

Aging, menopause, cardiovascular disease and HRT

INTERNATIONAL MENOPAUSE SOCIETY CONSENSUS STATEMENT

The Writing Group on behalf of the Workshop Consensus Group

This Statement is a result of a Workshop organized by the International Menopause Society, with the participation of the Task Force on Gender of the European Society of Cardiology. The Workshop was organized because of the urgent need to address the following items:

- Cardiovascular disease is the number-one killer of women in the Western world.
- The public, and many physicians, have a very low awareness of the relevance of cardiovascular disease to menopausal women.
- The public and many physicians are concerned that menopausal treatments (particularly hormonal therapies) increase the risk of cardiovascular disease, despite recent evidence showing that, in general, this is not the case in all age groups.

The aim of the Workshop was to produce a state-of-the-science view of the cardiovascular aspects of menopause and of the existing menopausal treatments. The results are based on current knowledge of the risks for cardiovascular disease in women and the effects of hormone and other therapies, and involved doctors from many different disciplines with an interest in adult women's health. It is intended to give a balanced perspective on the commonest cause of death in postmenopausal women. This statement has been seen and approved by all participants at the Workshop.

FINDINGS AND CONCLUSIONS

- Cardiovascular disease is the number-one killer of women in the Western world.

- Women and their physicians should be more aware of the unique factors that increase their risk of cardiovascular disease.
- Abnormal risk factors should be treated using evidence-based methodologies bearing in mind differences between men and women.
- Blood pressure measurement and assessment of other risk factors for cardiovascular disease are recommended in the routine management of all menopausal women.
- The effective management of even high-normal blood pressure will reduce the risk of cardiovascular disease.
- The consensus of the Workshop was that hormone replacement therapy (HRT) can be given to women around the age of natural menopause without increasing the risk of coronary heart disease and may even decrease the risk in this age group.
- HRT is not contraindicated in women with hypertension and, in some cases, HRT may even reduce blood pressure.
- HRT is contraindicated in women with a history of myocardial infarction, stroke, or pulmonary embolism.

INTRODUCTION

Many women and their physicians are unaware that cardiovascular disease (CVD) is the commonest cause of death in women overall and proportionally this is increasing in many parts of the world. In low-income countries, the loss of healthy years due to CVD is much higher than in high-income countries. In the Western world, women fear breast cancer most, particularly since it is more common than heart disease around the age of menopause, although the overall risk of

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dying from CVD is 1 in 2 compared to 1 in 26 for breast cancer when all ages are included. Many of the risk factors for CVD can be modified by lifestyle changes and especially by the effective management of hypertension and diabetes, combined with lipid modification. After the menopause, the risk of CVD increases, regardless of the age at which this occurs. Given the risks of CVD in this population, clinicians need to manage menopause symptoms in a way which is effective, but which at the same time minimizes the very significant dangers presented by the threat of CVD.

RISK FACTORS FOR CVD IN WOMEN

Lifestyle has a major impact on an individual's risk of CVD and simple modifications can have a significant impact on cardiovascular risk factors. Women also have gender-specific risk factors such as a history of pre-eclampsia and polycystic ovary syndrome. The impact of diabetes mellitus, smoking and raised triglycerides on CVD risk is greater in women than in men.

The effect of hypertension in women is underestimated and undertreated. The increase of blood pressure with age is more marked in older women, so that by the age of 60 years up to 80% of women will have hypertension. A high-normal blood pressure (140/90 mmHg) is associated with an increased risk for CVD and many studies have shown that even small reductions in blood pressure result in major reductions in CVD risk. It is estimated that, at the menopausal transition, a reduction of 10 mmHg in systolic blood pressure will result in a 25% reduction in cardiovascular events. There is a perception that HRT may adversely affect blood pressure and is contraindicated in hypertensive menopausal women. Hypertension is not a contraindication to HRT, but it is recommended that blood pressure is carefully monitored and well controlled.

THE ROLE OF HRT

After the menopause, the risk of CVD increases, regardless of the age at which this occurs, but the potential role of HRT in CVD management has remained controversial. However, HRT is the first-line and most effective treatment for menopausal symptoms but, despite extensive, good-quality clinical outcome data on efficacy and safety when HRT is begun for symptoms in the early postmenopause, many physicians and the general public now believe that hormones result

in increased cardiovascular risks and are therefore unsuitable for the relief of menopausal symptoms.

