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Special article

Management of cardiovascular risk in the peri-menopausal woman: a consensus statement of European cardiologists and gynaecologists

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Cardiovascular risk is poorly managed in women, especially during the menopausal transition when susceptibility to cardiovascular events increases. Clear gender differences exist in the epidemiology, symptoms, diagnosis, progression, prognosis, and management of cardiovascular risk. Key risk factors that need to be controlled in the peri-menopausal woman are hypertension, dyslipidaemia, obesity, and other components of the metabolic syndrome, with the avoidance and careful control of diabetes. Hypertension is a particularly powerful risk factor and lowering of blood pressure is pivotal. Hormone replacement therapy is acknowledged as the gold standard for the alleviation of the distressing vasomotor symptoms of the menopause, but the findings of the Women's Health Initiative (WHI) study generated concern for the detrimental effect on cardiovascular events. Thus, hormone replacement therapy cannot be recommended for the prevention of cardiovascular disease. Whether the findings of WHI in older post-menopausal women can be applied to younger peri-menopausal women is unknown. It is increasingly recognized that hormone therapy is inappropriate for older post-menopausal women no longer displaying menopausal symptoms. Both gynaecologists and cardiovascular physicians have an important role to play in identifying peri-menopausal women at risk of cardiovascular morbidity and mortality and should work as a team to identify and manage risk factors such as hypertension.

Introduction

Cardiovascular disease is often regarded as a problem that only men face. Most women do not perceive cardiovascular disease as an important health concern and report that they are not well informed about their risk.[1] The medical profession is equally at fault: primary-care physicians, gynaecologists, and cardiovascular physicians often fail to identify cardiovascular risk factors and underdiagnose and undertreat women with cardiovascular risk.[2] This is despite the fact that, over their lifespan, women are more likely to experience cardiovascular disease and disability than men and will require intervention to improve survival.

In Europe, 55% of women will die of cardiovascular disease as opposed to 43% of men.[3] Coronary heart disease (CHD) accounts for 23% of deaths in women, stroke for a further 18% and other cardiovascular disease for 15%.[3] By comparison, in men, CHD is responsible for 21% of deaths, stroke for 11% and other cardiovascular disease for 11%.[3] Many women have a great fear of cancer and identify breast cancer as a leading cause of death,[1] although in reality breast cancer is responsible for only 3% of female deaths (*Table 1*),[3] but is a considerable cause of morbidity.

The mission of the European Society of Cardiology is to improve the quality of life in the European population by reducing the impact of cardiovascular disease. The Society has recognized scientific gaps in our understanding of cardiovascular disease in women and has instigated its 'Women at Heart' programme.[4] The aim is to increase the awareness of cardiovascular disease in women, with the education of the general population as well as the medical and scientific community. As part of this programme, a meeting was conducted to build an expert opinion on the

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Table 1 Causes of death in women within the European Union[3]

Cause of death	Incidence (%)
Coronary heart disease	24
Stroke	18
Other cardiovascular diseases	15
Cancer	
Breast	3
Lung	2
Colorectal	2
Stomach	1
Other	9
Respiratory disease	6
Injuries and poisoning	4
Other	16

interdisciplinary treatment algorithm for menopausal women with climacteric symptoms, with particular emphasis on management of cardiovascular risk factors. This also met the recently identified need by gynaecologists for a consensus on cardiovascular risk in the menopause, with true dialogue between all parties concerned.[5] Furthermore, a recent Position Statement by the Executive Committee of the International Menopause Society stressed the importance of clinical research to improve clinical practice.[6] In particular, the International Menopause Society supports the expansion of research into the effects of hormones on the cardiovascular system.

Gender differences in epidemiology of cardiovascular disease

Epidemiology, symptoms, and progression of cardiovascular disease are different in women than in men. Typically, women are about 10 years older than men when they develop cardiovascular disease.[7] Although cardiovascular events are a rare occurrence in pre-menopausal women, their incidence increases most markedly after the age of 45–54 years (i.e. at the time of the menopause). Overall, there has been a decline in the prevalence of cardiovascular disease in developed countries in recent years due to the promotion of primary prevention.[8] Despite an encouraging fall in age-adjusted cardiovascular mortality in men, there has been a gradual increase in the incidence of cardiovascular events in women.[9] Furthermore, the prognosis of cardiovascular disease may differ with regard to gender. For example, the 1-year mortality after myocardial infarction is higher in women,[10] whereas in congestive heart failure the prognosis is better in women than in men.[11]

Marked gender differences also exist in the pattern of stable angina, the most common manifestation of CHD. New cases of angina pectoris as an initial presentation are more common in women, with the incidence of uncomplicated angina in women equal to and, after the menopause, even exceeding that in men.[12,13] Men are more likely to present with an acute event, either myocardial infarction or sudden death, as the initial presentation, of coronary disease in all age groups. After the menopause, the incidence of myocardial infarction in women also increases, although absolute rates remain lower than in men until the eighth decade. Angina is often regarded as benign in women, but despite normal or non-obstructive coronary disease, the morbidity is high.[14]

***Practice point 1*. Increases in the incidence of cardiovascular morbidity in women, in particular myocardial infarction and angina pectoris, coincide with the menopause.**

Table 2 Key cardiovascular risk factors

Non-modifiable	Modifiable
Age	Hypertension[a]
Gender	Dyslipidaemia[a]
Heredity	Obesity[a]
	Glucose intolerance[a]
	Cigarette smoking
	Diabetes mellitus
	Sedentarism

[a]Components of the metabolic syndrome.

