptors. Furthermore, in a number of studies, it has become clear that estrogen binds to these receptors in the cardiovascular system and causes important changes in how these tissues work. At the molecular level, estrogen works by binding to estrogen receptors, but other non-genomic mechanisms may play a role in inducing the estrogenic effects. Experimental data show that estrogens in animal models can improve endothelial function, inhibit LDL oxidation, intimal thickening, vascular smooth muscle cell migration and proliferation and, thus, can prevent or inhibit atherogenesis. In women, estrogens can exert an antiatherogenic effect through their actions on lipid and glucose metabolism. In addition, estrogen administration can cause coronary vasodilation, and can preserve endothelial function. Premenopausal normotensive women are protected against the effect of aging on endothelial function. Estrogen administration restores the endothelium-dependent vasodilation and/or nitric oxide availability. The role of estrogen administration in elderly postmenopausal women with various risk factors is still controversial. However, HRT can effectively reduce the intima-media thickness in hypercholesterolemic, postmenopausal women. Further studies (taking into account co-medication with drugs with an impact on cardiovascular disease such as statins) are needed to assess the effect of HRT upon the progression from its early stages of coronary atherosclerosis in women.

All available data support a role for estrogen receptors in preventing vascular injury. Thus,

these studies provide hope that new tissue-selective estrogens can act selectively on the heart and blood vessels, avoiding the possible side-effects associated with existing hormonal replacement therapies. In postmenopausal women, the selective estrogen receptor modulator, raloxifene, reduces some risk factors of coronary artery disease such as total cholesterol, LDL cholesterol, homocysteine and fibrinogen, while it does not induce any significant change in triglycerides, HDL cholesterol, PAI-1 and C-reactive protein. In addition, raloxifene exerts effects similar to those of estradiol at the endothelial level. Ongoing randomized clinical trials are evaluating the effect of raloxifene on the incidence of coronary events.

HRT AND CARDIOVASCULAR EVENTS

Deep venous thrombosis

Current, but not past, use of HRT in early postmenopausal women is associated with a 2–3-fold increase of venous thrombosis (VTE). Consistently, the results for all studies indicate that, among healthy postmenopausal women, an excess risk of one to two cases of idiopathic VTE per 10 000 women per year can be attributed to current use of HRT (estimated incidence of idiopathic VTE per 10 000 women per year of 1 in non-estrogen users and of 2–3 in estrogen users). Thus, the absolute risk is small and the mechanism largely unclear. The risk is more prominent in the first year of therapy and appears to be dose-dependent. However, caution in high-risk situations must be advised, such as low pretreatment PAI-1 values, which may negate any cardiovascular benefit and result in a substantial increase of the thromboembolic risk. Despite an increase in VTE events, no increase in mortality from pulmonary embolism has been reported. The use of raloxifene or tamoxifen is associated with an excess risk of VTE events similar to that associated with HRT. Transdermal estradiol seems to be associated with a lower risk of VTE but it is still higher than in untreated postmenopausal women.

Coronary heart disease

Data from human observational, non-randomized studies suggest that HRT may protect women from CHD, even if the effects on stroke are more debatable. The lack of data from prospective, randomized trials renders the prevention of CHD with HRT still uncertain. The results of epidemiological studies conducted among women without CHD show a 20–50% reduction in the risk of

CHD. Analysis of the effect of estrogen within different risk factor categories in the 16-year follow-up of the Nurses' Health Study confirms that, although relevant risk estimates are highly similar, the magnitude of the protective effect of estrogen is more pronounced among women with high baseline risk of disease.

The beneficial effects are present after 1–2 years of use, and cease 2–3 years after stopping HRT. Although based on few users, transdermal therapy appears to have a long-term cardioprotective effect similar to that of oral therapy. Women who are on HRT to prevent or cure clinical symptoms related to estrogen deprivation (such as hot flushes, urogenital atrophy, osteoporosis) may benefit from CHD prevention, which can be seen as a possible additional benefit. However, in observational population studies, potential confounders such as selection bias, autoselection of patients treated with HRT, changes in life-style and diet (the healthy user effect) may impact on the results of long-term studies on primary prevention. Randomized clinical trials are still needed to evaluate the impact of HRT on primary prevention of CVD. Background HRT does not preclude and cannot replace specific 'targeted' therapy in the at-risk woman (statins, aspirin, antihypertensive drugs).

Primary vs secondary prevention

From the data we have, it would appear that early intervention with HRT in postmenopausal females may be more effective in reducing the risk of CHD than if it is started after significant coronary artery disease has been allowed to develop. Results of prospective trials seem to suggest that, in elderly women with advanced coronary artery disease, HRT may not reduce the risk of coronary heart disease.

The Heart and Estrogen/progestin Replacement Study (HERS) – a randomized, blinded, placebo-controlled trial – was a secondary prevention trial, conducted to determine if estroprogestin therapy given in a fixed dose changes the risk for secondary CHD events in an older cohort of postmenopausal women (mean age, 67 years) with established coronary disease. The study was stopped prematurely at 4.1 years of follow-up. At that premature discontinuation time point, no demonstrated benefit of HRT was seen. A statistically significant ($p = 0.009$) time trend was noted, with more CHD events occurring in the hormone group than in the placebo group in year 1 and fewer events in years 3–5. The authors concluded that, 'given the favorable pattern of

CHD events after several years of therapy, it could be appropriate for women already receiving hormone treatment to continue'. Subsequent re-evaluations of the HERS results have shown that the effects of HRT on CHD risk are different for particular subgroups of patients (accordingly to the levels of lipoprotein(a) or statin use). The HERS is therefore *per se* inconclusive for the use of HRT in CHD secondary prevention. In addition, it should be underlined that the results of the HERS cannot be extended to all the HRT schedules and dosages used with different types of natural or synthetic hormones. Above all, HERS results cannot be applied to the use of HRT for the primary prevention of CHD.