This is a result of the concerns about HRT safety following the publication of the Women's Health Initiative (WHI) study in particular and the initial assessment of the data in 2002¹, which suggested that there was an increased risk of coronary heart disease (CHD) and breast cancer in users of HRT containing estrogens and a synthetic progestin. However, more detailed analyses of the WHI data have since shown that the apparent increased risk of CHD is not statistically significant^{2,3} and furthermore that, when HRT is started around the time of the menopause, there is no significant risk and there may even be a suggestion of some cardiovascular protection. This re-analysis in younger women by the WHI authors has received little publicity. Critics of this re-analysis express concerns regarding views based on such a small number of events; this is very pertinent since, in the vast majority of cases, HRT is prescribed to younger women to manage their climacteric symptoms, while the use of HRT in older women is uncommon.

The Workshop consensus view is that every woman suffering from menopausal symptoms should be given the opportunity to decide whether or not to take HRT based on what is appropriate for her as an individual. This means taking into account previous medical history, family medical history, age, etc. All medications carry some risks as well as benefits, and so every woman should be able to make an informed decision on the best way to treat menopausal symptoms in consultation with her clinician.

CONCLUSIONS

General

- The incidence of cardiovascular morbidity and mortality rapidly increases with age in women, particularly after the menopause.
- Hypertension, cigarette smoking, dyslipidemia, diabetes mellitus, high body mass index and the metabolic syndrome are all powerful predictors of cardiovascular events.
- Every opportunity should be taken when managing a menopausal woman to identify the extent of her cardiovascular risk⁴.
- The perimenopausal woman is increasingly likely to become hypertensive and will require blood pressure-lowering measures to reduce the incidence of target-organ damage. Slightly

elevated and even high-normal blood pressure poses a risk and should be addressed.

- Lifestyle changes and pharmacological intervention should be introduced in perimenopausal women to minimize cardiovascular risk.
- Cardiovascular risk factors should be aggressively managed.

Menopause, HRT and CVD

- HRT in women aged 50–59 years does not increase the risk of CHD in healthy women and may even decrease the risk in this age group². [A]*
- In the WHI study, estrogen-alone therapy in the age group 50–59 years was associated with significantly less coronary calcification (equivalent to a smaller plaque burden), which is consistent with findings of a lower coronary intervention score in women of this age. [A]
- Early harm (more coronary events during the first 2 years of HRT) was not observed in the early postmenopausal period. The number of CHD events decreased with duration of HRT in both WHI clinical trials⁵. [A]
- Data derived from randomized controlled trials in the age group 50–59 years are similar to the older observational data, suggesting a protective effect of HRT on coronary disease^{3,6}. [A, B]
- It is unclear at present whether there is an increase in ischemic stroke with standard HRT in healthy women aged 50–59 years. The WHI data showed no statistically significant increase in risk; nevertheless, even if statistically increased, as found in the Nurses' Health Study, the low prevalence of this occurrence in this age group makes the attributable risk extremely small^{7,8}. [A, B]
- The risk of venous thrombosis is approximately two-fold higher with standard doses of oral HRT, but is a rare event in that the background prevalence is low in a healthy woman under 60 years of age⁹. [A]
- The risk of venous thrombosis is possibly less with transdermal, compared with oral estrogen therapy¹⁰. [B]

*Levels of evidence: [A] evidence refers to data from randomized controlled trials and [B] evidence comes from case-controlled/observational studies.

Writing Group The members of the Writing Group were agreed by the final session of the

Workshop. This Writing Group comprised Dr David Sturdee, Professor Peter Collins (representing the Task Force on Gender of the European Society of Cardiology), Professor Andrea Genazzani and Dr Tommaso Simoncini. The Consensus Statement was circulated to the Board of the International Menopause Society (IMS), the Workshop Consensus Group (comprising all speakers at the Workshop) and all Workshop delegates. The IMS has received no dissenting opinions on the content of the final document.

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APPENDIX: Risk factors for cardiovascular disease in women

Lifestyle has a major impact on an individual's risk of CVD and simple modifications can have a major impact on risk. Women have gender-specific risk factors, such as a history of pre-eclampsia and/or fetal growth restriction, which double a woman's risk of future CVD. Early identification of the 5% of women who have had pre-eclampsia and/or fetal growth restriction and implementation of dietary, therapeutic and lifestyle changes may lead to a reduction of CVD in these women. Polycystic ovary syndrome is also a unique risk factor for CVD in women, but possibly the most important gender-related risk factor for CVD is menopause, which increases the risk of having a coronary event at any age. This particularly applies to premature menopause or to surgical menopause, before the age of 45 years. Ovarian failure or removal before this age is associated with a significant increase of CHD and stroke².