Gender differences in risk factors for cardiovascular disease

Risk factors can be defined as non-modifiable and modifiable (*Table 2*). The three key non-modifiable factors are age, gender, and family history. One of the mechanisms of the gender difference between younger men and pre-menopausal women in the incidence of cardiovascular disease may be explained by the cardioprotective effect of endogenous oestrogen. Low plasma oestrogen levels may explain some of the unfavourable lipid and carbohydrate metabolism changes rapidly occurring during menopausal transition and soon after menopause.[15] Similar changes are observed in women with premature ovarian failure with a mean age of 31 years and in those during natural menopausal transition with a mean age of 52.[15]

The presence of hypertension mirrors the prevalence of cardiovascular disease, with increases in prevalence in women after the menopause.[16] Hypertension is a powerful risk factor for cardiovascular disease. Between the ages of 40 and 69 years, each difference in usual systolic blood pressure of 20 mmHg is associated with a two-fold difference in the rate of death from stroke, ischaemic heart disease, and other vascular causes.[17]

Cigarette smoking and oral contraception

Cigarettes have been identified as an important modifiable risk factor for cardiovascular disease. Men have traditionally been more likely to smoke, but the once wide gender gap in smoking prevalence narrowed in the mid-1980s and has since remained fairly constant.[18] The risks associated with smoking, measured by both current and accumulated tobacco exposure, are consistently higher in women than in men and are not age-dependent.[19]

Combined smoking and oral contraceptive use can increase the number of cases of myocardial infarction occurring among women aged over 35.[20] However, regardless of oral contraceptive use, smoking accounts for most of the excess cases.[21] The increased risk of thrombogenesis associated with smoking appears to be affected through increased platelet aggregation and degenerative changes

in the vascular endothelium.[22–24] Among women using oral contraceptives containing less than 35 μg ethinyloestradiol, there was a significant increase in levels of fibrinogen and fibrinopeptide A in both smokers and non-smokers.[24] Unlike non-smokers, women who smoke do not have a compensatory increase in antithrombin III activity, leaving the procoagulant effects of oral contraceptives unopposed.[25] Thus, current or prior combined oral contraceptive use is not associated with a greatly increased risk of myocardial infarction in healthy non-smokers.[26] Despite the small risk of oral contraceptives causing myocardial infarction in non-smokers, caution should be observed when prescribing them to smokers over 34 years of age and specifically to smokers over 39 years old.[27]

The use of oral contraception is also associated with an increased risk of ischaemic stroke, especially in heavy smokers, but the increased risk has to be considered within the context of the very low absolute risk of cardiovascular disease in this population. In a British study, for example, it was observed that 5880 women needed to take oral contraceptives for 1 year to result in one extra stroke.[28]

Dyslipidaemia

Dyslipidaemia is another important modifiable risk factor for CHD. Serum cholesterol is a significant risk factor for myocardial infarction for both men and women, the relative risk being similar and increasing with age.[29] Lowering of low-density lipoprotein cholesterol until recently has been the primary objective in cardiovascular disease prevention.[30] It has now been demonstrated that plasma high-density lipoprotein cholesterol levels inversely correlate with the incidence of cardiovascular disease;[31] hence, elevated high-density lipoprotein cholesterol levels confer cardioprotection. In contrast, triglyceride risk is significantly higher for women and decreases with age.[29]

Diabetes mellitus

The prevalence of diabetes increases sharply with increasing age and is higher in older women than in older men.[32] High testosterone levels in women increase the likelihood of diabetes, whereas the risk is lowered in men.[33] Also, women with gestational diabetes are more likely to develop diabetes in later life.[34] Diabetes substantially increases the risk of cardiovascular disease.[35] Furthermore, individuals with a 2 h plasma glucose of 10.01–11.09 mmol/L have cardiovascular mortality risks similar to those with diabetes.[36] The European Heart Survey of Acute Coronary Events found that women with diabetes were more likely to have ST-segment elevation myocardial infarction than other women presenting with acute coronary symptoms and had a high incidence of hospital mortality.[37] Although the EUROASPIRE study based on data from 4437 patients with CHD shows that the prevalence of known diabetes, newly diagnosed diabetes, or impaired fasting glucose is similar in men (46%) and women (47%),[38] the relative risk of death from CHD and non-fatal myocardial infarction attributable to diabetes is greater in women.[39,40] A recent meta-analysis of 22 studies found that the relative risk for fatal CHD associated with diabetes is 50% higher in women.[39]

Adiposity

Adiposity is a powerful predictor of cardiovascular death, with the relative risk increasing with body mass index.[41] EUROASPIRE also reveals that obesity and central obesity (defined as a waist measurement of more than 88 cm in women and more than 102 cm in men) is more prevalent in females (70%) than in males (46%) with CHD.[42] Central adiposity is associated with the menopausal transition.[43] Even modest weight gain during adulthood, independent of physical activity, is associated with a higher risk of death in women; a body mass index of greater than 25 kg/m^2 and less than 3.5 h of exercise per week accounts for 59% of cardiovascular deaths.[44]

Metabolic syndrome

The metabolic syndrome is a clustering of risk factors for atherosclerotic disease and type 2 diabetes that include central obesity, impaired glucose regulation (i.e. glucose intolerance/insulin resistance), elevated triglyceride levels, reduced high-density lipoprotein cholesterol levels, and hypertension. The coexistence of three or more of these factors constitutes the syndrome and increases the probability of developing diabetes mellitus, as well as increasing the risk of coronary and cardiovascular mortality. A number of definitions of metabolic syndrome exist (*Table 3*), including those of the International Diabetes Federation (IDF),[45] American Heart Association/National Heart, Lung, and Blood Institute,[46] and National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII).[47]

On the basis of the NCEP-ATPIII and IDF definitions, EUROASPIRE found that 56 and 72% of women, respectively, surveyed had metabolic syndrome as opposed to 40 and 59%, respectively, of men.[42] Most notably, the prevalence of obesity is higher and high-density lipoprotein cholesterol levels are lower in women. Also, with ageing, levels of low-density lipoprotein cholesterol and lipoprotein(a) become higher in women than in men.[48] Sympathetic overactivity and increases in inflammation with ageing in women appear to be related to the increased prevalence of the metabolic syndrome.[49] Pre-eclampsia is an additional risk factor for metabolic syndrome,[50] and pre-eclampsia significantly increases the risk of subsequent coronary artery disease.[51]