The Estrogen Replacement and Atherosclerosis (ERA) trial is a randomized, double-blind, placebo-controlled study that evaluated the effects of ERT and HRT on the progression of coronary artery disease in normal cholesterolemic postmenopausal women with angiographically verified coronary artery disease at baseline. After 3.2 years of follow-up, 248 of the 309 subjects (80%) had final angiographic evaluations. The primary end-point was the mean minimum lumen diameter within each subject; secondary outcomes included alterations in plasma lipids, percentage stenosis, and new lesion development. No difference in mean lumen diameter was found between ERT, HRT, or placebo groups. One or more new lesions developed in 33% of patients in the placebo group, 30% of patients in the ERT group, and 20% of patients in the HRT group ($p = 0.06$ for HRT vs. placebo). Unlike the HERS, the ERA study did not show any increase in events during the first year of HRT treatment. It must be pointed out that the majority of patients randomized to receive placebo were on statin therapy and that, therefore, the real comparison of the study was HRT vs statins. It should be noted that this study evaluated a surrogate marker for clinical outcomes, that the 3.2 years of follow-up may not be long enough, and that the population was limited to older postmenopausal women with established CHD and normal cholesterol values. In addition, in similar populations, statin use has not been shown to reduce progression of coronary atherosclerosis.

After the concern raised by the HERS' demonstration of an increase in CHD events in the first year of HRT, the investigators carried out a critical revision of available data for the Nurses' Health Study. They evaluated the recurrence of CHD events in a subset of postmenopausal women ($n = 2245$) with documented heart disease with similar criteria to those for HERS. Similarly

to the HERS data, in women with a prior myocardial infarction, a decreased risk for recurrent events was noted only for women using ERT/HRT for 2 years or more. Conversely, women with prior CHD without myocardial infarction had a reduced risk ($RR = 0.50$) for both short- and longer-term duration of ERT/HRT use.

If the preclinical and clinical data are carefully evaluated, it is apparent that HRT has the most profound effect on CHD risk (and development of coronary artery atherosclerosis) if started soon after the menopause. Recently, the results of studies in premenopausal monkeys indicate that premenopausal risk and premenopausal hormone therapy (oral contraceptives) change the trajectory of development of coronary artery disease. Specifically, premenopausal monkeys at increased risk for CHD (females with stress-induced ovarian impairment) will develop more atherosclerosis postmenopausally than their non-stressed counterparts (whether or not they receive postmenopausal HRT). Importantly, premenopausal hormone therapy impairs development of postmenopausal coronary artery disease in estrogen-deficient females (unpublished data reported by K. Williams). These results indicate that premenopausal risk can affect development of coronary artery disease postmenopausally. Finally, it would appear that early intervention with HRT in postmenopausal females may be more effective in reducing the risk of CHD than if it is started after significant coronary artery disease has been allowed to develop. Acute cardiac events and the progression of atherosclerosis are two distinct phenomena and the progression of an atherosclerotic plaque does not lead to an acute ischemic event unless it becomes unstable. Thus, while it is possible to suggest that HRT can exert a primary prevention of CHD, at this time there is no indication for prescribing HRT for an immediate secondary prevention of CVD. If HRT is indicated in a postmenopausal woman with a previous coronary event, caution should be used in choosing the type, dosages and schedules of hormones used.

Low-dose therapies

Studies of low doses of estrogens and newer progestins have been the focus of recent and ongoing research. Preliminary data show beneficial effects on lipid profiles as well as on arterial reactivity, while controlling clinical symptoms and the excess of bone resorption occurring in the postmenopausal years. Further randomized clinical studies may clarify the possible cardiovascular effects of low-dose HRT.

SUMMARY

The clinical benefits of HRT are clearly established for the relief of menopausal symptoms, improving quality of life and the prevention of osteoporosis. Although research on the impact of HRT (oral, transdermal, tibolone, etc.) and on the effects of raloxifene on CVD is still ongoing, with certain unresolved controversies, studies using a variety of different HRT formulations have shown a clear benefit on surrogate markers of CHD and epidemiological and clinical, although not randomized, studies have demonstrated a CHD reduction in HRT-treated women. Today, HRT may be used for the primary prevention of CVD. Conversely, there is no clear reason to commence HRT solely or primarily to confer an immediate cardiovascular benefit in postmenopausal women with established CHD. Equally, there is no compelling evidence for discontinuing – or indeed not

initiating – HRT in women without CVD because of concern about cardiovascular risk. In any case, all medical interventions should be individualized to the specific woman's age, characteristics and needs. The ultimate effects of different dosages, schedules and type of hormones used should be clarified, avoiding inferring the effects of one form of HRT to others. The importance of increased attention to life-style factors such as healthy diet, exercise and cessation of smoking should be underlined since these can confer specific benefits also to menopausal women. For women with known risks for CVD, HRT may contribute to the beneficial effects of life-style improvements and well-established therapies (including blood pressure control, cholesterol-lowering drugs, aspirin, etc.). New strategies, including lower dosages, new estrogens, progestins, and new estrogen-like substances may be designed to target specific needs.

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