Many of the traditional cardiovascular risk factors differ in relevance as compared to their

weight in males. For instance, the impact of smoking, raised triglyceride levels or low levels of high density lipoproteins on CVD risk is far greater in women than in men. On the other hand, commonly used medications to treat high cholesterol levels, such as statins, are not effective for primary prevention of coronary events in women at low or intermediate cardiovascular risk, as opposed to men where they are effective in reducing cardiovascular events, even in those individuals at low risk.

Diabetes mellitus and hypertension are strong predictors of CVD in women, and the impact is increased by their high prevalence throughout the world. The effect of hypertension in women is underestimated and this condition is undertreated. The increase of blood pressure with age is more marked in women, so that, by the age of 60 years, up to 80% of women will have hypertension (as defined by blood pressure >140/90 mmHg). A high-normal blood pressure (140/90 mmHg) is

associated with an increased risk for CVD and many studies have shown that even small reductions in blood pressure result in major reductions in CVD risk. Lifestyle readjustments are recommended to help achieve this. It is estimated that, at the menopausal transition, a reduction of 10 mmHg in blood pressure will result in a 25% reduction in cardiovascular events.

Some epidemiological studies have suggested that women with intense climacteric symptoms, particularly hot flushes, are more likely to develop hypertension and may have a higher cardiovascular risk. If this is true, a novel group of women at risk of CVD will have been identified, requiring further monitoring and treatment. However, the mechanism for any relationship is as yet unknown.

Menopause, HRT and CVD: insights from research

The understanding of the biological actions of sex steroid hormones on cardiovascular tissues has increased significantly over the past 30 years. It is now appreciated that vascular endothelial and smooth muscle cells, and cardiomyocytes, all express functional sex steroid hormone receptors and function as ligand-activated transcription factors to regulate gene expression in these target tissues. By regulating gene expression and also by activating rapid signal transduction pathways, estrogens regulate a variety of effects that are important for the normal physiology and function of endothelial and other cardiovascular cells. There is enormous promise in applying these concepts to the development of more selective estrogen receptor modulators that have benefit for the cardiovascular system. This has begun and will create the next generation of hormone replacement therapies. Substantial experimental data from molecular, cellular and translational studies demonstrate that estrogen has beneficial effects on vascular and myocardial cells and can delay the development and progression of atherosclerosis. Estrogen supplementation with HRT is effective in most preclinical studies in delaying and/or preventing the progression of atherosclerosis and in limiting the response to vascular injury. Current thinking by leading experts in the field is that estrogens have beneficial actions on the cardiovascular system that contribute to the lower incidence of CVD in premenopausal women as compared to males. The available evidence clearly demonstrates that the effect of re-establishing estrogen exposure on the cardiovascular system in menopausal women is critically dependent on the timing of administra-

tion. Estrogen replacement, when begun shortly after the menopause, at the time when menopausal symptoms emerge, and continued for a sufficient amount of time retards the development of vascular disease. On the other hand, hormone administration, given a number of years after the menopause, as occurred in the WHI study and particularly in the presence of established atherosclerosis, does not confer benefits and can cause harm due to the very different vascular biology that exists following a number of years of atherosclerotic progression in the absence of hormones. Thus, hormone replacement given to the older woman can lead to unwanted side-effects related to enhanced vein thrombosis or plaque instability.

Managing cardiovascular risk in menopausal women

Evaluation of cardiovascular risk in menopausal women should be a standard part of a gynecological consultation. Tools such as the guide elaborated by the IMS/European Society of Cardiology/European Society of Hypertension provide general indications and recommendations on how to determine and manage cardiovascular risk in women, and their use is encouraged by both gynecologists and general practitioners. Gynecologists have the privileged position and opportunity of raising awareness in healthy women of the risks they incur from common lifestyle factors and hormonal changes, thus possibly making a difference for their future cardiovascular health.

Blood pressure

The aging process is characterized by a progressive increase in the stiffness of large vessels that results in increased blood pressure. In women, the menopausal transition is associated with increased sympathetic activity and sensitivity to salt, both of which are related to increased blood pressure. Menopause is also accompanied by progressive worsening of endothelial function in women. Although there is an association between being postmenopausal and having a higher blood pressure, this is found only around the time of natural menopause, but not later in life.