Physical inactivity

Sedantarism, defined as expending less than 10% of the daily energy intake in the performance of moderate- and high-intensity activities,[52] is highly prevalent in middle-aged women.[53] Physical inactivity is a well-recognized contributory factor and increase in body mass index is an additive risk factor for CHD, especially in women. Sedentarism, which is often combined with depression, is an important contributory factor to CHD.[54]

***Practice point 2*. Hypertension, smoking, dyslipidaemia, diabetes, body mass index, physical inactivity, and metabolic syndrome are all powerful predictors of cardiovascular events. The cardiovascular risk associated with hypertension, triglyceridaemia, and diabetes increases in women following menopause and with increasing age.**

Table 3 Definition of the metabolic syndrome in women according to the International Diabetes Federation,[45] the American Heart Assocation/National Heart, Blood and Lung Institute,[46] and the National Cholesterol Education Program Adult Treatment Panel III[47]

Parameter	IDF (obesity+two other parameters)	AHA/NHLBI (any three parameters)	NCEP-ATPIII (any three parameters)
Obesity	Waist circumference ≥80 cm (Europoid)	Waist circumference >35 in (>90 cm)	Waist circumference >88 cm
Serum triglycerides	≥1.7 mmol/L (or treatment for lipid abnormality	≥150 mg/dL (>1.7 mmol/L)	>1.7 mmol/L
Serum HDL cholesterol	<0.9 mmol/l (or treatment for lipid abnormality	≤50 mg/dL (≤1.3 mmol/L)	Low serum HDL cholesterol
Hypertension	SBP ≥130 mmHg or DBP ≥85 mmHg	SBP ≥130 mmHg or DBP ≥85 mmHg	SBP/DBP >130/85 mmHg
Glucose intolerance	FPG ≥5.6 mmol/L (or previously diagnosed diabetes)	FPG ≥100 mg/dL (5.6 mmol/L) (or drug treatment for elevated glucose)	FPG >6.1 mmol/L

DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; SBP, systolic blood pressure.

The menopause and resulting medical needs

The female population is ageing. In European countries, women have long been known to outlive men.[55] Western European data for 2002 reveal that, for every 100 women aged ≥60, there were only about 70 men.[56] At the end of the 20th century, the situation was less favourable in developing countries: throughout Latin America, Africa and the southern half of Asia less than 10% of women reached the age of 60.[57] However, the future is more promising: during 2006, even in the poorest countries, women started outliving men.[55] By 2050, life expectancy is set to improve greatly worldwide, more than 30% of the female population being 60 years of age or older.[57] Consequently, many more women will experience the menopausal transition. As age at menopause is not changing significantly, women in the future can soon expect to be post-menopausal for 30–40% of their lives.

Loss of ovarian function

The loss of ovarian follicular activity due to falling follicle-stimulating hormone levels explains the decline in oestrogen production at menopause.[58] These hormonal changes impact on the neuroendocrine system, resulting in hot flushes, night sweats, insomnia, mood changes, anxiety, irritability, and poor memory and concentration.[59] The urogenital tract is also affected, with genital atrophy and, as a consequence, may result in incontinence and dyspareunia. These features lead many women to seek medical help, but many are unaware of long-term implications. Management of cardiovascular disease places heavy demands on medical resources. Similarly, the medical and socioeconomic impact of osteoporosis is enormous, being responsible in the USA alone for 700 000 bone fractures each year, of which 300 000 are femoral neck (hip) fractures.[60] Cognitive decline may also be accelerated after the menopause due to oestrogen deficiency, and Alzheimer's disease is two to three times more common in women than in men.[61]

Menopausal symptoms

One of the most frequent, and most disturbing, symptoms reported by peri-menopausal women is hot flushes/night sweats, usually being most severe 6–12 months after the last menses.[62] However, hot flushes may persist for many years in some women.[62–64] Hormone replacement therapy rapidly reduces the intensity and severity of these flushes.[65] Oestrogen replacement is still the most reliable and effective therapy for vasomotor symptoms. Alternatives to hormone replacement therapy, such as soy isoflavones, appear to be of little benefit for hot flushes and other vasomotor symptoms.[66]

Post-menopausal women report that their quality of life has declined due to physical symptoms and increased anxiety and depression.[67] An improved quality of life rating can be achieved with hormone replacement therapy.[68] Short-term hormone replacement therapy has been shown to increase quality-adjusted life expectancy for women with menopausal symptoms.[69] In the longer term, osteoporosis is an important factor contributing to poor health-related quality of life in post-menopausal women.[70] The Women's Health Initiative (WHI) has demonstrated that hormone replacement therapy significantly reduced the overall incidence of fractures and of vertebral and hip fractures even in an unselected patient population.[71]

Specific recommendations on the duration of hormone replacement therapy should be based on the patient characteristics and the dose and type of replacement therapy used. After the WHI publication,[71] the Position Statement by the Executive Committee of the International Menopause Society stated that there are no new reasons to place mandatory limitations on the length of therapy.[6] It was considered that there was no justification for the arbitrary cessation in women who started replacement during the menopausal transition and remain symptom-free while on hormones.

***Practice point 3*. Oestrogen deficiency associated with the menopausal transition leads to many distressing vasomotor symptoms, including hot flushes and night sweats, sexual disorders and, in the long term, osteoporosis. All these symptoms negatively impact on quality of life. An improved quality of life is achievable with hormone replacement therapy due to the alleviation of troublesome menopausal symptoms.**

Menopause as a cardiovascular risk factor

The annual incidence of cardiovascular disease varies according to menopausal status.[72] Weight gain frequently

occurs in peri-menopausal women not receiving hormone replacement therapy.[73] This is mainly attributed to an increase in body fat, which is concentrated in the abdomen (android) rather than subcutaneously (gynoid). Increased body mass index tends to reduce insulin sensitivity and increase systolic blood pressure, especially in women.[74] The decline in serum high-density lipoprotein cholesterol levels and the increase in low-density lipoprotein cholesterol levels is an important contributor to increased CHD.[75] Increases in systolic and diastolic blood pressure coincide with the menopause.[16] Elevated systolic blood pressure is now considered a more important predictor of cardiovascular events than diastolic blood pressure.[76] Furthermore, a mild degree of insulin resistance is present in post-menopausal women not receiving hormone replacement therapy, leading to increased plasma glucose levels.[77] As well as addressing oestrogen deficiency, attention should focus on the treatment of hypertension, lipid imbalance, and glucose intolerance to minimize the cardiovascular risk in post-menopausal women.

***Practice point 4*. Hormonal changes at the menopausal transition result in changes in the individual components of the metabolic syndrome and increase the likelihood of diabetes and cardiovascular disease.**

The role of hormone replacement therapy

A number of hormone preparations are available (*Table 4*). The type, dose, and mode of administration of exogenous sex hormones may vary their physiological actions. The recent findings that transdermal oestrogens, in contrast to oral preparations, do not seem to be associated with increased risk of venous thrombosis are interesting and challenging.[78,79] This is based on the observation that oral, unlike transdermal, preparations containing oestradiol are associated with a marked and rapid increase in C-reactive protein.[79] Overall, hormone replacement therapy helps to maintain quality of life and, in the long term, can also have beneficial effects on the skeletal system and curtail osteoporosis.[6]

Table 4 Available hormone preparations (and route of administration) for women with and without a uterus

With uterus	Without uterus
Conjugated equine oestrogens+medroxyprogesterone acetate (oral)	Conjugated equine oestrogens (oral)
Oestradiol valerate+norethisterone (oral)	Oestradiol-17β (implant)
Oestradiol valerate+levonorgestrel (oral)	Oestradiol-17β (oral)
Oestradiol-17β+norethisterone (transdermal)	Oestradiol-17β (transdermal patch)
Oestradiol-17β (transdermal)+norethisterone (oral)	Oestradiol-17β (transdermal gel)
Oestradiol-17β+dydrogesterone (oral)	Oestradiol-17β (nasal)
Oestradiol-17β+norethisterone (oral)	Estriol (oral)
Oestradiol-17β+drospirenone (oral)	Estropipate (oral)

There has recently been confusion regarding the effect of hormone replacement therapy on the long-term risk of breast cancer. Data on breast cancer risk and hormone replacement therapy collected in the WHI confirm a possible link of long-term use and an increased risk,[80] and therefore this issue should be carefully evaluated and discussed with the woman before prescribing hormone replacement therapy. The conjugated equine oestrogen plus medroxyprogesterone acetate arm of the WHI randomized study showed that the hazard ratio (HR) for breast cancer in the overall patient population was 1.24 (95% CI 1.01–1.54).[80] The increased risk attributed to continuous combined hormone replacement therapy was comparable to that due to being overweight/obese or consuming alcohol.[81] However, the absolute risk for invasive breast cancer in the combination hormone replacement therapy arm was of the order of less than one case per 1000 women-years.[80] Interestingly, there was no risk for women who never used hormones prior to the study and in those aged <60. In other words, the WHI trial clearly demonstrates that the short- to medium-term hormone replacement therapy for up to 5 years does not induce a detectable increase in breast-cancer risk.

The WHI clearly demonstrates that not all hormone replacement therapies can be considered equal regarding the possible effects on breast cancer. In fact, in a hysterectomized woman treated for up to 9 years only with oral equine-conjugated oestrogen, the incidence of breast cancer displayed a non-significant decrease: compared with placebo, oral equine-conjugated oestrogen resulted in an HR of 0.80 (95% CI 0.62–1.04) for breast cancer.[82] Thus, oestrogen alone does not appear to increase significantly the risk of breast cancer in post-menopausal women. Considering adherence-adjusted analyses that censored follow-up 6 months after a woman became non-adherent, a larger and significant reduction in the incidence of invasive breast cancer was observed in the equine-conjugated group compared with the placebo group (HR 0.67; 95% CI 0.47–0.97; $P<0.03$).[82] In addition, the Nurses' Health Study confirms that oestrogen-only replacement is associated with no increase in breast-cancer risk in short-term users, but in very long-term users risk was elevated.[83] The multivariate relative risks and 95% CIs for breast cancer with the current use of unopposed oestrogen for <5, 5–9.9, 10–14.9, 15–19.9, and ≥ 20 years were 0.96 (0.75–1.22), 0.90 (0.72–1.12), 1.06 (0.87–1.30), 1.18 (0.95–1.48), and 1.42 (1.13–1.77) (P-value for trend <0.001). Therefore, breast cancer may not be an issue in women suffering from climacteric symptoms after hysterectomy if in receipt of oestrogen-only therapy.