While 140/90 mmHg is the threshold to diagnose stage I hypertension, from epidemiological studies there is no blood pressure threshold for increased cardiovascular risk, as the risk consistently increases related to increases in blood pressure. Thus individuals with blood pressure in the 'normal' or 'high-normal' range should not be disregarded in

primary prevention programs. In fact, it is estimated that at the menopausal transition any reduction of 10 mmHg in blood pressure will result in a 25% reduction in cardiovascular events. Low-fat diet, reduced salt, increased physical activity and weight reduction are effective in reducing blood pressure. From the clinical standpoint, uncontrolled high blood pressure is the single most important cardiovascular risk factor in postmenopausal women. The control of blood pressure is effective in reducing the incidence of cardiovascular events in women; however, there are some gender-specific differences in the clinical efficacy and side-effects of antihypertensives.

Metabolic syndrome

The bodily changes of menopause render women more prone to meet the diagnostic criteria of the metabolic syndrome. An increase in body weight and an android redistribution of fat are related to menopause and they both favor peripheral resistance to insulin and an increase of blood pressure, along with a worsened lipid profile. The changing hormonal status is also related to activation of the renin-angiotensin-aldosterone system, facilitating the increase in blood pressure.

Diet and physical exercise are highly effective in reducing metabolic syndrome and the risk of diabetes mellitus, and should be encouraged in all postmenopausal women. When necessary, drugs such as acarbose and metformin may be used, which clinical trials have shown to be helpful in controlling metabolic syndrome. All women with the features of metabolic syndrome should be aggressively encouraged to change lifestyle and diet and to achieve optimal levels of blood pressure, so as to prevent CVD.

The efficacy of statins in women has not been investigated as extensively as in men. Based on the available studies, statins are not effective in primary prevention of CVD in hypercholesterolemic women of any age who do not have any added risk factor. However, they reduce cardiovascular risk in the presence of high blood pressure or type 2 diabetes. Although there is no specific evidence to indicate that statins may not be effective in the setting of secondary prevention of CVD in postmenopausal women, all clinical trials have included a minority of women.

Body weight, diet and physical activity

Body weight is directly linked to cardiovascular risk and mortality rates, and the reduction of weight

results in significant improvements of key cardiovascular risk factors, such as abdominal adiposity, high cholesterol, insulin resistance and elevated blood pressure.

A healthy diet for women in their menopausal years should be rich in fruits, vegetables, fiber and proteins (including fish twice weekly). Diet should contain <1 teaspoon salt daily and cholesterol limited to <300 mg daily. One gram calcium and 800 IU vitamin D daily are recommended; however, there is no consensus on the role of other food supplements.

Regular physical exercise has been shown to induce a 75% decrease in cardiovascular risk, with figures that are even higher if the woman has one or more cardiovascular risk factors. An optimal training program for younger, healthy women after the menopause is represented by at least 30 min of moderate exercise at least three times per week, eventually combined with two sessions of resistance exercise.

HRT and CVD: the facts

HRT and blood pressure

There is a perception that HRT may adversely affect blood pressure and is contraindicated in hypertensive menopausal women. However, the impact of standard doses of oral or transdermal HRT on blood pressure is minor and inconsistent, and thus HRT does not increase blood pressure. Hypertension is not a contraindication to HRT, but it is recommended that blood pressure is well controlled. On the other hand, specific HRT preparations, such as those containing oral estradiol combined with sufficient amounts of drospirenone (at least 2 mg), a progestin that antagonizes the aldosterone receptor, are effective in reducing blood pressure in stage 1 hypertensive postmenopausal women and to synergize with angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor (ATR) inhibitors and diuretics (hydrochlorothiazide). Similar preparations containing higher amounts of drospirenone (3 mg) have also been shown to reduce blood pressure in postmenopausal women with type 2 diabetes.

HRT and CHD

The cumulative analysis of the WHI study shows that HRT does not increase CHD at any age in a population without prevalent CHD. Earlier observational studies enrolled a very different

population (lower age, symptomatic (hot flushes), earlier start of HRT after menopause, longer HRT durations, lower body mass index) as compared to the WHI. HRT does not have the same cardiovascular effect in all age ranges, as it is associated with beneficial effects in younger women, but not in older women. This is confirmed by all available studies, either observational or randomized, including the WHI, and, more recently, the Raloxifene Use for the Heart (RUTH) trial; the latter trial demonstrated the same pattern of protection from CHD for another class of medications, selective estrogen receptor modulators (SERMs). These findings are consistent with the available evidence from experimental studies, suggesting that estrogens slow the progression of atherosclerosis, and this was confirmed by the WHI finding of a significant protective effect on calcium deposition in coronary arteries in postmenopausal women receiving conjugated equine estrogens. In fact, estrogens are so far the only therapy that has been demonstrated to reduce coronary artery calcium deposition under randomized, controlled conditions. In agreement with these findings is that increasing duration of HRT is associated with increasing protection from coronary events and total mortality in observational studies and in the WHI. An extensive meta-analysis pooling all the available trials, including the more recent, randomized studies, has shown that HRT reduces mortality from all causes. The extent of reduction of mortality associated with postmenopausal HRT is greater than that found in meta-analyses looking at lipid-lowering medications and aspirin.

When discussing the unwanted side-effects of HRT, such as the potential increase of breast cancer, it is to be noted that the frequency of these events falls into the 'rare' category of the WHO-CIOMS classification and that equivalent increases of breast cancer risk have been found in trials with statins.

HRT, deep vein thrombosis and pulmonary embolism

Oral HRT is known to increase the risk of deep vein thrombosis and pulmonary embolism. While the frequency of deep vein thrombosis or pulmonary embolism is low in young and perimenopausal women, the incidence of venous thromboembolism (VTE) markedly rises with increasing age after menopause. Venous thromboembolism may cause significant disability and, therefore, it is an important contributor to the burden of CVD

among postmenopausal women. Within the available HRT preparations, there is a significant difference in VTE risk between oral estrogens, which induce activated protein C resistance, a marker of increased likelihood of thrombosis and transdermal estrogens. This is due to the lack of the hepatic first-pass effect associated with the non-oral route.

In women at high risk for deep vein thrombosis, such as those with thrombophilia or elevated body mass index, transdermal estrogens do not confer an additional thrombotic risk, while this happens with oral estrogens; thus, non-oral estrogens should be used for women at high risk for thrombosis.

Natural progesterone and pregnane derivatives do not increase thrombotic risk, while non-pregnane derivatives seem to increase the risk, although these results need to be confirmed with larger and more detailed studies. If estrogens are administered orally, an increased thrombotic risk is found independently from the associated progestin. Genetic markers, such as some polymorphisms of the *CYP3A5* gene, may help in the future to identify women at increased thrombotic risk when using oral estrogens.

HRT and stroke

Risk of stroke increases with age, but there is no gender difference, as opposed to CHD. In the 50–59-year-old age range, 6–8/10 000 women/year will have a stroke. The main risk factors are hypertension and obesity.

The effects of postmenopausal HRT on the incidence of ischemic stroke (there is no association with hemorrhagic stroke) are complex and still debated. In general, the cumulative analysis of the clinical trials suggests a trend towards an increased incidence of stroke in women using HRT. However, there are differences between the studies. In the WHI trial, the increased risk was absent in younger women (50–59 years), possibly due to the extremely low event rate, and was not significant in any group after adjustment for confounding factors. In the large cohort of the Nurses' Health Study, a significant increase in the incidence of stroke was noted in all age groups and was absent with low-dose HRT (0.3 mg conjugated equine estrogens (CEE)/day).

In the worst-case scenario, if the 1.4 hazard ratio for the incidence of stroke in users of HRT is assumed to be true, in young postmenopausal women (50–54 years old) this would imply an increase of 1.5 cases/10 000 women over a background

incidence of 3.8 cases/10 000 women/year, which makes this important, unwanted effect very rare.

HRT and CHD: special issues

Transdermal estrogens

Transdermal estrogens do not increase C-reactive protein levels, a different result from the oral route, but the clinical significance of this is uncertain, particularly because oral estrogens decrease other markers of inflammation. The metabolic and hemostatic effects of HRT vary according to the dose, the type of hormones as well as the route of administration. Patients with abnormal lipids, glucose or insulin levels may benefit from the oral route, while women with hemostatic abnormalities might benefit from transdermal administration. In general, in young healthy postmenopausal women, the choice between transdermal and oral estrogens might just be based on personal preference.