***Practice point 5*. Use of hormone replacement therapy in the peri-menopausal woman reduces vasomotor symptoms and maintains quality of life. There is no conclusive evidence that such treatment increases the risk of breast cancer.**

Cardiovascular effects of hormone replacement therapy

Data from observational studies have suggested that hormone replacement therapy may enhance survival in women after coronary artery bypass grafting[84] and

myocardial infarction.[85] Other potentially favourable actions of oestrogens include significant increases in high-density lipoprotein and decreases in low-density lipoprotein cholesterol levels in post-menopausal women with accompanying favourable effects on the coagulation profile.[86] With regard to added progestins for uterine protection in non-hysterectomized women, it appears that potential cardiovascular benefits of post-menopausal oestrogen treatment can be attenuated by medroxyprogesterone acetate, but possibly not by other progestins.[87] Medroxyprogesterone acetate has been shown to overcome the vasodilatory effect of oestrogens on coronary arteries, increase the progression of coronary artery atherosclerosis, accelerate the low-density lipoprotein uptake in plaque, increase the thrombogenic potential of atherosclerotic plaques, and promote insulin resistance and hyperglycaemia.[87]

Observational studies have suggested a cardiovascular benefit of hormone therapy. However, randomized clinical trials such as the WHI study, which enrolled women without known CHD, demonstrated that oestrogen plus progestin did not result in cardiovascular protection and may increase the risk of CHD in older post-menopausal women.[88] The overall risk of CHD did not reach statistical significance after combination therapy for an average of 5.6 years, the HR for CHD was 1.24 (95% CI 1.00–1.54). Similarly, the WHI findings show that conjugated equine oestrogen monotherapy provides no protection against myocardial infarction or coronary death in older post-menopausal women with prior hysterectomy during a 6.8-year period of use (HR 0.95; 95% CI 0.70–1.16).[89] There was a trend towards a lower risk among women aged 50–59 (i.e. peri-menopausal) at baseline (HR 0.63) (95% CI 0.36–1.09); however, this trend was not statistically significant.[90]

It has been hypothesized that the length of time since the menopause may be a better predictor of the cardiovascular risk of hormone therapy than the recipient's age. Since a recent analysis of the observational Nurses' Health Study showed that the relative risk of myocardial infarction was not increased in women who started hormone therapy within 10 years of the menopause.[91] The WHI also demonstrated that there was an increased risk of venous thrombosis associated with oestrogen plus progestin therapy that again was greater with age[92] and an increase in the risk of ischaemic stroke that amounted to about eight events per 10 000 women treated.[93]

To explore the 'younger woman effect', a recent secondary analysis of both randomized trials (oestrogen plus progestin and oestrogen alone) of the WHI study was performed. The question of whether the effects of hormone therapy on risks of cardiovascular disease vary by age or years since menopause was addressed. The analysis suggested that women who initiated hormone therapy closer to the menopause tended to have a reduced CHD risk compared with the increase in CHD risk among women more distant from the menopause. This trend, however, again did not achieve statistical significance.[94] It can be concluded that continuous equine oestrogen alone appears to be associated with a lower risk of CHD than continuous equine oestrogen plus medroxyprogesterone acetate. CHD tended to be non-significantly reduced by hormone therapy in younger women or in women less than 10 years since menopause.[94]

The effect of hormone therapy in women with established coronary disease was assessed in the Heart and Estrogen/progestin Replacement Study (HERS) clinical trial. This study failed to demonstrate any cardioprotective benefit of hormone replacement therapy in elderly women with proven coronary artery disease.[95] The HERS study was the first large randomized clinical trial of hormone therapy and cardiovascular outcomes. Almost 3000 women with proven CHD were randomly assigned to a hormone therapy (Prempro^{TM}) commonly used in the USA containing 0.625 mg of conjugated equine oestrogens and 2.5 mg of medroxyprogesterone acetate or placebo. After 4 years, the frequency of the primary outcome, namely fatal and non-fatal heart disease combined, did not differ between the two groups. There was also a 50% excess of coronary events in the first year in the hormone group, suggesting early coronary harm with this form of hormone therapy in this group of patients with documented heart disease.

It is important to point out that the clinical trial data of CHD outcomes are limited to only a few hormone therapy regimens and doses. The possibility that different oestrogens and progestins at different doses and routes of administration may have different cardiovascular outcomes remains to be tested.

***Practice point 6*. Cardiovascular risk associated with hormone therapy exceeds the benefit in elderly post-menopausal women; hence, hormone therapy should not be used for the primary or secondary prevention of cardiovascular disease in older women. In treating the younger, peri-menopausal woman for menopausal symptoms, the benefits should be weighed against the potential risks of hormone replacement therapy.**

Quantifying cardiovascular risk in the peri-menopausal woman

Identification of risk factors is crucial before embarking on hormone replacement therapy and, thereafter, patients should be regularly monitored to identify the emergence of any cardiovascular risk factors. Unfortunately, women are less likely than men to identify risk factors and to participate in screening programmes.[96]

All peri-menopausal women seeking medical help for menopausal symptoms should be regularly assessed for the risk of developing cardiovascular disease and for the risk of complications in the presence of existing disease. In particular, measurement of blood pressure following practice guidelines should be performed at each consultation.[97] All patients should be evaluated for the presence of central obesity, dyslipidaemia, fasting hyperglycaemia, or impaired glucose tolerance. A detailed personal history should be recorded, covering gestational diabetes mellitus and hypertension, alcohol intake and smoking, as well as a family history of cardiovascular disease.

The SCORE charts provide a means of determining the risk of dying of cardiovascular disease in the next 10 years (*Figure 1*).[98] The system is derived from data from 12 European Cohort studies that involved 93 298 women and considers systolic blood pressure and serum cholesterol in relation to age in establishing absolute risk in either high- or low-risk European countries. The alternative Framingham score, which is based on US epidemiology, may overestimate