Estrogen dose

Low doses of estrogens are effective in relieving menopausal symptoms and in protecting the bones. In addition, as a consequence of the need for less progestin, they also induce less progestogenic side-effects. The incidence of VTE is reduced with decreasing estrogen dose. Low doses of estrogens provided orally still induce improvements in the lipid profile, while being associated with lesser modification of protein S and with improvements of endothelial function. In a recent trial (WHISP), low-dose HRT given to older women with established CHD did not increase procoagulant activity and was associated with a trend towards a reduction of cardiovascular events. In general, women over 60 years should receive low doses of estrogens (e.g. 0.5 mg estradiol or 0.3 mg CEE, or 25 µg estradiol patches). Low-dose HRT may also have some bone-sparing effects, although the impact on fracture risk is as yet unknown.

Progestins

All progestins are agonists for the progesterone receptor, but they differ significantly in their ability to bind and activate/interfere with the binding of other steroid receptors. Some, but not all, progestins can be administered via non-oral routes: intrauterine, transdermally, vaginally. The non-androgenic progestins seem to have several

advantages vs. the androgenic ones for cardiovascular function. Studies in animals and humans suggest that some progestins might interfere with estrogen action in the vessels. For instance, androgenic progestins interfere significantly with the modifications of the lipid profile associated with estrogens. Different progestins might differ in their effects on clotting factors according to the type of associated estrogen. Non-androgenic or anti-androgenic progestins seem to be metabolically neutral. The antimineralocorticoid receptor progestins could have specific effects in reducing blood pressure. Vaginal administration of progestins increases bioavailability and may have specific advantages. Since progestins are not all the same, the results of the WHI trial on CVD, where a combination of CEE + medroxyprogesterone acetate was used, cannot be extrapolated to all other HRT combinations, and data on CVD events are not available on other estrogen/progestin combinations.

Androgens

Androgens are produced by the ovary and the adrenal gland, but there is a significant amount of extraglandular production from conversion of other steroids. Androgen receptors are expressed in most cardiovascular cells, but the effects on these cells seem to depend largely on the concentration of the steroids. Dehydroepiandrosterone (DHEA) and its sulfate form (DHEAS) are the major circulating androgens. Their concentrations progressively decline with aging, starting from early adulthood. This is associated with progressive increases in cortisol production, indicating a global change in the endocrine properties of the adrenal gland throughout aging. From age 20 to 40 years, there is a 50% reduction in androgen levels (DHEA, DHEAS and testosterone). While there is ample evidence of an association of low DHEAS levels with higher incidence of CVD in males, this has not been found in normal women, but only in postmenopausal women with cardiovascular risk factors. Administration of DHEA to postmenopausal women is linked to improved endothelium-dependent vasodilatation. The available data on different routes of testosterone administration suggest neutral effects on plasma lipids. Parenteral testosterone seems to improve endothelium-dependent vasodilatation. The effects of androgen supplementation in women at cardiovascular risk are not clear, but there are indications that the effects might be related to the molecule, the dose and the route of administration.

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) protect from vertebral (but not from non-vertebral) fractures, they reduce the risk of estrogen receptor-positive breast cancers and do not stimulate the endometrium. The effects on the cardiovascular system and on the brain are not fully established. The most investigated SERM, raloxifene, reduces total and low density lipoprotein cholesterol. In the MORE trial, no significant effect of raloxifene on CHD was found in the whole cohort, while a protection was seen in women at increased cardiovascular risk at baseline. In the same trial, an increased risk of VTE around the initiation of the therapy was seen. No effect on stroke was found. The RUTH trial, looking at women with established CHD or very high cardiovascular risk, and with a mean age of 67 years, found no protection from CHD and no harm, but a significant reduction in coronary events in women below the age of 60, along with no difference in total stroke, but an increased risk in fatal stroke. The risk of VTE was increased. Limited results are currently available for newer SERMs, such as bazedoxifene and lasofoxifene.

Vaginal estrogens

The menopausal transition is associated with a sharp increase in vaginal dryness, causing sexual dysfunction and distress that are higher in early menopause than later in life. It is important to treat these symptoms in a timely fashion, particularly for their disrupting impact on self-esteem and quality of life. Topical hormones, including estrogens or androgens, are effective in treating vaginal atrophy, with all estrogen preparations being equally effective in reversing vaginal atrophy. Their use should be continued indefinitely to maintain the effect. There is no contraindication or interaction between the use of vaginal estrogens and CVD.

Further reading

Risk factors for CVD in women

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Body weight, diet and physical activity

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