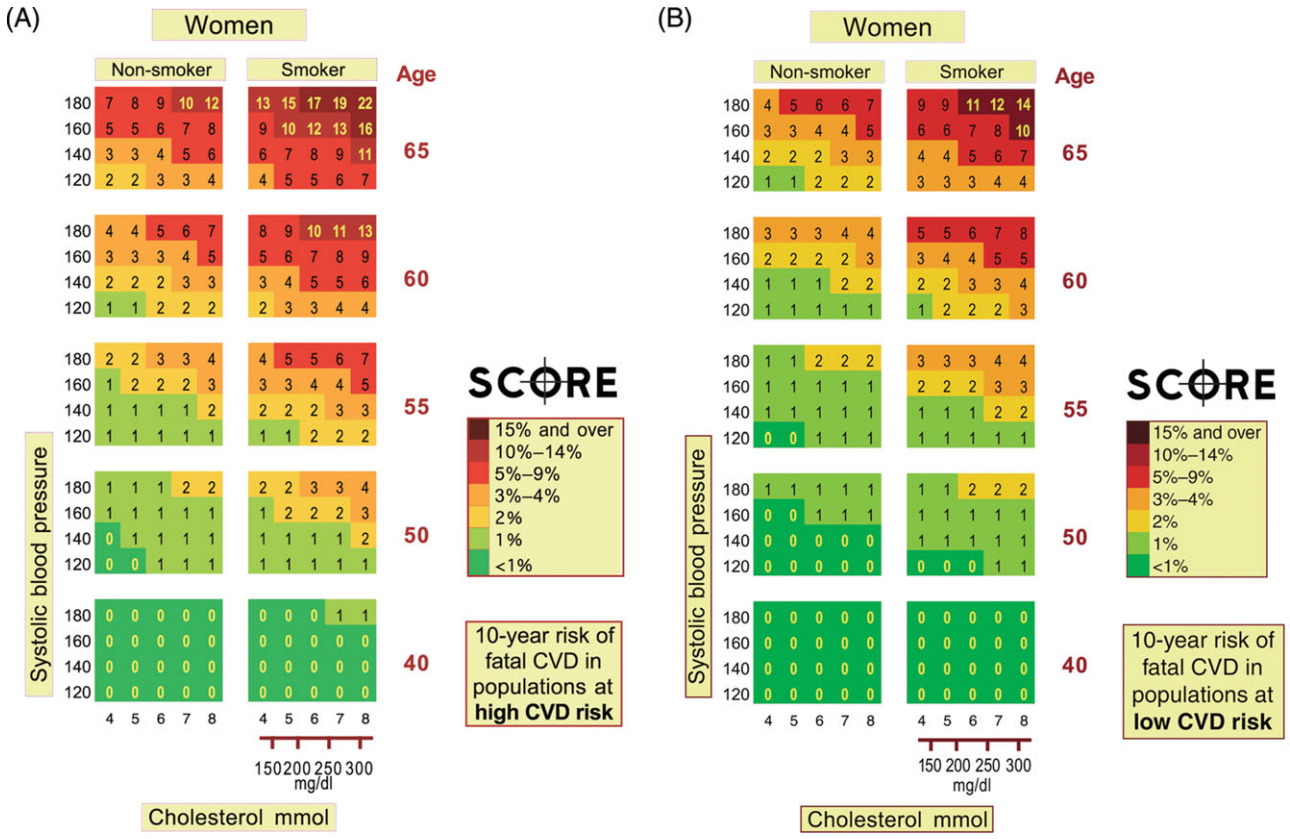

Figure 1 European Society of Cardiology SCORE charts for women in (*A*) high-risk and *(B)* low-risk countries.[100] Figure adapted from Conroy *et al.*,[98] with the permission of Oxford University Press.

risk in European populations. Because of the lag time for cardiovascular event rates in women, particularly fatal cardiovascular events as measured by SCORE, to catch up with those of men after the menopause, the absolute estimated rate of risk for a peri-menopausal or an early post-menopausal woman may be deceptively low. A low estimate of absolute risk of fatal events over 10 years may disguise large increases in relative risk. To avoid such problems, the SCORE card may be used to estimate the risk projected to age 60 years in patients with an unhealthy risk profile but with a low absolute level of risk. Also, unfortunately, the SCORE system may underestimate the risk in patients with low HDL, raised triglycerides, impaired glucose tolerance, and raised levels of inflammation, all features of the metabolic syndrome which is a major component of cardiovascular risk in post-menopausal women and does not take account of diabetes, which is relatively more important as a risk factor for cardiovascular disease in women than in men.[52]

Evaluation of angina, using exercise testing, stress echocardiography, or scintigraphy, and angiography when considered appropriate, also is of utmost importance in the peri-menopausal woman with chest pain as they are powerful predictors of death or non-fatal myocardial infarction.[99] In older women (>75 years), the presence of test-positive angina is associated with a similar, or even higher, absolute mortality than in men.[100]

***Practice point 7*. Every opportunity should be taken when managing a menopausal woman to identify the extent of her cardiovascular risk.**

Modifying cardiovascular risk factors

Increasing physical activity, stopping smoking, and maintaining moderate alcohol consumption are recommended in the 2003 European Society of Hypertension–European Society of Cardiology guidelines.[101] Such measures should be instigated in all patients with high normal blood pressure. Women with stage 1 hypertension usually require pharmacological intervention for hypertension, but lifestyle changes are also important. Changes in diet can also have a favourable effect on dyslipidaemia.[47]

Establishing lifestyle changes is difficult for many women. Counselling on the benefits of exercise, enrolment to a smoking cessation programme and/or an alcohol awareness programme may help, but it may prove difficult to maintain these changes. Many women will require pharmacological intervention with the use of antihypertensives to reduce blood pressure and statins to improve low-density lipoprotein cholesterol profiles, but statins have only a moderate beneficial effect on high-density lipoprotein cholesterol.[102] Careful prescribing of drugs for intensive antihypertensive therapy provides a cost-effective strategy in terms of per event prevented in patients at 10% risk of a coronary event over 5 years.[103] Hormone replacement therapy should not be regarded as a means of preventing CHD and should not be started for this purpose.

***Practice point 8*. Lifestyle changes and pharmacological intervention should be introduced in peri-menopausal women to minimize cardiovascular risk.**

Significance of hypertension in peri-menopausal women

In the adult population, hypertension is the most prevalent chronic disorder and is due to essential hypertension in 95% of cases. At the age of 60 years, over 80% of women are hypertensive.[104] In addition to increasing the risk of CHD and stroke, hypertension can lead to vascular damage within the kidneys that eventually results in end-stage renal disease.

Blood pressure, if measured carefully, is still one of the most powerful and accurate determinants of cardiovascular status and risk.[105] Despite its importance, hypertension often goes undiagnosed. Many physicians do not routinely measure blood pressure, and those who do may not be able to measure blood pressure to within ± 3 mmHg because of sphygmomanometer faults.[106] Even if high blood pressure is detected using correct procedures and using regularly serviced equipment, the condition frequently goes untreated, with reliance on patients making lifestyle changes, or is insufficiently managed using antihypertensive agents of different therapeutic classes,[36] with disregard to the treatment guidelines.[101] Although hypertension is defined as a systolic/diastolic blood pressure of $\geq$140/90 mmHg, it must be appreciated that target-organ damage extends to blood pressures below these values. Therefore, more rigorous control of blood pressure may be appropriate, particularly in the presence of additional risk factors and concomitant disease.

Treatment guidelines are based on evidence gained from large randomized trials, using endpoints of clinical relevance such as a cardiovascular event or stroke. The benefits of antihypertensive therapy come from data obtained from women showing that effective treatment reduces the risk of stroke by 38% and of CHD by 19%.[107]

The European Society of Hypertension–European Society of Cardiology guidelines recognize that the risk of target-organ damage extends to blood pressures well below 140/90 mmHg, and the true threshold for cardiovascular risk should be flexible and dependent on the total risk for each individual (*Table 5*).[101] Current guidelines have defined five levels of blood pressure. Within the so-called 'normal' (120–129/80–84 mmHg) and 'high-normal' (130–139/85–89 mmHg) categories, the cumulative incidence of cardiovascular events is higher than that observed in individuals with optimal blood pressure control ($<$120/80 mmHg).[108]

Some reduction in blood pressure is achievable in patients with high-normal blood pressure by lifestyle interventions,[109] but these measures may prove insufficient to achieve optimal or even normal levels. Recently, it has been shown that pharmacological treatment of high-normal hypertension using an angiotensin II receptor blocker reduces the risk of incident hypertension.[110]

***Practice point 9*. The peri-menopausal woman is increasingly likely to become hypertensive and will require blood pressure-lowering measures to reduce the incidence of target-organ damage. Even slightly elevated blood pressure poses a risk and should be addressed.**

Peri-menopausal hypertension in cardiovascular risk

In addition to factors comprising the metabolic syndrome and type 2 diabetes, various mechanisms at the molecular level have been proposed as playing a role in the increase in hypertension occurring in women at the time of the menopause.[111] Oxidative stress, endothelin levels, sympathetic nervous system activity, and plasma renin activity are increased. The resultant endothelial dysfunction leads to changes in vasomotor tone, arterial stiffness, arterial remodeling, and inflammation, which contribute to atherosclerosis and target-organ damage.[112]

The renin–angiotensin–aldosterone system (RAAS) plays a central role in regulating sodium balance, fluid volume, and blood pressure.[113] Chronic long-term inhibition of the RAAS using angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers, as well as lowering blood pressure, may prevent most of the deleterious effects due to ageing within the cardiovascular system.[114] Aldosterone, independent of angiotensin II, has also been implicated in cardiovascular disease.[115] Blockade of the aldosterone receptor prevents sodium and water retention, with the control of

Table 5 Stratification of risk according to the 2003 European Society of Hypertension – European Society of Cardiology guidelines[101]

Other risk factors and disease history	Blood pressure (mmHg)				
	Normal (SBP 120–129 or DBP 80–84)	High normal (SBP 130–139 or DBP 85–89)	Grade 1 (SBP 140–159 or DBP 90–99)	Grade 2 (SBP 160–179 or DBP 100–109)	Grade 3 (SBP $\geq$180 or DBP $\geq$110)
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors or TOD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
ACC	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

ACC, associated clinical conditions; TOD, target organ damage; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table reproduced from Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J. Hypertens* 2003;**21**:1011–1053, by permission of Lippincott Williams and Wilkins.

blood pressure, and may prevent vascular injury and fibrosis, arrhythmias, and cardiac fibrosis.[116] The aldosterone receptor antagonist spironolactone has been shown to reduce the risk of morbidity and death in patients with heart failure.[117] Similar benefits have been shown with the aldosterone receptor antagonist eplerenone in patients with left ventricular systolic dysfunction and congestive heart failure following myocardial infarction.[118] It has also been shown that one synthetic progestin, drospirenone, is an aldosterone receptor antagonist with antimineralocorticoid activity.[119] When combined with oestradiol as a hormone therapy for use in the peri-menopausal woman, it has been shown to have antihypertensive activity, a unique action. Further blood pressure reduction can be achieved in hypertensive post-menopausal women already treated with the angiotensin-converting enzyme-inhibitor enalapril.[120–122] This blood pressure lowering action of drospirenone has also shown in women with diabetes.[120] Drospirenone, however, has no effect on blood pressure in normotensive women.[123] It should be emphasized that hormone therapy containing drosperinone should not be used solely as an antihypertensive. However, it may be the hormone therapy of choice in hypertensive post-menopausal women who require hormone therapy for the treatment of menopausal symptoms.

***Practice point 10*. The RAAS plays a major role in the control of blood pressure, with both angiotensin II and aldosterone contributing to ensuing target-organ damage.**

Control of menopausal hypertension

The probability that blood pressure will increase with hormone replacement therapy in menopausal hypertensive women is low.[124] However, most of these women will require antihypertensive therapy to achieve target blood pressures. Although reduction of blood pressure *per se* is important,[101] the type of antihypertensive used may have to be considered.

In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm, the amlodipine/perindopril-based therapy was superior to that based on atenolol/diuretic therapy in women than it was in men.[125] However, in common with many other clinical trials, the number of men was disproportionately high at 77%. Attitudes to the use of beta-blockers in hypertension have changed recently, and they are now mainly indicated after myocardial infarction and in cases of tachyarrhythmia rather than hypertension. Their use should be avoided in women with increased risk for metabolic syndrome and especially in the presence of type 2 diabetes.[126]

Because of excessive RAAS activity at the time of the menopause,[127] angiotensin-converting enzyme-inhibitors and angiotensin receptor blockers may be particularly appropriate. These are the agents of choice in hypertensive individuals with diabetes, and they may prevent or delay the onset of diabetes in non-diabetic subjects.[128] Angiotensin-converting enzyme-inhibitors, however, may be associated with a high incidence of severe non-productive cough that some patients find intolerable.[129] Switching to an angiotensin receptor blocker may alleviate this problem.

***Practice point 11*. Treatment of hypertension with angiotensin-converting enzyme-inhibitors or angiotensin receptor blockers may be particularly appropriate.**

Control of menopausal dyslipidaemia

The NCEP-ATPIII has issued comprehensive guidelines for the interpretation of lipid abnormalities and the follow-up and treatment of patients with dyslipidaemia.[47] These guidelines do not advocate any difference in the treatment of men and women. Lifestyle changes can be helpful, but most patients will require pharmacological interventions, with statins being considered the treatment of choice. The primary lipid goal for the prevention of atherosclerotic vascular disease is to achieve a normal low-density lipoprotein cholesterol of $<$130 mg/dL by diet in normal individuals. The use of diet and/or statin therapy may be required in menopausal women according to the degree of risk. Recent data from the Heart Protection Study (HPS) suggest that even patients with low baseline low-density lipoprotein cholesterol may obtain cardiovascular benefit from statin therapy.[130] Simvastatin, the statin used in HPS, did not have any beneficial effect on non-cardiac events such as dementia or osteoporotic fractures.

***Practice point 12*. Statins should be first-line therapy in preventive strategies for lipid lowering, the goal being those recommended by the NCEP-ATPIII.**

Suggested roles and responsibilities of the gynaecologist and the cardiovascular physician in managing peri-menopausal patients

An aggressive approach to the identification and management of all cardiovascular risk factors is essential in primary prevention of cardiovascular disease. Gynaecologists should call upon the expertise of the cardiovascular physician to control blood pressure, dyslipidaemia, and other metabolic parameters contributing to increased cardiovascular risk. Gynaecologists should also refer any female patient with suspected cardiovascular disease to a cardiovascular physician or an internist. In particular, gynaecologists should be vigilant to the possibility of angina.[12] Women have tended to be less likely to be referred for diagnostic tests until advanced disease, less likely to receive secondary prevention and less likely to be revascularized.[131] This attitude should be actively addressed.

Hormone therapy should be discussed taking into account the prevalence and the relevance of the patient's symptoms and risk factors. Each patient must be counselled regarding the current data on the risks and perceived benefits of the therapy, so that she can make appropriate informed individual decisions about continuing or stopping treatment. Such discussions could be part of the annual risk–benefit analysis undertaken in each patient and in the context of timely mammographic and genital cancer studies. At every consultation, patients should also be closely monitored for the presence of cardiovascular risk factors and the emergence of

metabolic syndrome and should be given advice on the importance of lifestyle modification.

***Practice point 13*. In the management of the peri-menopausal women, the cardiologist and gynaecologist should work together to assess and control cardiovascular risk and to minimize vasomotor symptoms. For the primary prevention of cardiovascular disease, the gynaecologist should advise patients about the importance of lifestyle modification. Cardiovascular risk factors should be aggressively managed.**

Gender differences in responses to cardiovascular treatment

Women have been under-represented in clinical trials; more gender-specific data are required on the efficacy and safety of cardiovascular medication. Most of our knowledge of the pathophysiology of cardiovascular disease comes from studies in men, yet cardiac size and changes in left ventricular mass in response to age and hypertrophic stimuli exist between the sexes.[132] An understanding of the gender differences in cardiovascular disease is crucial for the management of female patients and for the development of new gender-specific diagnostic options.[133]

Although there is evidence of gender differences in pharmacokinetics and pharmacodynamics,[57] the efficacy and safety of drugs are frequently evaluated in men and the results extrapolated to women. In clinical trials conducted in the 1980s and 1990s, women were poorly represented: although they make up about 55% of the world's population, no more than one-quarter of the subjects evaluated were women. In more recent trials, this issue has been partially addressed by increasing the proportion of women enrolled, but the situation is still not ideal. There remains a need for clinical trials conducted exclusively in women or for trials that enrol sufficient women to allow a pre-specified gender analysis.[4] Among women, but not men, with heart failure and depressed left ventricular systolic function, digoxin is associated with an increased risk of death from any cause.[134] Aspirin reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischaemic stroke in women and myocardial infarction in men.[135]

Conclusions

Epidemiological data have clearly established a link between the menopause and increased cardiovascular risk. Oestrogen deficiency, which is responsible for the vasomotor and urogenital symptoms and osteoporosis in menopausal women, is also responsible for changes in metabolism and physiology to a more android pattern. Hormone replacement therapy, using an oestrogen or oestrogen plus progestin combination, helps alleviate the menopausal symptoms but cannot be recommended for the prevention of cardiovascular disease. Cardiovascular events can be reduced by the management of risk factors. Particularly important is the control of hypertension, lipids, and other factors contributing to the metabolic syndrome. The management of the peri-menopausal woman is not the exclusive responsibility of the gynaecologist. An interdisciplinary approach should be adopted by the gynaecologist not just evaluating vasomotor and urogenital symptoms, but also assessing the patient for cardiovascular risk, and cardiovascular physician helping in the aggressive treatment of women at increased risk of cardiovascular disease.

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